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REVIEW

Mechanobiology of inflammation: Pulling the strings of innate immunity

Marcin Krzysztof Maniak[1], Stephen J. Jenkins[1], and Carsten Gram Hansen[1]

Mechanical forces are increasingly recognized as potent regulators of inflammation. Physical cues such as stretch, tissue stiffness, and shear stress shape innate immune responses across barrier epithelia, stromal niches, and the vascular endothelium. By engaging conserved mechanotransduction pathways, these forces both modulate and initiate mechano-inflammatory programs, remodeling immune synapses, reconfiguring tissue architecture, and directing leukocyte trafficking. When tissue mechanics are chronically perturbed through sustained pressure, matrix remodeling, or disturbed flow, these same pathways drive pathological inflammation and contribute to diseases ranging from asthma and arthritis to fibrotic disorders and atherosclerosis. In this review, we position mechano-inflammation as a unifying framework linking physical forces to immune regulation. We also highlight diagnostic and therapeutic opportunities targeting the mechanical dimension of immunity.

Introduction

Inflammation is a fundamental protective process that safeguards tissue integrity and restores homeostasis in the face of infection or tissue injury. Yet when inflammatory responses become chronically activated, they shift from adaptive to pathological. With more than half of all deaths globally being attributable to inflammation-related diseases (Furman et al., 2019), understanding the mechanisms that determine whether inflammation resolves or persists remains a central challenge in modern medicine.

At its core, inflammation is orchestrated by innate immune cells, such as macrophages, dendritic cells, and neutrophils that sense danger and re-establish tissue function (Netea et al., 2017). Traditionally, research has focused on immune responses to chemical danger signals, including cytokines, chemokines, metabolites, and microbial molecules found in the microenvironment (Li and Wu, 2021; Ma et al., 2024). However, considerable advances in mechanobiology reveal that forces arising within tissues are equally potent regulators of cellular behavior (Vining and Mooney, 2017). Mechanical stretch, matrix remodeling, viscoelasticity changes, and fluid dynamics shape intracellular signaling and cytoskeletal remodeling across diverse organs (Trepat et al., 2007; Du et al., 2023; Di et al., 2023). The process by which cells convert these mechanical cues into biochemical signals and cellular responses is termed mechanotransduction (Hudspeth and Corey, 1977; Guharay and Sachs, 1984; Wang et al., 1993; Coste et al., 2010; Dupont et al., 2011).

Mechanotransduction mediators, including mechanosensitive ion channels, integrins, cytoskeleton, nuclear envelope, and the Hippo–Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) signaling pathway, directly intersect with pattern recognition receptors, inflammasome, and NF-κB signaling, suggesting that biomechanics constitutes a fundamental part of the immune regulatory network (see Box 1). Critically, immune cells experience a wide range of mechanical forces throughout their lifetime as they extravasate through the endothelium, migrate within tissues, perform phagocytosis, and interact with the extracellular matrix (ECM) and neighboring structural cells (Huse, 2017; Jaumouillé et al., 2019; Sutherland et al., 2023; Reis-Rodrigues et al., 2025). Furthermore, unlike other cell types, immune cells are often weakly adherent and highly deformable, while their mechanical properties are modified by inflammation (Bufi et al., 2015). Since epithelial, endothelial, and fibroblast cells also display substantial innate immune potential (Krausgruber et al., 2020), their mechanosensitivity is another important yet often overlooked inflammation contributor.

In this review, we take a whole-body perspective on how mechanical forces pull the strings of inflammation. We focus primarily on mammalian innate immunity and begin by examining barrier tissues, such as lungs, gut, and skin, where mechanical stress first interfaces with immunity. We then explore stromal inflammation across aging and fibrotic niches, joints, and lymphoid organs before turning to the vasculature, where hemodynamic forces govern endothelial activation and leukocyte trafficking. Although we emphasize innate immune

[1]Centre for Inflammation Research, Institute for Regeneration and Repair, University of Edinburgh, Edinburgh, UK.

Correspondence to Marcin Krzysztof Maniak: m.k.maniak@sms.ed.ac.uk; Carsten Gram Hansen: carsten.g.hansen@ed.ac.uk.

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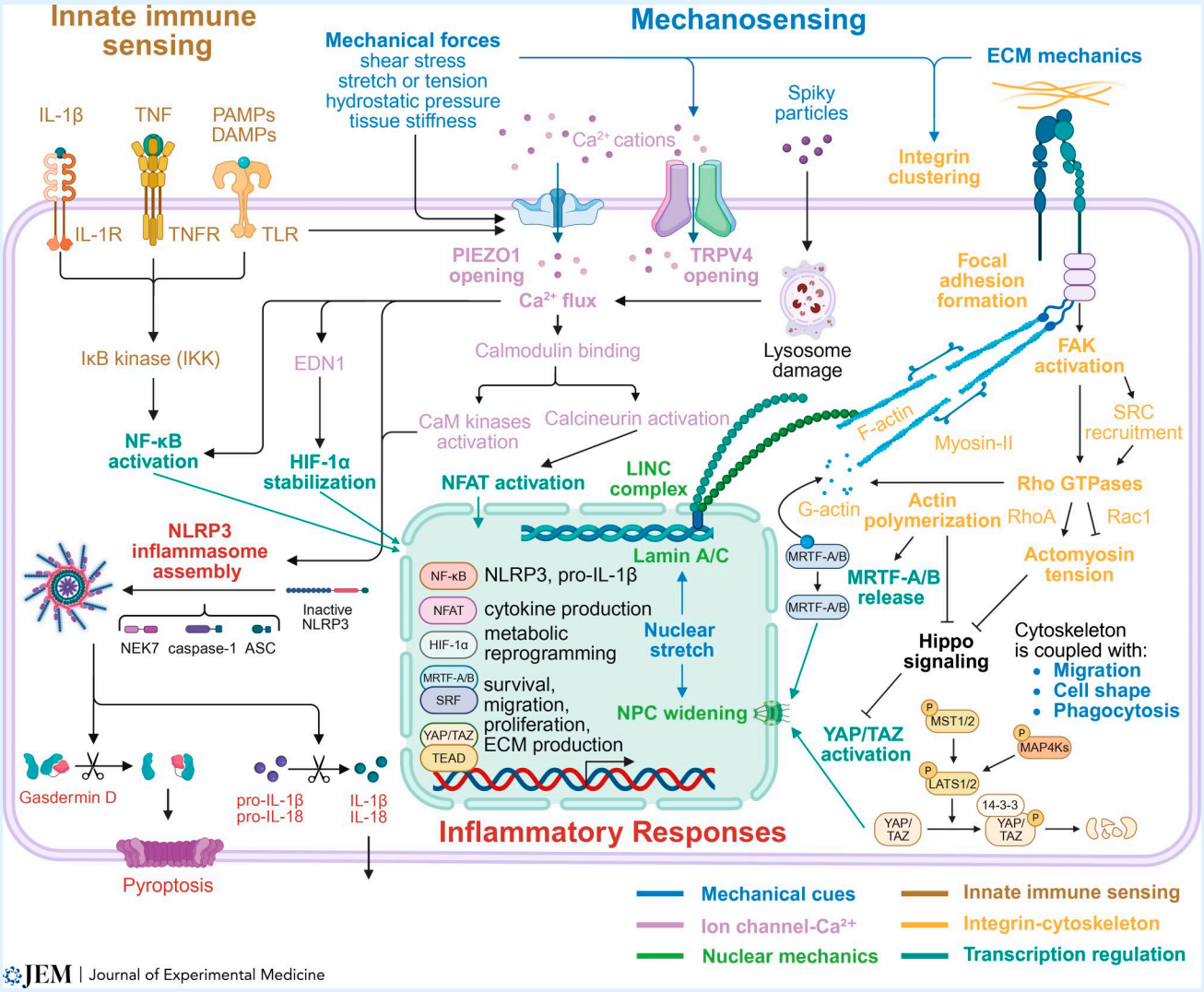
Box 1. **Mechano-immune signaling cross talk**



Mechanical forces are sensed at the plasma membrane by mechanosensitive ion channels, notably piezo-type mechanosensitive ion channel component 1 (PIEZO1) and transient receptor potential vanilloid 4 (TRPV4), which open in response to stretch, shear stress, hydrostatic pressure, or increased stiffness, triggering rapid Ca^{2+} influx. TLR4 also directly engages PIEZO1, thereby functionally coupling innate immune sensing of microbial or damage-associated ligands to mechanotransduction (Geng et al., 2021). Downstream Ca^{2+}/calmodulin signaling intersects with inflammatory pathways by contributing to NF-κB and inflammasome activation, linking mechanical stress to pyroptosis and IL-1β and IL-18 release (Wu et al., 2022; Ran et al., 2023; Fish and Kulkarni, 2024; Fish et al., 2025; Shi et al., 2025). Ca^{2+} signaling additionally stabilizes hypoxia-inducible factor 1-alpha (HIF-1α), in part through endothelin-1, and activates calcineurin, leading to dephosphorylation and nuclear translocation of NFAT, enabling metabolic reprogramming and driving cytokine production (Solis et al., 2019; Wang et al., 2022c; Mukhopadhyay et al., 2024b).

Concurrently, integrins transmit the ECM mechanics, including through focal adhesions where focal adhesion kinase (FAK) and SRC kinases coordinate downstream signaling (Rausch and Hansen, 2020; Yamaguchi and Knaut, 2022). Cytoskeletal dynamics controlled by Rho GTPases are context dependent and tightly coupled to cell migration, phagocytosis, and shape adaptation. Activation of Ras-related C3 botulinum toxin substrate 1 (RAC1) is associated with cell spreading and protrusion, while Ras homolog family member A (RhoA)–Rho-associated coiled-coil–containing protein kinase 2 (ROCK2) signaling enhances actomyosin contractility and tension (Biro et al., 2014). Actin polymerization additionally reduces cytosolic G-actin, enabling myocardin-related transcription factor A/B (MRTF-A/B) nuclear translocation and SRF-dependent transcription of genes involved in proliferation, survival, and inflammatory responsiveness (Olson and Nordheim, 2010; Jain and Vogel, 2018). High cytoskeletal tension and stiff ECM likewise suppress the Hippo pathway, allowing YAP/TAZ nuclear translocation and TEA domain transcription factor (TEAD)-mediated transcription of mechano-inflammatory gene programs (Meng et al., 2015; Meli et al., 2020). Beyond transcriptional control, YAP has been reported to stabilize the inflammasome, reinforcing IL-1β–driven inflammation (Wang et al., 2021).

The nucleus also directly functions as a mechanically responsive organelle. Lamin A/C, the LINC complex, and chromatin organization shape nuclear envelope stiffness and deformability, regulating transport across the nuclear pore complex and cell migration through confined environments (Crisp et al., 2006; Rowat et al., 2013; Raab et al., 2016; Thiam et al., 2016; Elosegui-Artola et al., 2017; Nava et al., 2020). Together, mechanotransduction pathways integrate mechanical cues with innate immune signaling, dynamically shaping inflammatory responses.

mechanisms, adaptive immune cells, including B and T lymphocytes, are likewise mechanosensitive and influence inflammatory responses (Natkanski et al., 2013; Aceitón et al., 2025; Sampietro et al., 2025; Basu et al., 2016; Meng et al., 2020; Huse, 2025). Lastly, we examine pathological and translational implications, discussing how mechanical dysregulation contributes to inflammatory disorders and how emerging mechanotherapeutic and diagnostic strategies may influence clinical practice. By integrating insights from immunology, mechanobiology, biophysics, materials science, and medicine, this review positions mechano-inflammation as a unifying and potent dimension of innate immunity (see Box 2).

Barrier tissues and mechanical stress

Damage and loss of integrity

Barrier tissues continuously experience mechanical stress, and breaches in their structural integrity rapidly trigger inflammation. Epithelial homeostasis is achieved by a coordinated control of cell division, differentiation, spatial organization, and removal (Gu et al., 2011; Eisenhoffer et al., 2012; Gudipaty et al., 2017). Epithelia sense crowding through mechanosensitive ion channels, including PIEZO1, which activate neighboring cell contraction, generating an actomyosin ring that squeezes out excess cells through apical cell extrusion (Eisenhoffer et al., 2012; Yamada et al., 2025). While mechanically driven turnover is normally protective, dysregulated extrusion disrupts epithelial continuity and renders tissues prone to inflammatory activation.

Asthma exemplifies how bronchoconstriction, the acute narrowing of the airways due to smooth muscle contraction, mechanically induces epithelial crowding and drives extrusion beyond homeostatic levels (Bagley et al., 2024). Excessive extrusion leads to denudation of the airway surface, increased mucus secretion, and inflammatory infiltration. While bronchodilators such as albuterol (a β-2 agonist) alleviate smooth muscle contraction, they do not prevent postattack inflammation. In contrast, inhibition of the extrusion pathway, for example, by blocking mechanosensitive ion channels with gadolinium (Gd^{3+}) or the peptide, GsMTx4 (Yang and Sachs, 1989; Suchyna et al., 2000), preserves epithelial integrity and prevents the inflammatory cascade in mouse models (Bagley et al., 2024). Mechanical stretch and compression further influence epithelial signaling through growth factor shedding into the extracellular space (Tschumperlin et al., 2004). Airway epithelial cells from asthmatic patients also exhibit altered cell shape and collective cell behavior (Park et al., 2015b; Atia et al., 2018), while compression of human bronchial epithelial cells is sufficient to induce a pro-inflammatory transcriptional profile that closely resembles the baseline state of asthmatic epithelium (Park et al., 2010; Kılıç et al., 2020). Bronchoconstriction and mechanically induced epithelial damage therefore reinforce inflammatory outputs and airway remodeling, establishing asthma as a fundamentally mechano-inflammatory disease (Grainge et al., 2011; Bagley et al., 2024; Mwase et al., 2025).

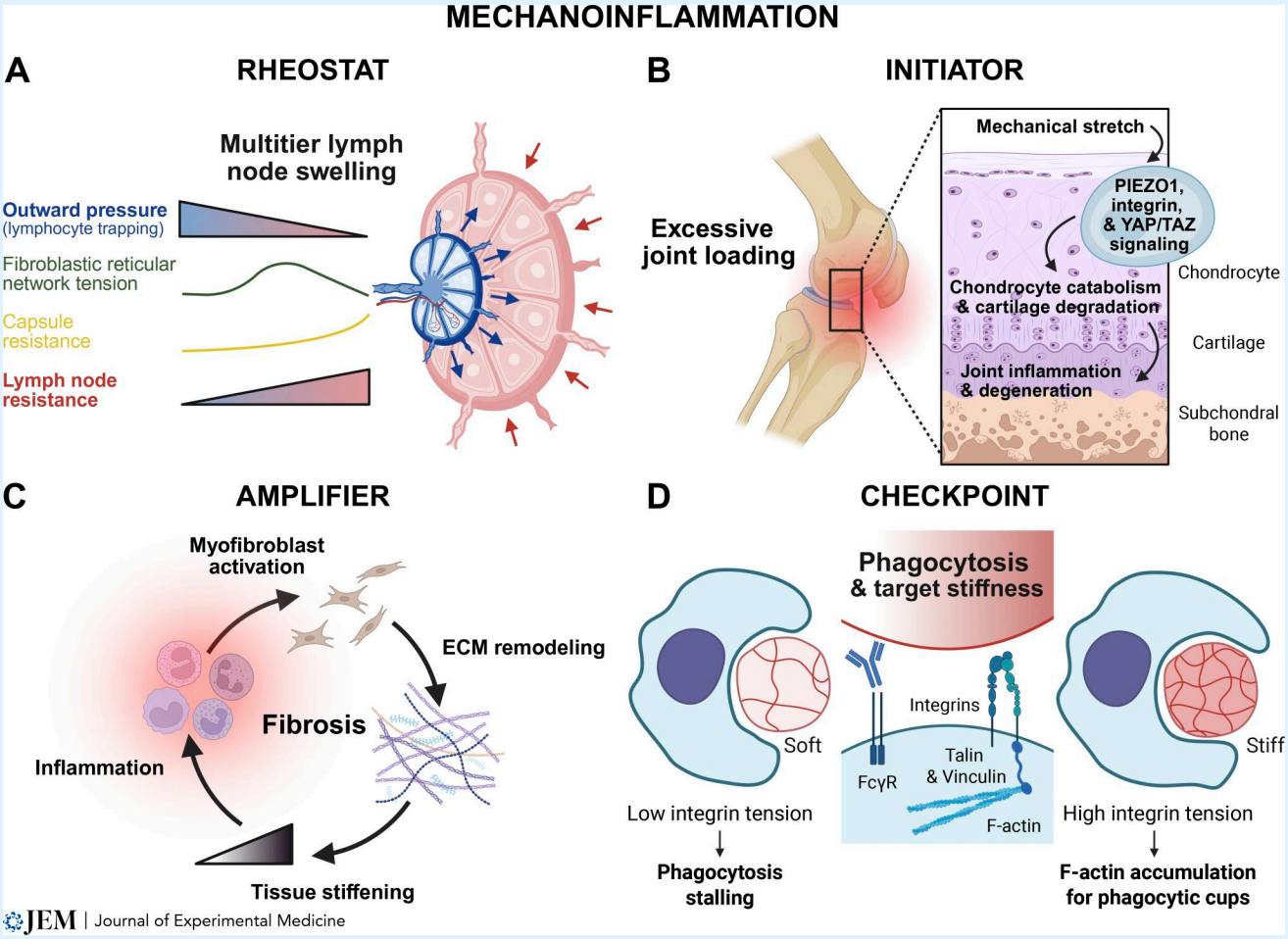
Mechanical dysregulation of cell turnover similarly drives chronic inflammation in the gut, where physiological extrusion requires cytoskeletal remodeling dependent on RAC1, a member of the Rho GTPase family, to enable cells to deform and separate during shedding (Martínez-Sánchez et al., 2023). Consequently, in *Rac1* knockout mice, cell extrusion stalls, leading to overcrowding, junctional disruption, epithelial leakage, and spontaneous mucosal inflammation even without overt immune triggers. Notably, inflamed gut tissue from patients with inflammatory bowel disease (IBD) shows signs of impaired RAC1 function and arrested cell shedding (Martínez-Sánchez et al., 2023). Cell extrusion also serves a protective role during enteric infections (Knodler et al., 2014; Sellin et al., 2014), as activation of innate immune pathways, including NF-κB, alters the mechanical properties of uninfected epithelial cells, enabling them to push softer infected neighbors into multicellular mounds that are collectively extruded to limit bacterial spread, exemplifying an innate immune defense executed through mechanical force (Bastounis et al., 2021).

Tissue damage also leads to water influx, osmotic cell swelling, and nuclear stretch, which, together with elevated cytosolic Ca^{2+}, drive the translocation of cytosolic phospholipase A2 (cPLA2) to the nuclear envelope (Enyedi et al., 2013; Enyedi et al., 2016). Nuclear membrane mechanotransduction is potentiated by endoplasmic reticulum (ER) disruption, which relieves membrane buffering and enhances cPLA2 recruitment to the nuclear envelope (Shen et al., 2026). There, cPLA2 releases arachidonic acid for conversion into pro-inflammatory eicosanoids by 5-lipoxygenase (Schievella et al., 1995; Pearce et al., 1996; Tatulian, 2001). The nucleus therefore acts as a mechanosensory organelle linking physical stress to inflammatory signaling (Enyedi et al., 2016; Gelashvili et al., 2026; Renkawitz et al., 2026). Conversely, inflammatory cytokines disturb tissue mechanics by weakening epidermal adherens junctions through Rho-associated kinase ROCK2-dependent cytoskeletal remodeling, thereby increasing barrier permeability and promoting mechanotransduction that feeds forward into activating psoriasis-associated inflammatory gene programs (Shutova et al., 2023; Jiang et al., 2026). These findings demonstrate that barrier tissues maintain a dynamic mechano-inflammatory homeostasis, wherein mechanical cues and immune signaling are reciprocally coupled. Disruptions in either component can initiate mechanosensory feedback loops that compromise tissue integrity and drive chronic inflammation.

Lungs

The lungs are one of the most mechanically dynamic organs, exposed to rhythmic stretch with each breath and pathological forces during bronchoconstriction, assisted ventilation, or smoking-related interstitial fibrosis (Nonomura et al., 2017; Zepp et al., 2021; Shiraishi et al., 2023). Early work showed that cyclic stretch of alveolar epithelial cells at magnitudes relevant to ventilator-induced lung injury (VILI) increased IL-8 expression and release, establishing mechanical cues as epithelial danger signals (Vlahakis et al., 1999). Lung stretching is sensed, at least partly, by the mechanosensitive ion channel TRPV4 in both alveolar epithelial cells (Nayak et al., 2015; Pairet et al., 2018) and pulmonary endothelial cells (Hamanaka et al., 2007; Huh et al., 2012), with its inhibition showing protective effects against

Box 2. **Principles of mechano-inflammation**



Mechano-inflammation is the bidirectional interplay between tissue mechanics and inflammatory signaling, in which mechanical forces regulate immune functions and inflammation reciprocally remodels tissue architecture. Mechano-inflammation can be understood through four nonexclusive principles that we illustrate through four biological examples:

(A) A rheostat that tunes immune set points

In healthy tissues, physiological forces continuously calibrate the baseline immune state. Lymph node swelling during immune activation (Acton et al., 2014; Horsnell et al., 2022; Assen et al., 2022), laminar blood flow in the vasculature (Baeyens et al., 2015), and cyclic pressure in the lungs (Solis et al., 2019) support homeostasis by modulating immune responsiveness. Progressive alterations in tissue mechanics, such as matrix remodeling during development, pregnancy, or aging, shift inflammatory thresholds and predispose tissues toward either immune tolerance or heightened inflammatory signaling (Timmons et al., 2010; Zhang et al., 2025; Atcha et al., 2021; Sladitschek-Martens et al., 2022).

(B) An initiator of sterile inflammation

Mechanical perturbations also function as primary inflammatory stimuli in the absence of infection. Excessive joint loading in osteoarthritis (Chang et al., 2019b), disturbed flow in atheroprone vascular regions (Albarrán-Juárez et al., 2018), sudden tissue overdistension, and cellular overcrowding (Martínez-Sánchez et al., 2023; Bagley et al., 2024) activate mechanosensitive pathways that trigger inflammatory signaling. In this context, mechanical stress acts analogously to classical danger signals, initiating sterile inflammation.

(C) An amplifier of inflammatory signaling

Mechanical changes generated during inflammation further reinforce and sustain immune responses. For instance, inflammatory signals promote tissue stiffening and enhance mechanotransduction, which in turn elevates the magnitude of cytokine production and leukocyte recruitment (Wong et al., 2012; Shimbori et al., 2019; Lee et al., 2021). These mechanosensitive positive feedback loops amplify inflammatory signaling and contribute to the persistence of chronic inflammation and fibrosis.

(D) A mechanical checkpoint system for immune licensing

Immune cells actively probe the mechanical properties of their surroundings, and many effector functions require force generation and sensing. Stiffness-sensitive macrophage phagocytosis (Jaumouillé et al., 2019; Hu et al., 2023; Settle et al., 2024; Cornell et al., 2025), force-dependent antigen extraction by B cells (Natkanski et al., 2013), mechanical control of cytotoxic T cell killing (Basu et al., 2016; Wang et al., 2022a), and dendritic cell migration influenced by cell shape (Alraies et al., 2024) exemplify how immune responses depend on passing mechanical checkpoints that license activation.

vascular barrier failure caused by overventilation (Michalick et al., 2017; Li et al., 2024b). In fetal lung epithelium, stretch upregulates TRPV4, which modulates differentiation and inflammation, driving IL-6 release (Nayak et al., 2015). In adult epithelial cells, stretch-mediated TRPV4 activation promotes pro-inflammatory cytokine release, whereas pharmacologic TRPV4 blockade attenuates the stretch-induced increase in barrier permeability in murine ventilation models (Pairet et al., 2018). However, *Trpv4* knockout in mice worsens pulmonary edema, underscoring that physiological TRPV4 activity supports barrier integrity (Weber et al., 2020). Complementing TRPV4-mediated stretch sensing, pulmonary microvascular hydrostatic pressure, often elevated during head trauma, left heart failure, and at high altitude, is sensed by endothelial PIEZO1, whose activation leads to disruption of adherens junctions, endothelial barrier failure, and pulmonary edema (Friedrich et al., 2019).

Lung-resident immune cells are also activated by stretch and pressure. Cyclic stretch of mouse alveolar macrophages *in vitro* and mechanical ventilation in the VILI mouse model both activate the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, leading to caspase-1–dependent IL-1β release (Wu et al., 2013). Monocytes and macrophages sense cyclical hydrostatic pressure via PIEZO1, which facilitates Ca^{2+} influx into the cytoplasm, activating a signaling cascade that stabilizes HIF-1α and drives a pro-inflammatory transcriptional program (Solis et al., 2019). Loss of PIEZO1 in myeloid cells blunts pulmonary cytokine production and neutrophil recruitment, leading to impaired host defense but also reduced tissue injury in models of bacterial pneumonia and fibrotic autoinflammation, respectively. These findings reveal a pressure-sensing signaling network supporting innate immune activation in the mechanically active lung environment (Solis et al., 2019).

Two recent studies identify PIEZO1 as a central regulator of type 2 innate lymphoid cells (ILC2s), the key drivers of allergic asthma. In one study, *Piezo1* is induced upon ILC2 activation and restrains type 2 immunity (Hurrell et al., 2024). Importantly, PIEZO1 agonist Yoda1 dampens ILC2 responses in humanized mouse models while loss of *Piezo1* augments cytokine production and airway hyperreactivity (Hurrell et al., 2024). However, in apparently contrasting studies, stimulation of ILC2s with increased stiffness or pressure activates PIEZO1, which selectively enhances mechanistic target of rapamycin (mTOR)-mediated IL-13 translation (Lim et al., 2025). Here, *Piezo1* deletion attenuates lung inflammation and fibrosis in bleomycin-induced lung fibrosis and IL-33–induced allergic airway inflammation model. These divergent outcomes may reflect distinct genetic strategies, developmental timings, or disease models, with constitutive deletion in progenitors in airway hyperreactivity (Hurrell et al., 2024) versus inducible targeting of mature ILC2s during lung injury (Lim et al., 2025). Consequently, PIEZO1 may either restrain or amplify type 2 responses, positioning ILC2s as tunable mechanosensors within the airways.

Mechanical stress further shapes fibrotic lung remodeling by activating mast cells (Shimbori et al., 2019). In idiopathic pulmonary fibrosis and TGF-β1–driven experimental fibrosis, mast cells accumulate within stiff, fibrotic ECM (Kawanami et al., 1979; Veerappan et al., 2013). When subjected to lung stretch or seeded onto decellularized fibrotic lung scaffolds, mast cells undergo degranulation and release profibrotic TGF-β1, a response that can be blocked with mast cell stabilizers (doxantrazole and cromoglycate) to attenuate collagen deposition *in vivo* (Shimbori et al., 2019). Thus, increased matrix stiffness and cyclic strain in the fibrotic lung constitute persistent mechanical cues that feed forward into profibrotic TGF-β signaling. Together, these findings reveal a multiscale mechano-inflammatory network in the lung, where stretch, compression, and cyclic pressure are sensed by epithelial, endothelial, and immune cells, supporting barrier maintenance and immune responses (Huh et al., 2010; Bai et al., 2022). Pathology arises when mechanical loads become excessive or persistent, disrupting mechano-immune homeostasis and driving chronic inflammation.

Gut

The gut possesses a unique mechanical environment, continuously exposed to peristaltic forces from smooth muscle contractions, luminal hydrostatic pressure, and shear stresses generated by food and fluids (Mercado-Perez and Beyder, 2022). Although cyclic stretch can be adaptive, static strain of intestinal smooth muscle cells and peritoneal macrophages upregulates pro-inflammatory mediators, including IL-6, IL-1β, cyclooxygenase-2, and monocyte chemoattractant protein-1 (MCP-1) (Wehner et al., 2010; Lin et al., 2014). In an *in vivo* model of colonic obstruction, mechanical distension alone is sufficient to trigger IL-6–dependent NF-κB activation, demonstrating that mechanical stress can initiate inflammation independently of microbial cues (Lin et al., 2014). Notably, while contraction-related genes decline in late-stage IBD, pharmacologically enhanced smooth muscle contraction increases YAP/TAZ activity, driving Wnt-dependent regenerative signaling (Ji et al., 2024). Given that YAP/TAZ can both respond to Wnt ligands and regulate their expression, these findings highlight a context-dependent, bidirectional cross talk between mechanical and Wnt signaling pathways (Park et al., 2015a; Ji et al., 2024). Mechanosensitive ion channels likewise contribute to gut inflammation. In intestinal epithelial cells, TRPV4 agonists trigger chemokine release and increase epithelial permeability, leading to acute colitis in mice (D'Aldebert et al., 2011). In Crohn's disease, PIEZO1 is highly upregulated in ileal epithelium, where its activation induces mitochondrial dysfunction, NLRP3 inflammasome activation, and downstream cytokine production, while PIEZO1 inhibition suppresses these responses (Liu et al., 2023). However, whether mechanical forces engage intestinal epithelial TRPV4 or PIEZO1 to drive inflammatory signaling *in vivo* is yet to be fully established.

Mechanical cues also govern the regulatory architecture of intestinal immunity. The enteric nervous system directly senses luminal forces through neuronal PIEZO1, which accelerates motility, maintains barrier–immune equilibrium, and limits inflammation during colitis (Xie et al., 2025b). Similarly, TRPV4 in muscularis macrophages residing in the gut's muscular layer mediates prostaglandin E2 release to induce contraction of intestinal smooth muscles and sustain motility (Luo et al., 2018). Selective TRPV4 inhibition, for example, through TRPV4

antagonists HC067047 or GSK2193874 (Everaerts et al., 2010; Thorneloe et al., 2012) or genetic deletion of macrophage *Trpv4*, reduces overall gastrointestinal motility and reverses chemotherapy-induced hypermotility in mice, potentially highlighting how immune cell force sensing coordinates neuromuscular function (Luo et al., 2018). In Peyer's patches, belonging to the gut-associated lymphoid tissue, fibroblastic reticular cells (FRCs) detect the flow of water absorbed from the gut via PIEZO1, thereby preserving the stromal and vascular organization required for lymphocyte entry and IgA responses (Chang et al., 2019a). When this mechanosensing is disrupted, mucosal adaptive immunity collapses. At the cellular level, biophysical forces control migration and retention of regulatory T cells (Tregs), as IL-3 receptor signaling modifies Treg cytoskeletal stiffness and deformability (Ullrich et al., 2023). In its absence, hyper-deformable Tregs escape the inflamed mucosa prematurely, exacerbating chronic colitis. These observations reveal that immune homeostasis in the gut depends not only on cytokine and microbial signals but also on mechanical regulation of inflammatory signaling and immune cell trafficking.

Skin and ocular surfaces

As the outer protective barrier, skin repeatedly endures compression, tensile forces, and shear generated by body movement, environmental contact, and cyclical stretching during growth and repair, all of which actively shape inflammatory responses. For instance, mechanical loading following skin injury promotes hypertrophic scar formation by activating FAK in dermal fibroblasts, which couples matrix tension to inflammatory chemokine production (Aarabi et al., 2007; Wong et al., 2012). Small-molecule FAK inhibitors injected intradermally reduce scarring in mice by decreasing MCP-1 signaling and monocyte recruitment, while localized delivery of FAK inhibitors via topical hydrogels similarly accelerates the healing of excisional and burn wounds (Wong et al., 2012; Ma et al., 2018). Mechanical wound milieu plays additional roles in diabetic foot ulcers, in which increased pressure and altered ECM remodeling, driven in part by dysregulated metalloproteinase activity, disrupt fibroblast and keratinocyte activity while sustaining chronic inflammation (Wong et al., 2014; Maione et al., 2016; Castleberry et al., 2016; Nguyen et al., 2018; Chakraborty et al., 2021b). These mechanical dysfunctions effectively hinder tissue regeneration and vascularization (Freedman et al., 2023). Notably, FAK and MAPK mechanosignaling pathways are downregulated in fibroblasts from mice with pathophysiological diabetes driven by high-fat diet and from genetically induced diabetic models (leptin receptor–deficient mice) when compared with fibroblasts from healthy mice, where they induce pro-healing and angiogenic phenotypes (Liu et al., 2017; Berryman et al., 2026). Together, these findings underscore precise control of mechanotransduction and inflammation in wound repair and regeneration.

Mechanical amplification of inflammation is also seen in psoriasis, which often develops in areas of frequent friction and is further exacerbated by dilator implant surgery that compromises skin barrier function (Qiao et al., 2019). Continuous stretching of primary human keratinocytes likewise induces pro-inflammatory cytokine production, including IL-1α, IL-6, and IL-23. At the same time, mechanical distension in a murine skin-expansion model aggravates psoriatic pathology, indicating that epidermal mechanosensing directly exacerbates inflammatory disease (Qiao et al., 2019). Direct mechanical stimulation of mucosal surfaces, such as eye rubbing, similarly induces inflammation, as stretched conjunctival epithelial cells and corneal fibroblasts activate PIEZO1, triggering pro-inflammatory cytokine production and neutrophil recruitment (Fukuoka et al., 2025; Zou et al., 2026). Chronic inflammation also aberrantly activates mechanotransduction pathways, such as the YAP/TAZ cascade in the regenerating corneal epithelia, driving pathological epidermal differentiation on the ocular surfaces (Nowell et al., 2016). Beyond disease, mechanical tension activates PIEZO1 to drive metabolic reprogramming of epidermal cells and subsequent immune cell recruitment in a murine tissue expansion model (Xue et al., 2025). Pharmacologic PIEZO1 activation further accelerates these responses and promotes tissue expansion *in vivo*, revealing a mechano-inflammatory network controlling skin growth (Xue et al., 2025).

Mechanical forces not only activate epithelial cells but also influence the immune compartments across cutaneous tissues. Mechanical injury by tape stripping mouse skin triggers systemic keratinocyte IL-33 release, which cooperates with gut-derived IL-25 to expand intestinal ILC2s and mast cells, enhancing susceptibility to food anaphylaxis and revealing a mechano-inflammatory skin–gut axis (Leyva-Castillo et al., 2019). Even *in utero*, fetal mast cells and sensory neurons are primed by maternal stress to overreact to harmless friction after birth, leading to early-onset eczema and demonstrating that mechanical sensitivity of the skin immune circuits can be developmentally programmed (Serhan et al., 2025). Similarly, skin myeloid cells sense mechanical stress via FAK, and disrupting their mechanotransduction reduces downstream profibrotic signaling in fibroblasts (Chen et al., 2025a), including engrailed-1, which plays critical roles in cutaneous fibrosis and inflammation (Györfi et al., 2021; Mascharak et al., 2021; Xu et al., 2025b). Plasmacytoid dendritic cells, which infiltrate the skin and frequently promote fibrosis in autoimmune disease, likewise integrate mechanical cues, such as elevated tissue stiffness which suppresses type I IFN (IFN-I) production by activating the nuclear factor erythroid 2-related factor 2 (NRF2) stress signaling pathway (Chaudhary et al., 2025). In systemic sclerosis, however, the profibrotic chemokine CXCL4 overrides this stiffness-mediated inhibition, permitting sustained IFN-I responses and thereby revealing a dysregulated mechanoregulatory mechanism in fibrotic skin (Chaudhary et al., 2025).

Dendritic cells also sense hydraulic resistance, ECM pore size, substrate topography, and cell shape changes, exploiting these mechanical cues to facilitate space exploration and control tolerogenic potential for efficient immune surveillance (Moreau et al., 2019; Renkawitz et al., 2019; Reversat et al., 2020; Kopf et al., 2020; Alraies et al., 2024; Calmettes et al., 2026). Strikingly, in 3D interstitial environments, leukocytes migrate independently of integrin-mediated adhesion, relying primarily on actin-network expansion at the leading edge, with myosin II–dependent trailing-edge contractions required to propel the

rigid nucleus through narrow gaps (Lämmermann et al., 2008; Lämmermann et al., 2009; Renkawitz et al., 2009; Gaertner et al., 2022). Intrinsic actomyosin cortex properties, including cortical contractility and rigidity transitions, further enable rapid amoeboid mode switching and efficient propulsion under mechanical confinement, principles that, although defined in broader metazoan contexts, are highly applicable to fast-moving leukocytes (Liu et al., 2015b; Maiuri et al., 2015; Ruprecht et al., 2015; Vargas et al., 2016; García-Arcos et al., 2024). Beyond force generation, myosin II also coordinates nucleokinesis and adaptive pathfinding, while functionally coupling cell motility to immune processes such as antigen capture (Chabaud et al., 2015; Kroll et al., 2023; Company-Garrido et al., 2026).

Migration through confined tissues poses an additional challenge by exposing cells to nuclear envelope stress, leading to transient ruptures and potential DNA damage that are mitigated by ESCRT III–mediated repair and fine-tuning of nuclear lamina stiffness, including Lamin A/C levels (Raab et al., 2016; Thiam et al., 2016; De Silva et al., 2023; Schmitt et al., 2025). Stretching and unfolding of the nuclear envelope during confinement also triggers calcium-dependent cPLA2 activation, regulating pro-inflammatory signaling, actomyosin contractility, and migration plasticity (Enyedi et al., 2016; Lomakin et al., 2020; Venturini et al., 2020; Arya et al., 2026). These mechanisms enable leukocytes to maintain nuclear integrity while deforming efficiently through narrow spaces (Karling and Weavers, 2025). Overall, mechanical stress is not merely a consequence of inflammation but a key driver of mechano-inflammatory homeostasis and pathology across barrier surfaces (Fig. 1 A).

Stroma and matrix remodeling

Aging and mechano-inflammation

Tissues exhibit a wide range of mechanical properties, which critically influence cellular functions (Discher et al., 2005; Engler et al., 2006; Swift et al., 2013). Tissue stiffness, for instance, spans more than seven orders of magnitude (Guimarães et al., 2020), from soft brain (<1 kPa) to rigid bone (>10 GPa) (Murphy et al., 2011; Budday et al., 2017; Morgan et al., 2018). Many healthy parenchymal organs, including the lungs, liver, pancreas, and kidneys (~1–7 kPa), as well as lymphoid organs such as bone marrow, thymus, spleen, and lymph nodes (up to 25 kPa), are relatively soft but stiffen markedly during fibrosis (Alkhouli et al., 2013; Sicard et al., 2018; Leung et al., 2013; Samir et al., 2015; Bayramoglu et al., 2020; Colecchia et al., 2012; Azizi et al., 2016). Intermediate stiffness is characteristic of contractile and structural tissues, notably skeletal muscle (~10–20 kPa at rest to ~50–100 kPa during contraction) and cartilage (>100 kPa) (Freed et al., 1997; Eby et al., 2015). These diverse mechanical profiles act as a physiological rheostat that tunes immune functions essential for tissue-specific homeostasis.

However, age-related ECM cross-linking, stiffening, and viscoelasticity changes disrupt force transmission, impairing immune cell migration and surveillance while promoting inflammation and fibrosis across organs (Lampi and Reinhart-King, 2018; Segel et al., 2019; Sladitschek-Martens et al., 2022; López-Otín et al., 2023; Fu et al., 2024; Gray et al., 2025) (Fig. 1 B). In aged skin, collagen matrix remodeling enhances melanoma cell invasion while simultaneously impairing T cell motility (Kaur et al., 2019), whereas in the aging lung, increased hyaluronan constrains alveolar macrophage proliferation and antiviral responses (McQuattie-Pimentel et al., 2021). ECM-derived elastin fragments further activate innate immunity and promote age-associated inflammation (Yi et al., 2025). These findings indicate that structural deterioration of the ECM not only alters tissue mechanics but actively drives immune dysfunction during aging.

A convergent pathway linking mechanical decline to sterile inflammation emerges at the nuclear envelope. Changes in nuclear mechanics, driven in part by altered lamin A/C levels, render nuclei more susceptible to deformation, rupture, and genomic instability (Lammerding et al., 2004; Swift et al., 2013; Harada et al., 2014; Denais et al., 2016). The transcriptional co-regulators YAP and TAZ act as key guardians of tissue integrity, yet their activity progressively diminishes in aging stromal and contractile cells *in vivo*, while their experimental inactivation is sufficient to induce premature tissue aging (Sladitschek-Martens et al., 2022). Mechanistically, YAP/TAZ depletion compromises nuclear envelope integrity by downregulating the components of nuclear lamina and the perinuclear actin cap, promoting DNA leakage and cyclic GMP-AMP synthase (cGAS)–stimulator of IFN gene (STING)-dependent senescence-associated secretory phenotype (SASP) (Sladitschek-Martens et al., 2022). Consistent with this model, a recent study of intervertebral disc degeneration in rats reported that enhancing YAP/TAZ-mediated mechanotransduction preserves nuclear membrane integrity, suppresses cGAS–STING-dependent SASP induction, including pro-inflammatory TNF-α and IL-1β, and improves disc regeneration (Li et al., 2025).

Nuclear damage is increasingly recognized as a central trigger of inflammation during aging (Decout et al., 2021; Zhao et al., 2023; Baechle et al., 2023). Lamin A/C protects alveolar macrophages from transient nuclear envelope rupture and DNA damage induced by confined migration through the lung parenchyma, further coupling mechanical stress on the nucleus to genomic instability and tumor protein p53–dependent senescence (De Silva et al., 2023). Lamin A/C degradation consequently promotes pro-inflammatory macrophage activation (Mehl et al., 2022), while loss of nuclear envelope integrity triggers sterile inflammation through activation of the cGAS–STING cytosolic DNA-sensing pathway (Glück et al., 2017; Frittoli et al., 2023; Luo et al., 2026). Consistently, chronic cGAS–STING activation is linked to premature aging phenotypes *in vivo* (Gulen et al., 2023; Şerifoğlu et al., 2025; Cancado de Faria et al., 2025; Tomaskovic et al., 2026), further suggesting that nuclear damage is a key event through which mechanical stress can be converted into chronic low-grade inflammation, known as inflammaging (Franceschi et al., 2000; Ferrucci and Fabbri, 2018; Li et al., 2023; Manwaring-Mueller et al., 2026).

However, the nucleus is not a passive recipient of mechanical stress but possesses intrinsic mechanoadaptive capacity (Guilluy et al., 2014; Cho et al., 2019). Mechanical stress is buffered by heterochromatin, which, together with nuclear lamins, dynamically regulates nuclear stiffness and thereby prevents deformation-

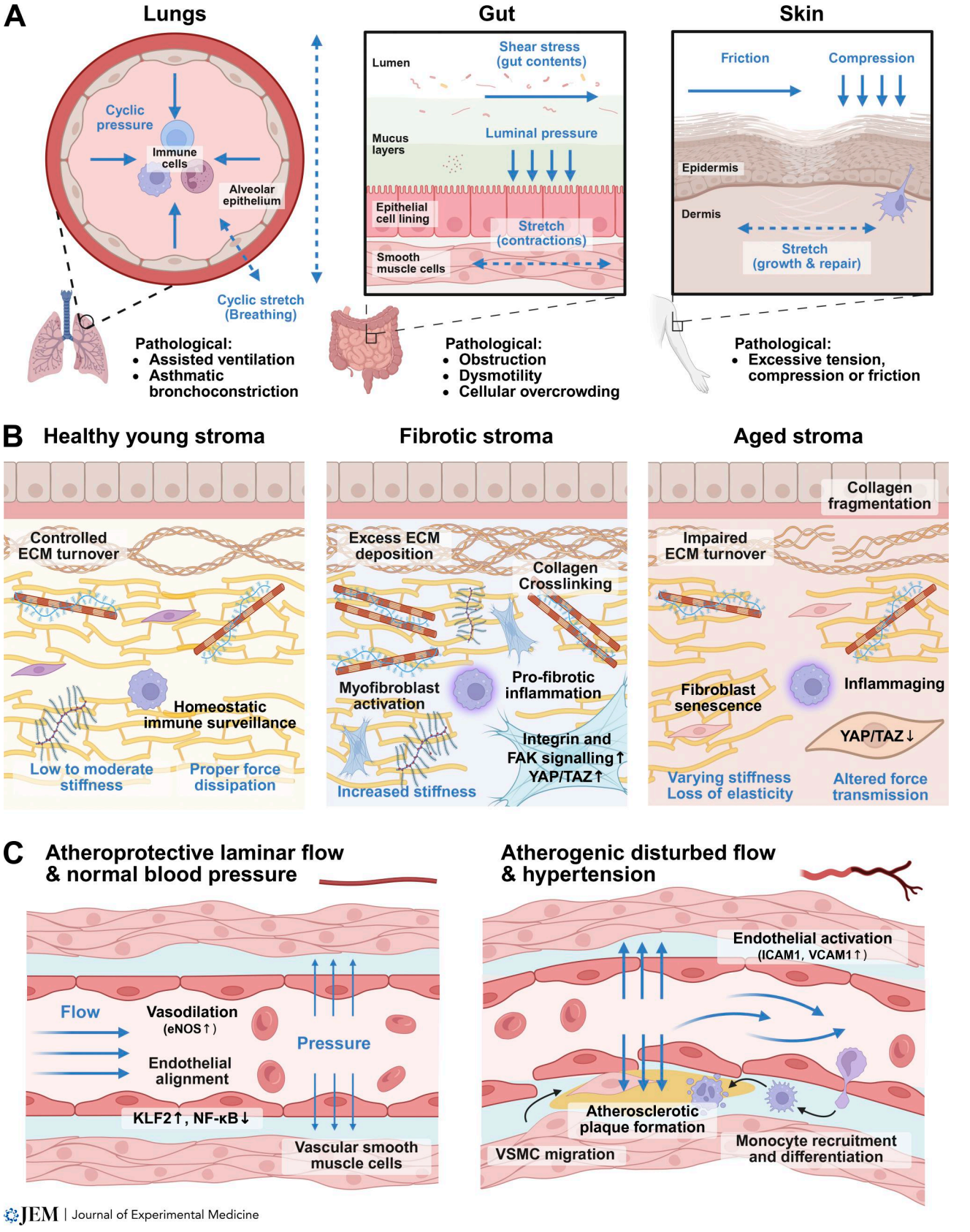


Figure 1. **Mechanical regulation of inflammatory responses across tissues. (A)** Barrier tissues such as the lungs, gut, and skin are constantly exposed to mechanical stress, including stretch, pressure, and shear, which shape epithelial and immune homeostasis. **(B)** In healthy young stroma, controlled ECM turnover supports physiological force transmission and immune surveillance, whereas fibrosis and aging drive pathological ECM remodeling, increased tissue

stiffness, and altered mechanotransduction that amplify inflammatory signaling. **(C)** Vascular inflammation is modulated by hemodynamic forces, with laminar flow and normal blood pressure maintaining endothelial homeostasis, while disturbed flow and hypertension promote endothelial dysfunction and accelerate atherosclerotic plaque development.

induced DNA damage (Stephens et al., 2017; Stephens et al., 2018; Stephens et al., 2019; Nava et al., 2020; Dupont and Wickström, 2022). Specifically, mechanical stretch induces rapid PIEZO1-mediated calcium release, resulting in a reduction of histone H3 lysine 9 trimethylation-marked heterochromatin and transient nuclear softening that dissipates mechanical stress (Nava et al., 2020). Disruption of this chromatin-based rheological program compromises nuclear mechanical resilience and promotes the accumulation of DNA damage (Nava et al., 2020). Aging-associated chromatin remodeling may therefore further alter mechanosensitivity and contribute to inflammatory dysregulation (Liao et al., 2026; Lu et al., 2026; Blanch et al., 2026, *Preprint*).

Mechanosensitive ion channels further integrate extracellular and nuclear changes into inflammatory signaling, amplifying cytokine responses and driving stem cell exhaustion across tissues. In intervertebral discs, PIEZO1-mediated sensing of abnormal mechanical load and stiffness triggers an NF-κB–dependent signaling loop that accelerates nucleus pulposus cell senescence and tissue degeneration (Wu et al., 2022). Furthermore, hair shaft miniaturization in aging and androgenic alopecia mechanically constrains hair follicle stem cells, triggering PIEZO1-dependent Ca^{2+} influx that amplifies TNF-α sensitivity and induces ectopic apoptosis, resulting in long-term stem cell depletion (Xie et al., 2022). In hematopoietic stem cells, both external shear stress sensed by PIEZO1 and intrinsic nuclear envelope tension mediated by RhoA signaling promote myeloid bias and functional exhaustion, revealing a conserved mechanobiological trade-off between rapid immune activation and long-term tissue maintenance (Shang et al., 2026; Mejía-Ramírez et al., 2025). Similarly, PIEZO1-dependent mechanosensing of altered muscle stiffness by mesenchymal stromal cells initiates inflammatory responses and is associated with age-related muscle inflammation (Langston et al., 2026). Consequently, mechano-inflammation provides a unifying framework linking age-related structural decline to inflammaging, highlighting mechanosensing and nuclear integrity as potential therapeutic targets.

Fibrosis and obesity

Alongside aging, fibrosis may arise when ECM stiffness itself becomes a dominant instructive cue that amplifies fibrotic and inflammatory signaling, rather than merely reflecting underlying disease (Liu et al., 2010; Liu et al., 2015a; Henderson et al., 2020; Mascharak et al., 2024). For example, experimentally increasing matrix stiffness elevates inflammation above a critical threshold and drives ECM deposition independently of TGF-β, whereas loss of the elastic-fiber protein fibulin-5 reduces tissue stiffness, dampens inflammatory signaling, and prevents fibrosis *in vivo* (Nakasaki et al., 2015). Similarly, genetic deletion of the early-activated ECM component ECM1 ameliorates kidney fibrosis, as modulation of ECM1-dependent integrin–YAP signaling reprograms fibroblast metabolism and promotes renal repair (Gui et al., 2026). Similar feed-forward behavior is evident in inflammatory conditions that arise after surgery, injury, or trauma, where scar formation drives progressive ECM remodeling and establishes pathological mechanical niches (Moretti et al., 2022). In a uterine-scar model recapitulating placenta accreta spectrum (PAS), an increasingly common condition during pregnancy following previous cesarean delivery, scar matrix activates PIEZO1 through glycolysis-driven cellular contraction (Wenqiang et al., 2024). PIEZO1-dependent Ca^{2+} influx subsequently leads to NF-κB activation, upregulating IL-8 and G-CSF that recruit trophoblasts into the scarred niche. Excess trophoblasts disturb stromal-epithelial homeostasis and placentation, instigating PAS. These findings support a feed-forward model in which ECM stiffening amplifies inflammatory and profibrotic signaling, progressively locking tissues into a fibrotic state (Wenqiang et al., 2024) (Box 2).

Likewise, extensive ECM remodeling in conditions such as obesity creates a stiff fibrotic environment driving metabolic inflammation (Sun et al., 2013; Pellegrinelli et al., 2023). In adipose tissue fibrosis, increased stiffness impairs adipocyte function and promotes pro-inflammatory cytokine expression via β1-integrin–dependent cytoskeleton remodeling (Pellegrinelli et al., 2014). Altered ECM also affects the immune compartment. Stiff matrix shifts macrophages toward a tumor-associated phenotype (Springer et al., 2019), while obesity-induced senescent macrophages feedback on adipose progenitors to reinforce ECM deposition and suppress healthy adipogenesis (Rabhi et al., 2022). Interestingly, mechanosensitive channels have context-dependent effects, as PIEZO1 drives obesogenic adipogenesis and local inflammation in peripheral adipose tissues (Wang et al., 2020a) but suppresses adipogenesis in bone marrow mesenchymal stem cells by inhibiting a mechano-inflammatory autocrine loop, thereby protecting against osteoporosis (Wang et al., 2025a). In organs such as the mammary gland and pancreas, obesity-associated fibrosis and adipocyte transformation enhance mechanosignaling and inflammation, which promote cancer progression and therapy resistance (Seo et al., 2015; Incio et al., 2016; Druso and Fischbach, 2018; Wishart et al., 2020; Song et al., 2024).

Within these mechanically altered niches, innate immune cells themselves act as mechanosensors (Patel et al., 2012; Previtera and Sengupta, 2015; Sridharan et al., 2019; Khanmohammadi et al., 2025a) that can either propagate or resolve fibrosis (Ramachandran et al., 2012; Misharin et al., 2017). Dendritic cells cultured on stiff substrates exhibit increased proliferation and inflammatory cytokine production, accompanied by enhanced glycolytic metabolism; this stiffness-driven phenotype requires TAZ and PIEZO1 and promotes more potent adaptive immune responses in models of autoimmunity and tumor immunity (Chakraborty et al., 2021a). Similarly, PIEZO1 in macrophages links mechanotransduction to RBC phagocytosis and iron

metabolism, with gain-of-function variants driving iron overload (Ma et al., 2021). PIEZO1 is also a key macrophage mechanosensor of substrate stiffness, with *Piezo1*-deficient macrophages showing reduced inflammatory polarization and altered responses to biomaterial implants *in vivo* (Atcha et al., 2021). Stiffness sensing via PIEZO1 can also be antifibrotic, as PIEZO1 activation enhances macrophage efferocytosis, promotes efficient phagolysosomal acidification and induction of anti-inflammatory genes, and is required for spontaneous resolution in early liver fibrosis, while PIEZO1 agonists further accelerate regression (Wang et al., 2024). Microglia, the resident immune cells of the central nervous system, also sense increased amyloid-β stiffness via PIEZO1, eliciting oxidative stress–driven neuroinflammation that impairs microglial phagocytosis within the amyloid plaque microenvironment, with relevance to neurodegenerative diseases such as Alzheimer's disease (Liu et al., 2025).

Pathophysiological ECM stiffness likewise sensitizes TRPV4 channels to mediate the LPS-enhanced phagocytosis and induce macrophage polarization (Scheraga et al., 2016; Scheraga et al., 2020; Dutta et al., 2020). Additionally, ECM's mechanical properties tune macrophage chromatin accessibility and induce tissue repair–associated transcriptional programs through integrin-independent cytoskeletal remodeling (Meizlish et al., 2024). Thus, mechanical cues in the fibrotic niche not only activate immune cells but can be harnessed to bias them toward resolving rather than perpetuating fibrosis. Macrophage YAP also appears to be mechanically regulated (Meli et al., 2020), although the role of the Hippo–YAP/TAZ signaling in myeloid differentiation and specific macrophage functions remains an area of active investigation, with studies reporting varied expression of YAP and TAZ (Wang et al., 2017; Feng et al., 2018; Mia et al., 2020; Mia et al., 2025; Zhou et al., 2019; Liu et al., 2020; Meizlish et al., 2024; Park et al., 2025). Macrophage adhesion to soft matrices reduces nuclear YAP and dampens mechano-inflammatory gene expression, whereas YAP overexpression enhances macrophage inflammation both *in vitro* and *in vivo* around implanted stiff materials (Meli et al., 2020). Although immune responses to matrix stiffness have been comparatively well explored, the effects of viscoelasticity remain far less understood (Adebowale et al., 2021; Adebowale et al., 2025; Adu-Berchie et al., 2023; Liu et al., 2024; Jung et al., 2025, *Preprint*). Given the inherently complex mechanical behavior of the ECM, including time-dependent deformation, viscoelasticity represents an important avenue for future research (Chaudhuri et al., 2015; Chaudhuri et al., 2020; Fan et al., 2024; Wu et al., 2025).

Immune cells additionally communicate with fibroblasts through mechanical rather than purely chemical cues. In fibrillar collagen matrix, dynamic fibroblast contractions generate long-range deformation fields that attract macrophages toward the force source, and this directed migration depends on α2β1 integrins and mechanosensitive ion channels in macrophages, enabling mechanosensing of substrate displacements extending far beyond the reach of chemotactic gradients (Pakshir et al., 2019). Fibroblast contractions also release latent ECM-sequestered TGF-β1, reinforcing profibrotic signaling (Wipff et al., 2007). Fibroblasts further regulate macrophage population size through microenvironmental sensing, as density- and force-dependent fibroblast YAP activation upregulates *Csf1*, thereby controlling local macrophage numbers and tying stromal space-sensing directly to growth factor supply for resident macrophages (Zhou et al., 2022). Conversely, direct contact with profibrotic macrophages also mechanically activates fibroblasts even in otherwise nonpermissive soft environments, requiring macrophage αvβ3 integrins to engage fibroblast PIEZO1, causing rapid Ca^{2+} influx, NFAT and YAP nuclear translocation, and myofibroblast differentiation (Ezzo et al., 2024). Macrophages themselves become mechanically activated in fibrotic stromal microenvironment, undergoing integrin αMβ2– and ROCK2-dependent alignment with collagen fibers and fibroblasts, driving widespread fibrogenesis (Xu et al., 2024). Notably, the antifibrotic drug pirfenidone disrupts this mechanical macrophage activation, inhibiting both macrophage polarization and downstream fibrosis (Xu et al., 2024). Combined, these studies highlight aging and fibrotic niches as mechano-immune systems in which stromal and immune cells co-interpret and rewire the mechanical tissue architecture, thereby functionally determining whether tissues resolve inflammation and regenerate or transition to chronic inflammation and fibrosis.

Joint mechanics

Articular joint cartilage is a highly specialized tissue in which sparsely distributed chondrocytes are embedded within dense ECM that confers tensile strength and resistance to compression. Chondrocytes continually interpret both matrix mechanics and forces generated during joint loading through a repertoire of mechanosensing mechanisms that shape anabolic and catabolic pathways essential for cartilage homeostasis (Hodgkinson et al., 2022). However, excessive joint loading can equally drive mechanotransduction beyond homeostatic thresholds, initiating sterile inflammation (Box 2). For instance, PIEZO1 and PIEZO2 synergistically generate large calcium transients in response to injurious mechanical stretch, while their pharmacological blockade protects chondrocytes from mechanically induced cell death (Lee et al., 2014). In degenerative joint disease, known as osteoarthritis, IL-1α–driven inflammatory signaling upregulates *PIEZO1* expression, increasing basal intracellular Ca^{2+}, destabilizing the actin cytoskeleton, and ultimately sensitizing chondrocytes to even modest mechanical deformation (Lee et al., 2021). Excessive PIEZO1 activity within chondrocytes induces mitochondrial Ca^{2+} overload and mitochondrial DNA release, thereby initiating cGAS–STING-dependent innate immune responses (Sun et al., 2025). Similarly, PIEZO1 activation in mesenchymal stem cells enhances glycolysis-mediated cross talk with T helper 17 cells, promoting cartilage and bone erosion under aberrant mechanical loading (Zhou et al., 2025b).

A parallel dimension of osteoarthritis pathogenesis arises from the ECM remodeling, which alters the mechanical chondrocyte niche. Aging-associated collagen cross-linking and excessive joint loading activate Rho–ROCK and RAC1 signaling pathways that promote chondrocyte catabolism, including upregulation of ECM-degrading metalloproteinases (Kim et al., 2015; Chang et al., 2019b). These mechanotransduction pathways converge on shared transcriptional nodes such as NF-κB

and YAP/TAZ, forming a regulatory network that integrates mechanical and inflammatory cues to control cartilage matrix homeostasis (Deng et al., 2018; Chang et al., 2019b). Chondrocytes further interpret ECM viscoelasticity and mechanical loading through TRPV4, which regulates cell volume, anabolic gene expression, and inflammatory signaling, but becomes dysregulated in osteoarthritis, uncoupling cellular responses from matrix mechanics (O'Conor et al., 2014; Lee et al., 2017; Lee et al., 2019; Agarwal et al., 2021). In parallel, tissue-scale mechanics influence growth factor signaling, as subchondral bone architecture governs load distribution, aligning high-stress regions with increased cytoskeletal tension, αV-integrin–mediated activation of latent TGFβ, and metabolic dysfunction (Zhen et al., 2021). At the extreme, pathological mechanical environments directly induce cell death, as mechanical confinement triggers ferroptosis via nuclear deformation–driven mitochondrial dysfunction, ROS accumulation, and lipid peroxidation (Zhou et al., 2025a). These studies emphasize that matrix remodeling and cellular mechanotransduction are deeply intertwined, with altered ECM mechanics directly feeding into catabolic signaling pathways driving cartilage degeneration.

Beyond cartilage-specific mechanisms, mechanical forces shape the broader inflammatory landscape of arthritic joints. Even in systemic autoimmunity, joint inflammation emerges in discrete, mechanically vulnerable regions. For instance, mechanical strain activates stromal cells to produce and release chemokines such as CXCL1 and CCL2 (MCP-1), recruiting monocytes that differentiate into osteoclasts and drive localized bone erosion (Cambré et al., 2018). As such, mechanically sensitive microanatomical niches determine where systemic inflammatory potential translates into local tissue damage. Mechanical loading also modulates the chronicity of arthritis, exemplified by voluntary running, which enhances complement activation, increases danger signal expression, alters fibroblast phenotype, and interferes with Treg-mediated resolution, resulting in more persistent joint inflammation (Cambré et al., 2019). Exercise-induced changes in synovial fluid metabolites further suggest that mechanical loading modulates inflammatory and stress-response pathways across the joint (Hahn et al., 2022). In parallel, daily rhythms of mechanical loading arising from human behaviors such as locomotion and rest, along with oscillations in tissue osmolarity, regulate the circadian clock in articular cartilage, while excessive mechanical strain disrupts cartilage chronobiology, thereby linking mechanical forces to temporal regulation of skeletal tissue homeostasis and osteoarthritis progression (Dudek et al., 2023; Xu et al., 2025a). These studies, although challenging to fully control, reveal both systemic and niche-specific perspectives in which mechanical forces govern the persistence of inflammatory disease.

Lymphoid organs

Bone marrow, a primary lymphoid tissue that plays a key role in hematopoiesis, is a mechanically heterogeneous viscoelastic material whose physical properties vary significantly between individuals and even within the same individual, depending on age and disease state (Jansen et al., 2015; Chen et al., 2020; Shi et al., 2024). For example, murine bone marrow with myelofibrosis, a condition characterized by monocytosis and pathological ECM remodeling, exhibits significantly increased stiffness and altered viscoelasticity (Vining et al., 2022). This fibrotic bone marrow niche promotes a pro-inflammatory microenvironment and contributes to aberrant monocyte differentiation, a key cellular driver of myelofibrosis (Vining et al., 2022).

Furthermore, bone marrow experiences external mechanical forces associated with body movement, which in mice are sensed by a mechanosensitive population of bone-cell progenitors expressing osteolectin (Oln) and leptin receptor (LepR) (Shen et al., 2021). During exercise, increased bone loading activates PIEZO1 in these mechanosensitive cells, leading them to secrete stem cell factor (SCF) that maintains nearby common lymphoid progenitors. This pathway demonstrates how physical activity enhances lymphocyte generation and host defense, connecting skeletal mechanobiology directly to immune response. Interestingly, these mechanosensitive $LepR^{+}Oln^{+}$ cells are depleted during aging, pointing toward a potential role for mechanical stimulation in age-related decline in immunity (Shen et al., 2021).

Within lymph nodes, specialized stromal cells called FRCs form a contractile network that maintains the organ shape. Actomyosin contractility is regulated by podoplanin, a surface glycoprotein, which generates tension across the FRC network under resting conditions (Acton et al., 2014; Astarita et al., 2015). However, following contact with pathogens, migratory dendritic cells express C-type lectin-like receptor 2 (CLEC-2), which triggers relaxation of FRCs by binding to podoplanin and inhibiting RhoA-driven contractility (Acton et al., 2014). This relaxation allows the FRC network to expand, accommodating massive lymphocyte influx without extensive stromal proliferation. In mice lacking dendritic CLEC-2, lymph node expansion after immunization is significantly impaired, while podoplanin deletion in the fibroblastic stroma lowers its immunoregulatory properties and increases inflammatory signaling in lymph nodes (Acton et al., 2014).

Lymph node swelling involves a multitiered mechanical rheostat that regulates tissue expansion, starting with the elevated outward pressure generated by lymphocyte influx, followed by remodeling of the FRC network and lymph node enlargement, which is eventually countered by capsular fibroblasts forming a shell around the organ (Assen et al., 2022) (Box 2). While FRC network tension initially decreases during early inflammation, higher tension is ultimately re-established as the tissue stabilizes, demonstrating that FRCs actively modulate actomyosin contractility in response to mechanical cues (Horsnell et al., 2022). Crucially, perturbing podoplanin-dependent signaling disrupts these mechanical transitions *in vivo* and consequently impairs T cell activation as lymph nodes lose the ability to stretch and accommodate accumulating T cells (Horsnell et al., 2022).

As inflamed lymph nodes expand, FRCs prioritize maintaining network connectivity over matrix production, causing preexisting ECM fibers to stretch and fragment (Martinez et al., 2019). This mechanical disruption drives ECM remodeling, which in turn may influence antigen presentation by subcapsular sinus macrophages and immune synapse formation with B cells (Iliopoulou et al., 2024). Persistent mechanical remodeling of the

lymph node is likewise linked to sustained stromal and immune cell proliferation (Najibi et al., 2024). Importantly, unlike conventional adjuvants, vaccination with mesoporous silica nanoparticles prolongs tissue expansion for up to 100 days and is associated with enhanced antitumor immunity, highlighting the potential of modulating lymph node mechanics to improve vaccine-induced immunity (Najibi et al., 2024). Beyond the lymph node, podoplanin is often upregulated in fibroblasts under inflammatory conditions across diverse organs (Nazari et al., 2016; Shindo et al., 2013). However, it remains to be determined whether ECM deposition by these fibroblasts is also influenced by CLEC-2–expressing myeloid cells often found in inflamed vessels (Martinez et al., 2019). Collectively, these studies redefine lymphoid organs as dynamic mechanoresponsive systems in which physical forces regulate lymphoid tissue expansion and immune responsiveness.

Vascular inflammation and flow patterns

Endothelium and hemodynamics

One of the best-documented inflammatory effects of mechanical forces is in the vasculature (Davies, 1995). Distinct blood flow patterns and hemodynamic environments impose opposing phenotypes on the endothelium, influencing the development of atherosclerosis, a chronic inflammatory condition characterized by plaque buildup in the arterial walls (Hahn and Schwartz, 2009). In straight arterial segments, high, unidirectional laminar flow induces atheroprotective and anti-inflammatory programs. For instance, the transcription factor Kruppel-like factor 2 (KLF2) is upregulated and broadly suppresses cytokine-induced expression of adhesion molecules E-selectin and vascular cell adhesion molecule-1, both of which facilitate leukocyte tethering and recruitment (SenBanerjee et al., 2004; Parmar et al., 2005). By contrast, at arterial bifurcations and curvatures, sites naturally prone to atherosclerosis, blood flow is low, oscillatory, or multidirectional (Jongstra-Bilen et al., 2006). These disturbed flow patterns activate endothelial NF-κB, which upregulates *CCL2* (MCP-1) and *ICAM1*, directing monocyte recruitment and adhesion to the lesion-prone regions (Chappell et al., 1998; Hsiai et al., 2003; Tamargo et al., 2023).

These flow pattern–dependent responses originate from a specialized junctional mechanosensory complex composed of platelet endothelial cell adhesion molecule-1 (PECAM-1), vascular endothelial cadherin (VE-cadherin), and vascular endothelial growth factor receptor-2 (VEGFR2) (Tzima et al., 2005). PECAM-1 transmits mechanical force at cell–cell junctions, VE-cadherin acts as an adaptor, and VEGFR2 transduces the signal upon flow in a ligand-independent manner, stimulating NF-κB–driven inflammation and endothelial nitric oxide synthase (eNOS), a key enzyme producing vasodilatory, anti-inflammatory nitric oxide (Tzima et al., 2005; Fleming et al., 2005; Collins et al., 2012; Conway et al., 2013; Coon et al., 2015; Shaka et al., 2024). Additional receptors, including plexin D1, a guidance receptor capable of acting as a direct force sensor, integrate upstream of this complex to regulate site-specific atheroprotective versus atherogenic signaling (Mehta et al., 2020).

Beyond the junctional complex, shear stress and flow also regulate YAP and TAZ, the transcriptional co-regulators of the Hippo pathway (Wang et al., 2016a, 2016b; Rausch et al., 2019; Yuan et al., 2020). Disturbed flow promotes YAP/TAZ nuclear localization and induces gene programs that enhance endothelial proliferation and inflammation, whereas atheroprotective laminar flow suppresses YAP/TAZ activity (Wang et al., 2016a). Mechanistically, unidirectional flow activates endothelial integrins, leading to the inhibition of the small GTPase RhoA and subsequent YAP phosphorylation. Resulting YAP inactivation restrains JNK signaling, inflammatory cytokine expression, and monocyte adhesion, whereas disturbed flow fails to activate this braking mechanism, leaving YAP/TAZ active and atherogenic (Wang et al., 2016b).

Mechanosensitive ion channels further diversify endothelial flow sensing and responses. PIEZO1 converts frictional shear forces into intracellular Ca^{2+} signals that either support vascular development under physiological flow (Li et al., 2014; Ranade et al., 2014) or promote integrin-FAK–NF-κB inflammatory signaling under disturbed flow (Albarrán-Juárez et al., 2018). During oscillatory shear stress, PIEZO1-dependent Ca^{2+} influx promotes YAP nuclear localization and amplifies disturbed flow–induced inflammation and plaque growth (Lan et al., 2024). Conversely, under high laminar shear, TRPV4, enriched in caveolin-1–rich plasma membrane domains, initiates Ca^{2+} bursts within these domains, which preferentially activate eNOS and dampen inflammatory gene expression, illustrating how distinct ion channel circuits encode atheroprotective versus atheroprone flow environments (Hong et al., 2024). PIEZO1 also exhibits context-dependent control over endothelial ferroptosis, as its activation exacerbates ischemia–reperfusion injury in limb microvasculature by inducing ferroptotic cell death through Ca^{2+}-dependent cPLA2 activation (Chen et al., 2026), while in other settings it preserves endothelial homeostasis by suppressing ferroptosis (Miao et al., 2025).

Endothelial signaling across cellular compartments is further regulated by diverse mechanosensitive mediators (Aitken et al., 2023). These include the glycocalyx (Baeyens et al., 2014), primary cilia (Goetz et al., 2014), potassium ion channels (Brohawn et al., 2014; Ahn et al., 2017), and caveolae, highly abundant plasma membrane invaginations that can constitute >20% of the total endothelial surface (Yu et al., 2006; Hansen et al., 2013; Sinha et al., 2011; Cheng et al., 2015; Rausch et al., 2019; Ramírez et al., 2019). Mechanical forces also modulate G-protein–coupled receptors (GPCRs) (Xu et al., 2018; Erdogmus et al., 2019; Tanaka et al., 2024), the TGF-β family receptors ALK1 and ALK5 (Park et al., 2021; Mehta et al., 2021), and Notch signaling (Gordon et al., 2015; Mack et al., 2017; Singh et al., 2026).

Beyond membrane-proximal sensing, flow patterns shape mitochondrial morphology and functions. Disturbed flow drives mitochondrial fragmentation, fostering a glycolytic, proinflammatory endothelial phenotype, whereas unidirectional flow or voluntary exercise restores oxidative metabolism and suppresses endothelial activation (Hong et al., 2022). Atheroprotective effects of laminar flow similarly depend on mitochondrial metabolism, involving calcium transients, ROS, and mitophagy (mitochondrial autophagy), which together amplify

MAPK/ERK signaling to induce *Klf2* (Coon et al., 2022). These findings position mitochondria as central mechano-metabolic signaling hubs (Tharp et al., 2021; Zhang et al., 2024a; Dupont, 2025; Horton et al., 2026).

Multi-omic profiling further suggests that flow influences endothelial chromatin architecture, with unidirectional flow inducing super-enhancers that control antioxidant genes, whereas disturbed flow upregulates prothrombotic and inflammatory genes (Li et al., 2024a). Mechanotransduction also extends beyond individual cells as shear stress stimulates endothelial cells to release extracellular RNA, which subsequently engages VEGFR2 and initiates leukocyte recruitment required for arteriogenesis during natural bypass growth (Lasch et al., 2019). Similarly, in the brain, mechanical forces regulate blood–brain barrier integrity, influencing vascular permeability and neural health, with important implications for cerebrovascular diseases such as stroke, aneurysms, and vascular dementia (Hansen et al., 2024; Konig et al., 2025).

While endothelial cells are primarily exposed to shear stress, underlying vascular smooth muscle cells (VSMCs) experience hemodynamic pressure and variable matrix stiffness. As risk factors for atherosclerosis, elevated blood pressure and matrix stiffness synergistically induce a switch from contractile to synthetic, matrix-remodeling VSMC phenotype characterized by podosome formation and cytoskeletal reorganization, which further contributes to plaque formation (Swiatlowska et al., 2022). Hypertensive pressure alone is sufficient to induce rapid lipid droplet accumulation and metabolic rewiring via PIEZO1-dependent mechanosignaling and epigenetic remodeling, culminating in transdifferentiation of VSMCs into foam cells that frequently drive inflammation in atherosclerosis (Swiatlowska et al., 2024).

Leukocyte extravasation and mechanics

Leukocytes experience profound mechanical challenges as they transit through the inflamed vasculature, including hemodynamic forces and mechanical constraints imposed by the ECM and basement membrane, and their cell-intrinsic physical properties critically shape this journey (François et al., 2021; Jiang et al., 2023; Gao et al., 2025; Sorokin, 2026). Classic work showed that chemoattractant stimulation causes neutrophil stiffening via actin assembly, thereby impairing their deformability and leading to retention in narrow pulmonary capillaries, independent of integrin adhesion (Worthen et al., 1989). As neutrophils migrate and establish a leading edge, their membrane tension almost doubles, acting as a long-range inhibitor restricting Rac GTPase activity and actin polymerization to a single front, thereby preventing secondary protrusions (Houk et al., 2012). This mechanosensory feedback cascade is controlled, at least in part, by mTOR complex 2, which limits actin network assembly and whose inhibition disrupts coordination of front-to-back polarity, impairing persistent neutrophil migration in confined environments (Diz-Muñoz et al., 2016; Saha et al., 2023). In addition, the GTPase-activating protein Arf-GAP with Rho-GAP domain, ankyrin repeat and PH domain-containing protein 3 (ARAP3) regulates adhesion turnover by mediating integrin inactivation as a downstream negative feedback loop, enabling neutrophils to efficiently navigate complex microvascular networks (McCormick et al., 2019). *Arap3*-deficient neutrophils display impaired transendothelial migration and recruitment to inflammatory sites, whereas endothelial-specific loss enhances microvascular leakage, highlighting its role in coordinating leukocyte mechanics with vascular integrity (McCormick et al., 2019; Chu et al., 2024).

Neutrophils migrating in large numbers through branched capillary networks also exploit external mechanical forces to guide efficient trafficking upon infection or injury. For instance, cells occluding one branch locally increase hydraulic resistance and distort chemoattractant gradients, biasing trailing neutrophils into alternate paths (Wang et al., 2020b). Migration through confined environments leads to mechanical deformation, which both primes and, when repeated, rapidly depolarizes neutrophils, providing a mechanical mechanism by which the pulmonary capillaries can influence immune response (Ekpenyong et al., 2017). Indeed, chronic confinement in the pulmonary microvasculature and spontaneous PIEZO1-mediated Ca^{2+} signaling drive a distinct proangiogenic transcriptional program in neutrophils, promoting capillary growth and vascular homeostasis, while neutrophilic *Piezo1* deletion (*Piezo1*$^{fl/fl}$;*Vav1*-iCre) abrogates this lung-specific specialization and impairs both angiogenesis and antibacterial defense (Wang et al., 2025b).

PIEZO1 activation by shear stress also instigates calcium-mediated cytoskeletal remodeling and subsequent neutrophil extracellular trap (NET) release (NETosis) (Baratchi et al., 2024), implicating mechanotransduction in prothrombotic inflammation (Warnatsch et al., 2015; Papayannopoulos, 2018; Khanmohammadi et al., 2025b). Indeed, NETosis requires coordinated cytoskeletal rearrangement and nuclear rupture (Thiam et al., 2020; Sprenkeler et al., 2022) and is regulated by hemodynamic forces, substrate stiffness, and cyclic stretch (Yu et al., 2018; Abaricia et al., 2021; Zhu et al., 2024; Khanmohammadi et al., 2024; Khanmohammadi et al., 2025b). In parallel, platelets function as mechanosensitive effectors of thromboinflammation, in which shear gradients and compressive forces regulate platelet adhesion, aggregation, and clot stiffening (Nesbitt et al., 2009; Lam et al., 2011; Din et al., 2024). These mechanical cues are transduced via integrins, the platelet glycoprotein Ib–von Willebrand factor axis, and mechanosensitive ion channels, enabling platelets to coordinate thrombus formation with clearance and immune interactions, including mechano-dependent pathogen scavenging (Shen et al., 2013; Ju et al., 2016; Ju et al., 2018; Chen et al., 2019; Dayananda et al., 2010; Deng et al., 2016; Gaertner et al., 2017; Petzold et al., 2022; Mammadova-Bach et al., 2023; Solarz et al., 2025).

Mechanical forces encountered during and after diapedesis further reprogram leukocyte effector functions. Neutrophil squeezing through the narrow endothelial junctions has been proposed to activate PIEZO1 and generate Ca^{2+} signals that lead to HIF-1α stabilization and enhanced bactericidal capacity (Mukhopadhyay et al., 2024b). Additionally, *Piezo1*-deficient neutrophils fail to mount effective antibacterial responses in the lungs, whereas mechanically or pharmacologically activating PIEZO1 restores microbial clearance (Mukhopadhyay et al.,

2024b). However, ongoing debates exist regarding the robustness of the transmigration-associated increase in bactericidal functions and the proposed upregulation of NADPH oxidase 4 in neutrophils following PIEZO1 activation (Knaus et al., 2024; Wu et al., 2024b). Although these discrepancies likely reflect differences in experimental design and methodology (Mukhopadhyay et al., 2024a; van Grinsven et al., 2026), the precise source of divergence remains unresolved.

While transmigrating through adherens junctions, neutrophils also exert forces along endothelial borders, which are significantly higher than those exerted by non-migrating adherent leukocytes, thereby triggering transient VE-cadherin disruption (Rabodzey et al., 2008). Clustering of ICAM-1 induced by adherent leukocytes, along with low blood shear, increases membrane tension in endothelial cells and activates PIEZO1, leading to Ca^{2+} influx, SRC kinase and myosin light chain phosphorylation, and localized junctional opening (Wang et al., 2022b). Consequently, endothelial *Piezo1* deficiency markedly reduces leukocyte diapedesis. Interestingly, tensile forces transmitted through neutrophilic LFA-1–endothelial ICAM-1 bonds also couple hemodynamic shear to localized Ca^{2+} influx within neutrophils, amplifying chemokine signaling and thereby licensing their arrest, polarization, and transmigration at sites where adhesive bond tension is sufficiently high (Morikis et al., 2017; Morikis et al., 2020). In parallel, traction forces exerted by leukocyte PECAM on endothelial PECAM at borders initiate a mechanotransduction cascade via the PECAM–VE-cadherin–VEGFR2 junctional complex, where VEGFR2 tyrosine phosphorylation, independent of VEGF ligand or intrinsic kinase activity, is required for efficient neutrophil transmigration (Fu et al., 2023). Collectively, these studies indicate that the mechano-inflammatory landscape of the vascular endothelium is shaped by diverse mechanical forces, which orchestrate leukocyte trafficking and migration, endothelial activation, and atherosclerotic plaque formation (Fig. 1 C).

Pathological and translational implications

Mechanical dysregulation in disease

Mechanical dysregulation can directly initiate or amplify inflammation across diverse organ systems. Beyond the inflammatory disorders discussed earlier (asthma, inflammatory gut and skin conditions, aging, fibrosis, obesity, arthritis, and atherosclerosis—summarized in Table 1), many conditions illustrate that mechanical cues escalate pathological feedforward loops driving disease development. Heart disease and blood disorders are prominent examples.

The heart is a highly mechanically active organ in which forces such as stretch, stiffness, and load regulate the behavior of cardiomyocytes, fibroblasts, endothelial cells, and immune cells, shaping processes from myocardial contractility and metabolic regulation to structural remodeling and inflammatory signaling (Engler et al., 2008; Jacot et al., 2008; Prosser et al., 2011; Bassat et al., 2017; Saucerman et al., 2019; Caporizzo et al., 2020; Ciucci et al., 2026). Resident C–C chemokine receptor type 2 $(CCR2)^-$ cardiac macrophages, for instance, sense mechanical stretch through TRPV4 channels and form stable contacts with neighboring cardiomyocytes, activating growth factor programs that support adaptive remodeling and coronary angiogenesis (Wong et al., 2021). Loss of this protective mechanosensitive population, coupled with increased infiltration of $CCR2^+$ monocyte-derived macrophages, shifts the myocardium toward maladaptive inflammation and accelerates heart failure progression, implicating physiological mechanosensing in cardiac homeostasis (Wong et al., 2021). Following myocardial infarction, aberrant mechanotransduction further amplifies inflammation through a distinct neurogenic pathway in which activation of PIEZO1 in thoracic dorsal root ganglion neurons triggers an IL-6–dependent cascade that exacerbates ventricular remodeling (Sun et al., 2024). Mechanosensitive signaling similarly contributes to structural heart disease, as PIEZO1 activation in aortic valve interstitial cells drives YAP-dependent metabolic reprogramming toward glutaminolysis, promoting osteogenic differentiation and valve calcification (Zhong et al., 2023). Targeting mechanotransduction may also represent a promising therapeutic strategy, as suggested by a swine model of ischemic heart disease in which sedentary animals exhibit increased collagen deposition and elevated inflammatory cytokine expression (Lee et al., 2026). In this context, endurance training is associated with improved myocardial function alongside enhanced fibronectin–mediated cardiomyocyte adhesion, increased FAK activation, and reduced markers of inflammatory remodeling (Lee et al., 2026).

Blood disorders offer parallel examples in which altered cell mechanics directly initiate vascular inflammation. In sickle cell disease, poorly deformable RBCs preferentially marginate toward vessel walls, generating localized shear stress and mechanically inducing endothelial inflammation (Caruso et al., 2024). Iron deficiency anemia exhibits similar principles, with stiff, microcytic erythrocytes producing abnormal shear profiles that activate endothelial inflammatory pathways (Caruso et al., 2022). Additionally, changes in erythrocyte rigidity or shape hyperactivate macrophage myosin II and override CD47-mediated self-recognition, thereby enhancing inflammatory phagocytosis (Sosale et al., 2015).

Mechanical dysregulation is also an important driver of tumor-promoting inflammation, as altered tissue stiffness, matrix architecture, and force transmission within the tumor microenvironment profoundly shape immune signaling and therapeutic response (Frittoli et al., 2023; Zhang et al., 2024c; Song et al., 2025; Maiques et al., 2025; Xie et al., 2025a; Wang et al., 2026; Fusilier et al., 2026). This rapidly expanding field of cancer mechanoimmunology lies beyond the scope of this review and is discussed elsewhere (Mittelheisser et al., 2024; Golo et al., 2024).

Mechanically guided diagnostics

As the mechanical properties of cells change markedly during inflammation (Bufi et al., 2015), they provide an underused diagnostic dimension. Features such as cell size, shape, stiffness, viscoelasticity, and deformability reflect cytoskeletal and nuclear remodeling and may serve as label-free indicators of cell state, in addition to biochemical markers (McWhorter et al., 2013; Zak et al., 2021; Fernando et al., 2025).

Table 1. **Inflammatory diseases associated with mechanical dysregulation**

Disease	Mechanical dysregulation	Cell types involved	Mechanotransducers	Inflammatory pathways and mediators	Pathophysiological outcomes	Relevant literature
Barrier tissue dysfunctions						
Asthma	Bronchoconstriction-induced compression; excess cell extrusion	Airway epithelial cells; ILC2	PIEZO1	Damage-associated inflammatory signaling	Airway denudation; mucus hypersecretion; immune cell infiltration; barrier dysfunction	Bagley et al. (2024), Grainge et al. (2011), Kılıç et al. (2020), Mwase et al. (2025), Hurrell et al. (2024), and Lim et al. (2025)
VILI	Excessive mechanical stretch; high tidal volume and pressure; cyclical strain	Alveolar epithelial cells; endothelial cells; alveolar macrophages	TRPV4; PIEZO1	NLRP3 inflammasome activation; pro-inflammatory cytokine release	Barrier failure; pulmonary edema; acute lung inflammation and injury	Hamanaka et al. (2007), Wu et al. (2013), Michalick et al. (2017), Pairet et al. (2018), Solis et al. (2019), Bobba et al. (2021), and Li et al. (2024b)
IBD	Excess cell extrusion; mechanical stretch from peristalsis and obstruction; stiffened inflamed tissue	Intestinal epithelial cells; smooth muscle cells; Tregs	RAC1; cytoskeleton	Mucosal inflammation; mechanoregulation of immune cell migration and tissue egress	Barrier failure and dysregulated immune responses	Lin et al. (2014), Kim et al. (2016), Stewart et al. (2018), Chang et al. (2019a), Martínez-Sánchez et al. (2023), and Ullrich et al. (2023)
Inflammatory skin and eye conditions	Mechanical stretch; excessive tension, compression, and friction	Keratinocytes; mast cells; conjunctival epithelial cells	PIEZO1; cytoskeleton	Psoriatic inflammation and cytokine production; mast cell reprogramming; neutrophil infiltration	Epidermal hyperproliferation; barrier dysfunction; eczema susceptibility	Qiao et al. (2019), Serhan et al. (2025), and Fukuoka et al. (2025)
Stromal inflammation						
Fibrosis (multiple organs)	Increased tissue stiffness; ECM remodeling	Fibroblasts; macrophages; dendritic cells	YAP/TAZ; PIEZO1; integrins; cytoskeleton	Fibroblast–immune feedback loops	Persistent inflammation; amplified fibrotic remodeling	Pakshir et al. (2019), Meli et al. (2020), Chakraborty et al. (2021a), Zhou et al. (2022), and Ezzo et al. (2024)
Pulmonary fibrosis	Repetitive mechanical stretch; increased tissue stiffness	Mast cells; macrophages; fibroblasts	Integrins; cytoskeleton	Mast cell degranulation; TGF-β1 signaling	ECM accumulation; loss of lung compliance	Shimbori et al. (2019), Xu et al. (2024), and Zhang et al. (2026)
Liver fibrosis	Increased tissue stiffness	Hepatocytes; macrophages (Kupffer cells); hepatic stellate cells	PIEZO1 YAP	Enhanced efferocytosis upon PIEZO1 activation (Kupffer cells); lipogenesis (hepatocytes)	Clearance of apoptotic cells, fibrotic resolution (mechano-inflammatory feedback in Kupffer cells); MASLD progression	Georges et al. (2007), Olsen et al. (2011), Mitten and Baffy (2022), Greuter et al. (2022), Luo et al. (2023), Wang et al. (2024), and Ma et al. (2026)
Cutaneous fibrosis	Persistent tensile strain and pressure; ECM remodeling; wound contracture	Fibroblasts; keratinocytes; dendritic cells	FAK; integrins; cytoskeleton; MAPK/ERK	NF-κB activation; NRF2-mediated regulation of inflammation	Excess ECM deposition; fibroblast persistence; chronic inflammatory scarring	Wong et al. (2012), Nakasaki et al. (2015), Chen et al. (2021), Chen et al. (2022), Chen et al. (2025a), and Chaudhary et al. (2025)
Cardiac fibrosis	Pathological mechanical loading; increased stiffness	Myofibroblasts	Integrins; cytoskeleton PIEZO1	Inflammatory and profibrotic transcriptional programs	Collagen deposition; myocardial stiffening; impaired cardiac function	Blythe et al. (2019) and Cho et al. (2025)

Table 1. **Inflammatory diseases associated with mechanical dysregulation (*Continued*)**

Disease	Mechanical dysregulation	Cell types involved	Mechanotransducers	Inflammatory pathways and mediators	Pathophysiological outcomes	Relevant literature
Myelofibrosis (bone marrow)	Tissue stiffening; mechanical constraint of hematopoietic cells	Monocytes	Cytoskeleton; TRPV4	Myeloid-specific PI3K-γ signaling	Monocytosis (pathological monocyte differentiation and pro-inflammatory activation)	Vining et al. (2022)
PAS	Uterine scar matrix–induced tissue stiffening	Decidual stromal cells (fibroblasts)	PIEZO1	NF-κB activation; pro-inflammatory cytokine release (IL-8 and G-CSF)	Pathological placental trophoblast invasion; sustained inflammation	Wenqiang et al. (2024)
Aging	ECM remodeling, altered stiffness, viscoelasticity, and force transmission	Stromal cells; immune cells; stem cells; nucleus pulposus cells	Nucleus (LINC, lamin A/C, chromatin); YAP/TAZ; PIEZO1	cGAS–STING activation; SASP	Cellular senescence; inflammaging; degenerative tissue remodeling	Sladitschek-Martens et al. (2022), Wu et al. (2022), De Silva et al. (2023), Li et al. (2025), Mejía-Ramírez et al. (2025), Shang et al. (2026)
Obesity and metabolic diseases	ECM remodeling; increased adipose tissue stiffness and tension	Adipocytes; macrophages; fibroblasts	YAP/TAZ; integrins; cytoskeleton	Chronic adipose inflammation; SASP; tumor-associated macrophage phenotypes	Metabolic dysfunction; impaired thermogenesis; cancer-promoting microenvironment	Pellegrinelli et al. (2014), Pellegrinelli et al. (2023), Rabhi et al. (2022), Springer et al. (2019), Seo et al. (2015), and Incio et al. (2016)
Osteoarthritis	Excessive mechanical loading; ECM remodeling, stiffening, and cross-linking	Chondrocytes; synovial fibroblasts; macrophages	PIEZO1/2; integrins; cytoskeleton; RhoA-ROCK2 signaling	NF-κB, TGF-β, cGAS–STING, and complement activation; monocyte recruitment	Cell death; cartilage degeneration; osteoclast differentiation; bone erosion	Lee et al. (2014), Lee et al. (2017), Lee et al. (2021), Kim et al. (2015), Chang et al. (2019b), Zhen et al. (2021), Cambré et al. (2018), Cambré et al. (2019), Dudek et al. (2023), and Xu et al. (2025a)
Circulatory system diseases						
Atherosclerosis	Disturbed flow; oscillatory shear stress; increased vascular stiffness; hypertensive pressure	Endothelial cells; VSMCs; macrophages (foam cells)	Junctional complex; YAP/TAZ; caveolae; glycocalyx; TRPV4; PIEZO1	NF-κB, JNK, and inflammasome activation; eNOS downregulation; metabolic rewiring; lipid droplet accumulation	Vascular inflammation; reduced vasodilation; monocyte recruitment; foam cell formation; plaque development	Tzima et al. (2005), Baeyens et al. (2014), Wang et al. (2016a), Wang et al. (2016b), Albarrán-Juárez et al. (2018), Ramírez et al. (2019), Atcha et al. (2024), Swiatlowska et al. (2022), and Swiatlowska et al. (2024)
Heart disease	Altered myocardial load; tissue strain after injury	Macrophages; neurons; fibroblasts; cardiomyocytes	PIEZO1; cytoskeleton	Neurogenic inflammation; macrophage-mediated inflammatory remodeling	Impaired ventricular remodeling, coronary angiogenesis, and heart failure progression	Baratchi et al. (2020), Wong et al. (2021), Zhong et al. (2023), Sun et al. (2024), Cho et al. (2025), and Li et al. (2026)
Blood disorders	Altered cell rigidity and deformability; shear stress	Erythrocytes; endothelial cells; neutrophils	PIEZO1; cytoskeleton	Hyperactivation of phagocytosis; endothelial activation; NETosis	Anemia; impaired vascular remodeling; thrombosis	Sosale et al. (2015), Lasch et al. (2019), Caruso et al. (2022), and Caruso et al. (2024)

LINC, linker of nucleoskeleton and cytoskeleton; NRF2, nuclear factor erythroid 2-related factor 2.

Early advances in mechanophenotyping reveal that these physical signatures can be clinically informative (Guck et al., 2005). Deformability of leukocytes and malignant cells from lung pleural effusions detected through hydrodynamic single cell stretching accurately predicts disease states in patients with immune activation and cancer (Gossett et al., 2012). This approach, termed deformability cytometry enables classification of benign, malignant, and acutely or chronically inflamed samples based on mechanical signatures, including cases missed by standard cytology and highlighting the potential of mechanophenotyping as a powerful prescreening tool (Tse et al., 2013; Asghari et al., 2024).

Further advances allowed for the development of real-time deformability cytometry (RT-DC), which continuously characterizes large cell populations as they flow through microfluidic channels and deform under shear stress and pressure gradients (Otto et al., 2015; Rosendahl et al., 2018). RT-DC enabled mechanical profiling directly in diluted whole blood and revealed disease-associated mechanical fingerprints across malaria, bacterial and viral infections, leukemia, and other conditions (Toepfner et al., 2018). RT-DC studies during the COVID-19 pandemic revealed persistent mechanical changes in immune cells and RBCs, including altered lymphocyte stiffness and changes in monocyte and neutrophil size and deformability, highlighting their potential as biomarkers for monitoring long COVID recovery and postviral inflammation resolution (Kubánková et al., 2021).

Recent technological advances enable mechanical phenotyping at throughputs of up to 10,000 cells per second in real time, making this approach feasible for both liquid and solid biopsies in clinical settings (Urbanska et al., 2020; Soteriou et al., 2023; Asghari et al., 2024; Lee et al., 2025). Although these developments demonstrate that mechanically driven changes are promising label-free biomarkers of inflammation and disease, several hurdles remain for clinical translation. A primary challenge in mechanodiagnostics is the inherent biological plasticity of cell mechanics, as physical signatures observed in microfluidic channels or *ex vivo* assays may not fully capture the dynamic state of cells in their complex native microenvironments. Furthermore, significant methodological diversity across different mechanophenotyping platforms complicates the establishment of standardized diagnostic baselines. Overcoming this context dependence and achieving cross-platform reproducibility will be essential to transition mechanophenotyping from a powerful research tool to a validated clinical diagnostic.

Mechanotherapeutics

Physical forces, whether applied externally or generated internally, influence inflammatory responses and have been proposed as potential therapeutic modulators, although robust clinical evidence is still needed (Khan and Scott, 2009; Ward et al., 2025). Massage therapy is a prominent example, as it attenuates NF-κB–mediated inflammatory signaling and enhances mitochondrial biogenesis in skeletal muscles after exercise-induced injury (Crane et al., 2012). Compressive loading applied by a robotic device to hindlimb muscles likewise reduces pro-inflammatory cytokine levels, enhances neutrophil clearance, and improves muscle regeneration in a mouse muscle injury model combining myotoxin injection with ischemic surgery (Seo et al., 2021). Importantly, these effects are likely age-dependent, as robot-actuated mechanical loading alone is ineffective or even detrimental in aged muscles unless combined with anti-inflammatory therapy that restores its regenerative potential (McNamara et al., 2023). Modulating the body's internal mechanical environment also confers anti-inflammatory benefits. For instance, reducing shear stress via transcatheter aortic valve implantation suppresses PIEZO1-mediated monocyte activation and lowers inflammatory cytokine expression (Baratchi et al., 2020). However, despite widespread use, the molecular and cellular mechanisms underlying mechanotherapy remain incompletely understood.

Targeting mechanosensitive pathways provides a complementary molecular approach to modulating inflammation, fibrosis, and tissue repair. Intradermal injection of first-generation YAP inhibitor verteporfin prevents scarring and promotes excisional wound regeneration in a Duroc pig model of skin healing, demonstrating translational potential (Mascharak et al., 2025). However, although verteporfin potently inhibits YAP transcriptional activity, caution is warranted as it also exhibits YAP-independent off-target effects, including proteotoxicity, that contribute to its biological activity (Liu-Chittenden et al., 2012; Zhang et al., 2015). Targeting YAP/TAZ signaling has also been proposed for treating liver inflammation and cancer (Wang et al., 2016c; Hagenbeek et al., 2018; Song et al., 2020; Zhang et al., 2024b; Ma et al., 2026). More broadly, compounds that target the Hippo pathway through diverse mechanisms of action are currently under clinical evaluation, representing a promising future therapeutic avenue (Cunningham and Hansen, 2022; Cunningham et al., 2025). Similarly, selective inhibition of the focal-adhesion–associated mechanosensor SRC reprograms activated cardiac fibroblasts to quiescence and synergizes with TGF-β blockade to reverse profibrotic gene programs and improve cardiac function (Cho et al., 2025). In large animal models, FAK inhibition promotes regenerative skin repair, including restoration of hair follicles, while also improving postgrafting tissue biomechanics by reducing contracture, restoring collagen architecture, and limiting CXCL14-mediated pro-inflammatory myeloid and fibroblast recruitment (Chen et al., 2021, 2022).

Elucidating mechanotransduction pathways might further uncover the mechanistic basis of existing therapeutics. Escin, a mixture of saponins from horse chestnut seeds with established anti-inflammatory effects in tissue swelling, inhibits mechanically induced PIEZO1 activation in vascular endothelial cells, thereby reducing NF-κB signaling and downstream inflammatory cytokines such as IL-1β and IL-6 (Wang et al., 2023). Similarly, nanoparticle delivery of microRNA-146a, whose endogenous upregulation in alveolar macrophages during injurious ventilation is insufficient to prevent damage, attenuates VILI by regulating macrophage mechanotransduction (Bobba et al., 2021). In the context of surgical vein grafting for coronary bypass, modulation of PIEZO1 activity could likewise enhance graft integration, as PIEZO1-dependent donor-derived lymphatic remodeling promotes integration with autologous lymphangiogenesis, while limiting inflammation and scar tissue formation

(Chen et al., 2025b). PIEZO1 inhibition in myeloid cells also reduces the expansion of immunosuppressive populations in cancer and sepsis, revealing a tunable mechanosensitive immune checkpoint (Aykut et al., 2020).

At the level of immune cell–target interactions, phagocytic and immunological synapses are likewise regulated by mechanical cues, including target geometry, stiffness, and membrane tension (Champion and Mitragotri, 2006; Paul et al., 2013; Masters et al., 2013; Spillane and Tolar, 2017; Liu et al., 2021; Zhou et al., 2024; Cornell et al., 2025; Yu et al., 2025). Such mechanical inputs are transduced through actin–integrin coupling and myosin-dependent force generation, forming mechanical checkpoints that control adhesion dynamics, force transmission, and synapse maturation (Barger et al., 2019; Jaumouillé et al., 2019; Merino-Cortés et al., 2020; Vorselen et al., 2020; Vorselen et al., 2021; Wang et al., 2022a; Hu et al., 2023; Settle et al., 2024) (Box 2). These mechanically gated processes ultimately determine functional outcomes, including antigen uptake, phagocytic efficiency, cytotoxic responses, and the spatial organization and duration of immune synapses (Hong et al., 2018; Tamzalit et al., 2019; Leithner et al., 2021; Hoijman et al., 2021; de Jesus et al., 2024; Rollins et al., 2025).

Building on this mechanistic framework, mechanotherapeutics can leverage nanomedicine approaches to modulate mechanotransduction (Yang et al., 2024; Liu et al., 2026). For instance, the intrinsic elasticity of nanoparticles influences their uptake by immune and cancer cells, providing a tunable mechanical parameter that can be engineered to enhance therapeutic delivery (Hui et al., 2020). Engineered nanoparticles attached to dendritic cells *in vivo*, known as cellular backpacks, further demonstrate how exogenous mechanical inputs can shape immunity as they activate PIEZO1-dependent signaling even without cargo, sustaining dendritic cell maturation and enhancing antitumor T cell responses when combined with radiotherapy (Yu et al., 2024). Similarly, mechanically active adjuvants incorporated into stiffness-regulated whole-cell vaccines enhance dendritic cell mechanotransduction, phagocytosis, and IFN signaling, while combining these vaccines with radiotherapy inhibits postoperative tumor recurrence in a breast cancer mouse model (Gu et al., 2024). Complementing these engineered approaches, endogenous mechanical cues likewise regulate immune activation. For instance, dendritic cell cortical stiffening during maturation enhances T cell priming (Blumenthal et al., 2020), while PIEZO1 signaling within dendritic cells directs type 1 helper T cells versus Treg differentiation within tumors (Wang et al., 2022c). These findings align with the broader concept of mechanosurveillance, whereby cytotoxic lymphocytes eliminate metastatic cancer cells by sensing their mechanical vulnerabilities such as altered cytoskeletal rigidity (Tello-Lafoz et al., 2021).

Together, these studies illustrate how engineering nanoscale mechanical inputs and tuning endogenous mechanosensing pathways can be harnessed to manipulate immune responses and potentially limit inflammation (Kalukula et al., 2025; Quan et al., 2026). However, clinical translation is complicated by the ubiquity of mechanosensors, including mechanosensitive ion channels such as PIEZO1, integrin signaling networks, and the Hippo–YAP/TAZ pathway, which are essential for homeostasis across nearly all organ systems. As such, systemic modulation carries a high risk of off-target effects. Future progress will therefore likely depend on the development of cell type–specific delivery strategies or spatially restricted, engineered "mechanoniches," such as tunable hydrogels or 3D-printed scaffolds, designed to localize mechanical inputs while minimizing unintended systemic consequences.

Biomaterials and bioengineering

Biomaterials and bioengineering approaches are emerging as powerful translational tools harnessing mechanical cues for immunomodulation. Changes in cell shape and volume directly influence cellular functions, independent of soluble factors (Jain et al., 2013; Park et al., 2022). Notably, imposing defined cell geometries through micropatterning reveals that elongation alone drives macrophages toward a pro-healing phenotype by engaging actomyosin contractility and cytoskeletal signaling while protecting cells from pro-inflammatory stimuli such as LPS and IFN-γ (McWhorter et al., 2013; Luu et al., 2015). Spatial confinement, limiting cell spreading in crowded environments, also suppresses inflammatory transcriptional programs and alters chromatin organization by reducing actin polymerization and MRTF-A/SRF activity (Jain and Vogel, 2018). Similarly, surface topology provides potent mechanical signals that activate innate immunity as particles decorated with nanospikes generate mechanical stress during phagocytosis, inducing potassium efflux and inflammasome activation in myeloid cells, thereby enhancing protection against tumors and viral infection (Wang et al., 2018).

Mechanobiological insights now inform the design of biomaterials that modulate immune responses *in situ* to limit foreign-body response, control inflammation, and promote tissue repair (Theocharidis et al., 2022; Padmanabhan et al., 2023; Abebayehu et al., 2024). Nanoscale engineering of titanium implants, such as honeycomb-like surface topographies, promotes filopodia formation in macrophages, activating Rho family GTPases, and driving an anti-inflammatory phenotype that shapes an immune microenvironment conducive to osteogenic differentiation and implant-to-bone integration (Zhu et al., 2021). Hydrogels provide additional strategies for harnessing mechanical cues, as mechanochemical synergistic therapy combining FAK inhibition with ROS scavenging attenuates scratch-exacerbated inflammation in atopic dermatitis (Jia et al., 2023), while tuning hydrogel cross-linking independently modulates macrophage infiltration and profibrotic signaling, with softer gels enhancing wound healing (Butenko et al., 2024). In cartilage tissue engineering, viscoelastic hydrogels that rapidly relax stress enable chondrocyte volume expansion and matrix deposition, whereas slow-relaxing elastic gels impose confinement that drives IL-1β–associated catabolic and cell death programs, highlighting stress relaxation as a critical biomaterial design parameter for controlling inflammation (Lee et al., 2017).

Lastly, engineered cell culture systems with tunable mechanical inputs are also being leveraged to potentiate cell-free therapies. For instance, perfusion bioreactors incorporating aligned topographical cues and fluid shear enhance macrophage

extracellular vesicle (EV) yield via PIEZO1-dependent Ca^{2+} influx and YAP nuclear translocation, leading to EVs with improved efficacy in promoting angiogenesis and osteogenic differentiation in a rat cranial defect model (Huang et al., 2025). Similarly, acoustofluidic stimulation, which applies mechanical forces to adherent or suspension cells (Yang et al., 2026), enhances cell–cell interactions in mesenchymal stem cells, subsequently inducing production of secretomes with increased anti-inflammatory potential and tunable cytokine profiles (He et al., 2023).

Conclusions and future perspectives

Mechano-inflammation emerges as a unifying framework linking physical forces to immune regulation, governed by several key principles. First, tissue mechanics act as a rheostat, continuously tuning immune set points under homeostatic conditions. Second, mechanical perturbations function as primary initiators of sterile inflammation, analogous to classical danger signals. Third, inflammation-associated changes in tissue mechanics create positive feedback loops that amplify and sustain immune responses. Fourth, immune cells rely on force-dependent checkpoints that license activation, embedding mechanical sensing directly within core immune effector functions.

However, key challenges remain, including identifying bona fide mechanosensors that integrate mechanical cues with spatiotemporal precision *in vivo*, and disentangling mechanical from biochemical signaling in complex tissue environments. Addressing these gaps requires experimental systems that better recapitulate physiological forces, particularly considering the widespread use of rigid plastic cultureware, which imposes supraphysiological stiffness and distorts immune functions (Caliari and Burdick, 2016; Chaudhuri et al., 2016; Chakraborty et al., 2021a). Advanced nonanimal model systems, such as organoids and organs-on-chips, will be central to advancing inflammation research by enabling precise interrogation of spatiotemporal mechanical cues, although further refinement is needed to fully capture *in vivo* complexity (Zhao et al., 2022; Leung et al., 2022; Ingber, 2022; Rupar et al., 2024). Integrating multimodal datasets through computational approaches, including machine learning and artificial intelligence, will also be critical to determine how mechanical cues are encoded across scales, from molecular signaling to tissue-level dynamics (Hao et al., 2021; Greener et al., 2022; Bunne et al., 2024; Jin et al., 2025; Oria et al., 2025; Keshavanarayana et al., 2025; Valanarasu et al., 2026; Jiménez-Gracia et al., 2026).

Mechano-inflammation opens new frontiers at the interface of immunology and physiology, as systemic mechanical states, such as those induced by physical exercise, altered environmental conditions, or tissue remodeling in aging and disease, shape immune functions (Fiuza-Luces et al., 2024; Walzik et al., 2026; Wu et al., 2024a; Winer et al., 2026). In parallel, growing translational efforts leverage mechanophenotyping to map cellular mechanical states, alongside mechanotherapies and engineered biomaterials designed to modulate force-dependent signaling and immune responses.

Taken together, the concept of mechano-inflammation represents not merely an incremental advance but an integrative paradigm shift that unifies mechanical and biochemical regulation of immunity. Realizing its clinical potential, however, will require careful consideration, as targeting mechanotransduction pathways carries the risk of adverse effects given their essential roles in normal physiology. Recognizing forces as fundamental determinants of immune behavior will reshape how inflammation is modeled, interpreted, and ultimately treated.

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References

Aarabi, S., K.A. Bhatt, Y. Shi, J. Paterno, E.I. Chang, S.A. Loh, J.W. Holmes, M.T. Longaker, H. Yee, and G.C. Gurtner. 2007. Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. *FASEB J.* 21:3250–3261. https://doi.org/10.1096/fj.07-8218com

Abaricia, J.O., A.H. Shah, and R. Olivares-Navarrete. 2021. Substrate stiffness induces neutrophil extracellular trap (NET) formation through focal adhesion kinase activation. *Biomaterials*. 271:120715. https://doi.org/10.1016/j.biomaterials.2021.120715

Abebayehu, D., B.N. Pfaff, G.C. Bingham, A.E. Miller, M. Kibet, S. Ghatti, D.R. Griffin, and T.H. Barker. 2024. A Thy-1–negative immunofibroblast population emerges as a key determinant of fibrotic outcomes to biomaterials. *Sci. Adv.* 10:eadf2675. https://doi.org/10.1126/sciadv.adf2675

Aceitón, P., I. Riobó, F. Del Valle Batalla, J. Diaz-Muñoz, R. Ulloa, F. Cabrera Reyes, T. Contreras, S. Hernández-Pérez, P.K. Mattila, and M.I. Yuseff. 2025. B cell mechanotransduction via ATAT1 coordinates actin and lysosomal dynamics at the immune synapse. *J. Cell Biol.* 224:e202407181. https://doi.org/10.1083/jcb.202407181

Acton, S.E., A.J. Farrugia, J.L. Astarita, D. Mourão-Sá, R.P. Jenkins, E. Nye, S. Hooper, J. van Blijswijk, N.C. Rogers, K.J. Snelgrove, et al. 2014. Dendritic cells control fibroblastic reticular network tension and lymph node expansion. *Nature*. 514:498–502. https://doi.org/10.1038/nature13814

Adebowale, K., Z. Gong, J.C. Hou, K.M. Wisdom, D. Garbett, H.-P. Lee, S. Nam, T. Meyer, D.J. Odde, V.B. Shenoy, and O. Chaudhuri. 2021. Enhanced substrate stress relaxation promotes filopodia-mediated cell migration. *Nat. Mater.* 20:1290–1299. https://doi.org/10.1038/s41563-021-00981-w

Adebowale, K., C. Allan, B. Ha, A. Saraswathibhatla, J. Zhu, D. Indana, M.C. Popescu, S. Demirdjian, H.A. Martinez, A. Esclamado, et al. 2025. Monocytes use protrusive forces to generate migration paths in viscoelastic collagen-based extracellular matrices. *Proc. Natl. Acad. Sci. USA*. 122:e2309772122. https://doi.org/10.1073/pnas.2309772122

Adu-Berchie, K., Y. Liu, D.K.Y. Zhang, B.R. Freedman, J.M. Brockman, K.H. Vining, B.A. Nerger, A. Garmilla, and D.J. Mooney. 2023. Generation of functionally distinct T-cell populations by altering the viscoelasticity of their extracellular matrix. *Nat. Biomed. Eng.* 7:1374–1391. https://doi.org/10.1038/s41551-023-01052-y

Agarwal, P., H. Lee, P. Smeriglio, F. Grandi, S. Goodman, O. Chaudhuri, and N. Bhutani. 2021. A dysfunctional TRPV4–GSK3β pathway prevents osteoarthritic chondrocytes from sensing changes in extracellular matrix viscoelasticity. *Nat. Biomed. Eng.* 5:1472–1484. https://doi.org/10.1038/s41551-021-00691-3

Ahn, S.J., I.S. Fancher, J. Bian, C.X. Zhang, S. Schwab, R. Gaffin, S.A. Phillips, and I. Levitan. 2017. Inwardly rectifying K^+ channels are major contributors to flow-induced vasodilatation in resistance arteries. *J. Physiol.* 595:2339–2364. https://doi.org/10.1113/JP273255

Aitken, C., V. Mehta, M.A. Schwartz, and E. Tzima. 2023. Mechanisms of endothelial flow sensing. *Nat. Cardiovasc. Res.* 2:517–529. https://doi.org/10.1038/s44161-023-00276-0

Albarrán-Juárez, J., A. Iring, S. Wang, S. Joseph, M. Grimm, B. Strilic, N. Wettschureck, T.F. Althoff, and S. Offermanns. 2018. Piezo1 and Gq/G11 promote endothelial inflammation depending on flow pattern and integrin activation. *J. Exp. Med.* 215:2655–2672. https://doi.org/10.1084/jem.20180483

Alkhouli, N., J. Mansfield, E. Green, J. Bell, B. Knight, N. Liversedge, J.C. Tham, R. Welbourn, A.C. Shore, K. Kos, and C.P. Winlove. 2013. The mechanical properties of human adipose tissues and their relationships to the structure and composition of the extracellular matrix. *Am. J. Physiol. Endocrinol. Metab.* 305:E1427–E1435. https://doi.org/10.1152/ajpendo.00111.2013

Alraies, Z., C.A. Rivera, M.-G. Delgado, D. Sanséau, M. Maurin, R. Amadio, G. Maria Piperno, G. Dunsmore, A. Yatim, L. Lacerda Mariano, et al. 2024. Cell shape sensing licenses dendritic cells for homeostatic migration to lymph nodes. *Nat. Immunol.* 25:1193–1206. https://doi.org/10.1038/s41590-024-01856-3

Arya, S.B., F. Jordan-Javed, K. Loesel, Y. Choi, S.P. Collie, L.E. Hein, B.M. Baker, E. Yoon, and C.A. Parent. 2026. cPLA $_2$ α targeting to exosomes connects nuclear deformation to LTB $_4$ -signaling during neutrophil chemotaxis. *Sci. Adv.* 12:eaea2784. https://doi.org/10.1126/sciadv.aea2784

Asghari, M., S.D. Ivetich, M.K. Aslan, M. Aramesh, O. Melkonyan, Y. Meng, R. Xu, M. Colombo, T. Weiss, S. Balabanov, et al. 2024. Real-time viscoelastic deformability cytometry: High-throughput mechanical phenotyping of liquid and solid biopsies. *Sci. Adv.* 10:eabj1133. https://doi.org/10.1126/sciadv.abj1133

Assen, F.P., J. Abe, M. Hons, R. Hauschild, S. Shamipour, W.A. Kaufmann, T. Costanzo, G. Krens, M. Brown, B. Ludewig, et al. 2022. Multitier mechanics control stromal adaptations in the swelling lymph node. *Nat. Immunol.* 23:1246–1255. https://doi.org/10.1038/s41590-022-01257-4

Astarita, J.L., V. Cremasco, J. Fu, M.C. Darnell, J.R. Peck, J.M. Nieves-Bonilla, K. Song, Y. Kondo, M.C. Woodruff, A. Gogineni, et al. 2015. The CLEC-2–podoplanin axis controls the contractility of fibroblastic reticular cells and lymph node microarchitecture. *Nat. Immunol.* 16:75–84. https://doi.org/10.1038/ni.3035

Atcha, H., A. Jairaman, J.R. Holt, V.S. Meli, R.R. Nagalla, P.K. Veerasubramanian, K.T. Brumm, H.E. Lim, S. Othy, M.D. Cahalan, et al. 2021. Mechanically activated ion channel Piezo1 modulates macrophage polarization and stiffness sensing. *Nat. Commun.* 12:3256. https://doi.org/10.1038/s41467-021-23482-5

Atcha, H., D. Kulkarni, V.S. Meli, P.K. Veerasubramanian, Y. Wang, M.D. Cahalan, M.M. Pathak, and W.F. Liu. 2024. Piezo1-mediated mechanotransduction enhances macrophage oxidized low-density lipoprotein uptake and atherogenesis. *PNAS Nexus.* 3:pgae436. https://doi.org/10.1093/pnasnexus/pgae436

Atia, L., D. Bi, Y. Sharma, J.A. Mitchel, B. Gweon, S. Koehler, S.J. DeCamp, B. Lan, J.H. Kim, R. Hirsch, et al. 2018. Geometric constraints during epithelial jamming. *Nat. Phys.* 14:613–620. https://doi.org/10.1038/s41567-018-0089-9

Aykut, B., R. Chen, J.I. Kim, D. Wu, S.A.A. Shadaloey, R. Abengozar, P. Preiss, A. Saxena, S. Pushalkar, J. Leinwand, et al. 2020. Targeting Piezo1 unleashes innate immunity against cancer and infectious disease. *Sci. Immunol.* 5:eabb5168. https://doi.org/10.1126/sciimmunol.abb5168

Azizi, G., J.M. Keller, M.L. Mayo, K. Piper, D. Puett, K.M. Earp, and C.D. Malchoff. 2016. Shear wave elastography and cervical lymph nodes: Predicting malignancy. *Ultrasound Med. Biol.* 42:1273–1281. https://doi.org/10.1016/j.ultrasmedbio.2016.01.012

Baechle, J.J., N. Chen, P. Makhijani, S. Winer, D. Furman, and D.A. Winer. 2023. Chronic inflammation and the hallmarks of aging. *Mol. Metab.* 74:101755. https://doi.org/10.1016/j.molmet.2023.101755

Baeyens, N., M.J. Mulligan-Kehoe, F. Corti, D.D. Simon, T.D. Ross, J.M. Rhodes, T.Z. Wang, C.O. Mejean, M. Simons, J. Humphrey, and M.A. Schwartz. 2014. Syndecan 4 is required for endothelial alignment in flow and atheroprotective signaling. *Proc. Natl. Acad. Sci. USA*. 111:17308–17313. https://doi.org/10.1073/pnas.1413725111

Baeyens, N., S. Nicoli, B.G. Coon, T.D. Ross, K. Van den Dries, J. Han, H.M. Lauridsen, C.O. Mejean, A. Eichmann, J.-L. Thomas, et al. 2015. Vascular remodeling is governed by a VEGFR3-dependent fluid shear stress set point. *Elife*. 4:e04645. https://doi.org/10.7554/eLife.04645

Bagley, D.C., T. Russell, E. Ortiz-Zapater, S. Stinson, K. Fox, P.F. Redd, M. Joseph, C. Deering-Rice, C. Reilly, M. Parsons, et al. 2024. Bronchoconstriction damages airway epithelia by crowding-induced excess cell extrusion. *Science*. 384:66–73. https://doi.org/10.1126/science.adk2758

Bai, H., L. Si, A. Jiang, C. Belgur, Y. Zhai, R. Plebani, C.Y. Oh, M. Rodas, A. Patil, A. Nurani, et al. 2022. Mechanical control of innate immune responses against viral infection revealed in a human lung alveolus chip. *Nat. Commun.* 13:1928. https://doi.org/10.1038/s41467-022-29562-4

Baratchi, S., M.T.K. Zaldivia, M. Wallert, J. Loseff-Silver, S. Al-Aryahi, J. Zamani, P. Thurgood, A. Salim, N.M. Htun, D. Stub, et al. 2020. Transcatheter aortic valve implantation represents an anti-inflammatory therapy via reduction of shear stress–induced, piezo-1–mediated monocyte activation. *Circulation*. 142:1092–1105. https://doi.org/10.1161/CIRCULATIONAHA.120.045536

Baratchi, S., H. Danish, C. Chheang, Y. Zhou, A. Huang, A. Lai, M. Khanmohammadi, K.M. Quinn, K. Khoshmanesh, and K. Peter. 2024. Piezo1 expression in neutrophils regulates shear-induced NETosis. *Nat. Commun.* 15:7023. https://doi.org/10.1038/s41467-024-51211-1

Barger, S.R., N.S. Reilly, M.S. Shutova, Q. Li, P. Maiuri, J.M. Heddleston, M.S. Mooseker, R.A. Flavell, T. Svitkina, P.W. Oakes, et al. 2019. Membrane-cytoskeletal crosstalk mediated by myosin-I regulates adhesion turnover during phagocytosis. *Nat. Commun.* 10:1249. https://doi.org/10.1038/s41467-019-09104-1

Bassat, E., Y.E. Mutlak, A. Genzelinakh, I.Y. Shadrin, K. Baruch Umansky, O. Yifa, D. Kain, D. Rajchman, J. Leach, D. Riabov Bassat, et al. 2017. The extracellular matrix protein agrin promotes heart regeneration in mice. *Nature*. 547:179–184. https://doi.org/10.1038/nature22978

Bastounis, E.E., F. Serrano-Alcalde, P. Radhakrishnan, P. Engström, M.J. Gómez-Benito, M.S. Oswald, Y.-T. Yeh, J.G. Smith, M.D. Welch, J.M. García-Aznar, and J.A. Theriot. 2021. Mechanical competition triggered by innate immune signaling drives the collective extrusion of bacterially infected epithelial cells. *Dev. Cell*. 56:443–460.e11. https://doi.org/10.1016/j.devcel.2021.01.012

Basu, R., B.M. Whitlock, J. Husson, A. Le Floc'h, W. Jin, A. Oyler-Yaniv, F. Dotiwala, G. Giannone, C. Hivroz, N. Biais, et al. 2016. Cytotoxic T cells use mechanical force to potentiate target cell killing. *Cell*. 165:100–110. https://doi.org/10.1016/j.cell.2016.01.021

Bayramoglu, Z., M. Ozturk, E. Caliskan, H. Ayyildiz, and I. Adaletli. 2020. Normative values of thymus in healthy children; stiffness by shear wave elastography. *Diagn. Interv. Radiol.* 26:147–152. https://doi.org/10.5152/dir.2019.19344

Berryman, K.S., A.M. Alsharif, M. Singh, F. Quintero, A.B. Knochel, M.G. Mora Pinos, D. Sivaraj, L. Latifi, F. Saenz, Jr., P.M. Pinos, et al. 2026. Mechanotransduction unifies healthy nondiabetic wound healing over time by promoting a Cd14+/C1qa+ fibroblast subpopulation. *J. Invest. Dermatol.* S0022-202X(26)01035-3. https://doi.org/10.1016/j.jid.2026.02.027

Biro, M., M.A. Munoz, and W. Weninger. 2014. Targeting Rho-GTPases in immune cell migration and inflammation. *Br. J. Pharmacol.* 171:5491–5506. https://doi.org/10.1111/bph.12658

Blanch, T.E., E.Y. Zhang, S. Kim, B.-I. Tumenbayar, X. Jiang, I.K. Kwon, N.A. Dyment, I. Jung, and S.C. Heo. 2026. Age-dependent chromatin

remodeling drives inflammatory dysregulation in tendon cells. *bioRxiv*. https://doi.org/10.64898/2026.01.05.697725 (Preprint posted January 05, 2026).
Blumenthal, D., V. Chandra, L. Avery, and J.K. Burkhardt. 2020. Mouse T cell priming is enhanced by maturation-dependent stiffening of the dendritic cell cortex. *Elife*. 9:e55995. https://doi.org/10.7554/eLife.55995
Blythe, N.M., K. Muraki, M.J. Ludlow, V. Stylianidis, H.T.J. Gilbert, E.L. Evans, K. Cuthbertson, R. Foster, J. Swift, J. Li, et al. 2019. Mechanically activated Piezo1 channels of cardiac fibroblasts stimulate p38 mitogen-activated protein kinase activity and interleukin-6 secretion. *J. Biol. Chem.* 294:17395–17408. https://doi.org/10.1074/jbc.RA119.009167
Bobba, C.M., Q. Fei, V. Shukla, H. Lee, P. Patel, R.K. Putman, C. Spitzer, M. Tsai, M.D. Wewers, R.J. Lee, et al. 2021. Nanoparticle delivery of microRNA-146a regulates mechanotransduction in lung macrophages and mitigates injury during mechanical ventilation. *Nat. Commun.* 12:289. https://doi.org/10.1038/s41467-020-20449-w
Brohawn, S.G., Z. Su, and R. MacKinnon. 2014. Mechanosensitivity is mediated directly by the lipid membrane in TRAAK and TREK1 K^+ channels. *Proc. Natl. Acad. Sci. USA*. 111:3614–3619. https://doi.org/10.1073/pnas.1320768111
Budday, S., G. Sommer, C. Birkl, C. Langkammer, J. Haybaeck, J. Kohnert, M. Bauer, F. Paulsen, P. Steinmann, E. Kuhl, and G.A. Holzapfel. 2017. Mechanical characterization of human brain tissue. *Acta Biomater*. 48:319–340. https://doi.org/10.1016/j.actbio.2016.10.036
Bufi, N., M. Saitakis, S. Dogniaux, O. Buschinger, A. Bohineust, A. Richert, M. Maurin, C. Hivroz, and A. Asnacios. 2015. Human primary immune cells exhibit distinct mechanical properties that are modified by inflammation. *Biophys. J.* 108:2181–2190. https://doi.org/10.1016/j.bpj.2015.03.047
Bunne, C., Y. Roohani, Y. Rosen, A. Gupta, X. Zhang, M. Roed, T. Alexandrov, M. AlQuraishi, P. Brennan, D.B. Burkhardt, et al. 2024. How to build the virtual cell with artificial intelligence: Priorities and opportunities. *Cell*. 187:7045–7063. https://doi.org/10.1016/j.cell.2024.11.015
Butenko, S., R.R. Nagalla, C.F. Guerrero-Juarez, F. Palomba, L.-M. David, R.Q. Nguyen, D. Gay, A.A. Almet, M.A. Digman, Q. Nie, et al. 2024. Hydrogel crosslinking modulates macrophages, fibroblasts, and their communication, during wound healing. *Nat. Commun.* 15:6820. https://doi.org/10.1038/s41467-024-50072-y
Caliari, S.R., and J.A. Burdick. 2016. A practical guide to hydrogels for cell culture. *Nat. Methods*. 13:405–414. https://doi.org/10.1038/nmeth.3839
Calmettes, V., M.A. Quintanilla, L. Lacerda Mariano, M. Piel, H.D. Moreau, and A. Lennon-Duménil. 2026. Mechanosensing in dendritic cells. *Immunol. Rev.* 337:e70086. https://doi.org/10.1111/imr.70086
Cambré, I., D. Gaublomme, A. Burssens, P. Jacques, N. Schryvers, A. De Muynck, L. Meuris, S. Lambrecht, S. Carter, P. de Bleser, et al. 2018. Mechanical strain determines the site-specific localization of inflammation and tissue damage in arthritis. *Nat. Commun.* 9:4613. https://doi.org/10.1038/s41467-018-06933-4
Cambré, I., D. Gaublomme, N. Schryvers, S. Lambrecht, R. Lories, K. Venken, and D. Elewaut. 2019. Running promotes chronicity of arthritis by local modulation of complement activators and impairing T regulatory feedback loops. *Ann. Rheum. Dis.* 78:787–795. https://doi.org/10.1136/annrheumdis-2018-214627
Cancado de Faria, R., L.N.D. Silva, B. Teodoro-Castro, K.S. McCommis, E.V. Shashkova, and S. Gonzalo. 2025. A noncanonical cGAS–STING pathway drives cellular and organismal aging. *Proc. Natl. Acad. Sci. USA*. 122:e2424666122. https://doi.org/10.1073/pnas.2424666122
Caporizzo, M.A., C.Y. Chen, K. Bedi, K.B. Margulies, and B.L. Prosser. 2020. Microtubules increase diastolic stiffness in failing human cardiomyocytes and myocardium. *Circulation*. 141:902–915. https://doi.org/10.1161/CIRCULATIONAHA.119.043930
Caruso, C., M.E. Fay, X. Cheng, A.Y. Liu, S.I. Park, T.A. Sulchek, M.D. Graham, and W.A. Lam. 2022. Pathologic mechanobiological interactions between red blood cells and endothelial cells directly induce vasculopathy in iron deficiency anemia. *iScience*. 25:104606. https://doi.org/10.1016/j.isci.2022.104606
Caruso, C., X. Cheng, M.E. Michaud, H.M. Szafraniec, B.E. Thomas, M.E. Fay, R.G. Mannino, X. Zhang, Y. Sakurai, W. Li, et al. 2024. Less-deformable erythrocyte subpopulations biomechanically induce endothelial inflammation in sickle cell disease. *Blood*. 144:2050–2062. https://doi.org/10.1182/blood.2024024608
Castleberry, S.A., B.D. Almquist, W. Li, T. Reis, J. Chow, S. Mayner, and P.T. Hammond. 2016. Self-assembled wound dressings silence MMP-9 and improve diabetic wound healing in vivo. *Adv. Mater.* 28:1809–1817. https://doi.org/10.1002/adma.201503565
Chabaud, M., M.L. Heuzé, M. Bretou, P. Vargas, P. Maiuri, P. Solanes, M. Maurin, E. Terriac, M. Le Berre, D. Lankar, et al. 2015. Cell migration and antigen capture are antagonistic processes coupled by myosin II in dendritic cells. *Nat. Commun.* 6:7526. https://doi.org/10.1038/ncomms8526
Chakraborty, M., K. Chu, A. Shrestha, X.S. Revelo, X. Zhang, M.J. Gold, S. Khan, M. Lee, C. Huang, M. Akbari, et al. 2021a. Mechanical stiffness controls dendritic cell metabolism and function. *Cell Rep.* 34:108609. https://doi.org/10.1016/j.celrep.2020.108609
Chakraborty, S., D. Sampath, M.O. Yu Lin, M. Bilton, C.-K. Huang, M.H. Nai, K. Njah, P.-A. Goy, C.-C. Wang, E. Guccione, et al. 2021b. Agrin-matrix metalloproteinase-12 axis confers a mechanically competent microenvironment in skin wound healing. *Nat. Commun.* 12:6349. https://doi.org/10.1038/s41467-021-26717-7
Champion, J.A., and S. Mitragotri. 2006. Role of target geometry in phagocytosis. *Proc. Natl. Acad. Sci. USA*. 103:4930–4934. https://doi.org/10.1073/pnas.0600997103
Chang, J.E., M.B. Buechler, E. Gressier, S.J. Turley, and M.C. Carroll. 2019a. Mechanosensing by Peyer's patch stroma regulates lymphocyte migration and mucosal antibody responses. *Nat. Immunol.* 20:1506–1516. https://doi.org/10.1038/s41590-019-0505-z
Chang, S.H., D. Mori, H. Kobayashi, Y. Mori, H. Nakamoto, K. Okada, Y. Taniguchi, S. Sugita, F. Yano, U.-I. Chung, et al. 2019b. Excessive mechanical loading promotes osteoarthritis through the gremlin-1-NF-κB pathway. *Nat. Commun.* 10:1442. https://doi.org/10.1038/s41467-019-09491-5
Chappell, D.C., S.E. Varner, R.M. Nerem, R.M. Medford, and R.W. Alexander. 1998. Oscillatory shear stress stimulates adhesion molecule expression in cultured human endothelium. *Circ. Res.* 82:532–539. https://doi.org/10.1161/01.RES.82.5.532
Chaudhary, V., B. Mishra, M.D. Ah Kioon, Y. Du, L.B. Ivashkiv, M.K. Crow, and F.J. Barrat. 2025. Mechanosensing regulates pDC activation in the skin through NRF2 activation. *J. Exp. Med.* 222:e20240852. https://doi.org/10.1084/jem.20240852
Chaudhuri, O., L. Gu, M. Darnell, D. Klumpers, S.A. Bencherif, J.C. Weaver, N. Huebsch, and D.J. Mooney. 2015. Substrate stress relaxation regulates cell spreading. *Nat. Commun.* 6:6365. https://doi.org/10.1038/ncomms7365
Chaudhuri, O., L. Gu, D. Klumpers, M. Darnell, S.A. Bencherif, J.C. Weaver, N. Huebsch, H.-P. Lee, E. Lippens, G.N. Duda, and D.J. Mooney. 2016. Hydrogels with tunable stress relaxation regulate stem cell fate and activity. *Nat. Mater.* 15:326–334. https://doi.org/10.1038/nmat4489
Chaudhuri, O., J. Cooper-White, P.A. Janmey, D.J. Mooney, and V.B. Shenoy. 2020. Effects of extracellular matrix viscoelasticity on cellular behaviour. *Nature*. 584:535–546. https://doi.org/10.1038/s41586-020-2612-2
Chen, Y., L.A. Ju, F. Zhou, J. Liao, L. Xue, Q.P. Su, D. Jin, Y. Yuan, H. Lu, S.P. Jackson, and C. Zhu. 2019. An integrin αIIbβ3 intermediate affinity state mediates biomechanical platelet aggregation. *Nat. Mater.* 18:760–769. https://doi.org/10.1038/s41563-019-0323-6
Chen, X., R. Hughes, N. Mullin, R.J. Hawkins, I. Holen, N.J. Brown, and J.K. Hobbs. 2020. Mechanical heterogeneity in the bone microenvironment as characterized by atomic force microscopy. *Biophys. J.* 119:502–513. https://doi.org/10.1016/j.bpj.2020.06.026
Chen, K., S.H. Kwon, D. Henn, B.A. Kuehlmann, R. Tevlin, C.A. Bonham, M. Griffin, A.A. Trotsyuk, M.R. Borrelli, C. Noishiki, et al. 2021. Disrupting biological sensors of force promotes tissue regeneration in large organisms. *Nat. Commun.* 12:5256. https://doi.org/10.1038/s41467-021-25410-z
Chen, K., D. Henn, M. Januszyk, J.A. Barrera, C. Noishiki, C.A. Bonham, M. Griffin, R. Tevlin, T. Carlomagno, T. Shannon, et al. 2022. Disrupting mechanotransduction decreases fibrosis and contracture in split-thickness skin grafting. *Sci. Transl. Med.* 14:eabj9152. https://doi.org/10.1126/scitranslmed.abj9152
Chen, K., M. Griffin, D. Henn, K.S. Berryman, D. Sivaraj, H.C. Kussie, C.A. Bonham, E. McKenna, M.G. Mora Pinos, A.M. Alsharif, et al. 2025a. Targeting circulating mechanoresponsive monocytes and macrophages to reduce fibrosis. *Nat. Biomed. Eng.* https://doi.org/10.1038/s41551-025-01479-5
Chen, K., R. Mou, Z. Guan, P. Teng, M. Aihemaiti, J. Cheng, S. Xu, P. Zhu, X. Hu, D. Li, et al. 2025b. PIEZO1-activated donor lymphatic remodeling integrates with autologous lymphangiogenesis to enhance vein graft patency in mice. *Sci. Transl. Med.* 17:eads7438. https://doi.org/10.1126/scitranslmed.ads7438
Chen, F., Y. Zhang, Z. Wu, K. Du, X. Chen, Y. Lu, Q. Hu, A. Du, S. Du, J. Wang, et al. 2026. Piezo1 activation in endothelial cells aggravates

microvascular ischemia–reperfusion injury in limbs by enhancing ferroptosis. *Exp. Mol. Med.* 58:143–160. https://doi.org/10.1038/s12276-025-01616-9

Cheng, J.P.X., C. Mendoza-Topaz, G. Howard, J. Chadwick, E. Shvets, A.S. Cowburn, B.J. Dunmore, A. Crosby, N.W. Morrell, and B.J. Nichols. 2015. Caveolae protect endothelial cells from membrane rupture during increased cardiac output. *J. Cell Biol.* 211:53–61. https://doi.org/10.1083/jcb.201504042

Cho, S., M. Vashisth, A. Abbas, S. Majkut, K. Vogel, Y. Xia, I.L. Ivanovska, J. Irianto, M. Tewari, K. Zhu, et al. 2019. Mechanosensing by the lamina protects against nuclear rupture, DNA damage, and cell-cycle arrest. *Dev. Cell*. 49:920–935.e5. https://doi.org/10.1016/j.devcel.2019.04.020

Cho, S., S. Rhee, C.M. Madl, A. Caudal, D. Thomas, H. Kim, A. Kojic, H.S. Shin, A. Mahajan, J.W. Jahng, et al. 2025. Selective inhibition of stromal mechanosensing suppresses cardiac fibrosis. *Nature*. 642:766–775. https://doi.org/10.1038/s41586-025-08945-9

Chu, J.Y., B. McCormick, K. Sundaram, G. Hardisty, U. Karmakar, C. Pumpe, E. Krull, C.D. Lucas, J. Amado-Azevedo, P.L. Hordijk, et al. 2024. ARAP3 protects from excessive formylated peptide-induced microvascular leakage by acting on endothelial cells and neutrophils. *J. Pathol.* 263:347–359. https://doi.org/10.1002/path.6288

Ciucci, G., D. Lorizio, N. Bartoloni, M. Budini, A. Colliva, S. Vodret, A.-V. Nguyen, L. Ciacci, B. Texler, B. Cardini, et al. 2026. Mechanical load inhibits cancer growth in mouse and human hearts. *Science*. 392:eads9412. https://doi.org/10.1126/science.ads9412

Colecchia, A., L. Montrone, E. Scaioli, M.L. Bacchi-Reggiani, A. Colli, G. Casazza, R. Schiumerini, L. Turco, A.R. Di Biase, G. Mazzella, et al. 2012. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology*. 143:646–654. https://doi.org/10.1053/j.gastro.2012.05.035

Collins, C., C. Guilluy, C. Welch, E.T. O'Brien, K. Hahn, R. Superfine, K. Burridge, and E. Tzima. 2012. Localized tensional forces on PECAM-1 elicit a global mechanotransduction response via the integrin-RhoA pathway. *Curr. Biol.* 22:2087–2094. https://doi.org/10.1016/j.cub.2012.08.051

Company-Garrido, I., A. Zurita Carpio, M. Colomer-Rosell, B. Ciraulo, R. Molkenbur, P. Lanzerstorfer, F. Pezzano, C. Agazzi, R. Hauschild, S. Jain, et al. 2026. Myosin II regulates cellular thermo-adaptability and the efficiency of immune responses. *Dev. Cell*. 61:356–371.e12. https://doi.org/10.1016/j.devcel.2025.10.006

Conway, D.E., M.T. Breckenridge, E. Hinde, E. Gratton, C.S. Chen, and M.A. Schwartz. 2013. Fluid shear stress on endothelial cells modulates mechanical tension across VE-cadherin and PECAM-1. *Curr. Biol.* 23:1024–1030. https://doi.org/10.1016/j.cub.2013.04.049

Coon, B.G., N. Baeyens, J. Han, M. Budatha, T.D. Ross, J.S. Fang, S. Yun, J.-L. Thomas, and M.A. Schwartz. 2015. Intramembrane binding of VE-cadherin to VEGFR2 and VEGFR3 assembles the endothelial mechanosensory complex. *J. Cell Biol.* 208:975–986. https://doi.org/10.1083/jcb.201408103

Coon, B.G., S. Timalsina, M. Astone, Z.W. Zhuang, J. Fang, J. Han, J. Themen, M. Chung, Y.J. Yang-Klingler, M. Jain, et al. 2022. A mitochondrial contribution to anti-inflammatory shear stress signaling in vascular endothelial cells. *J. Cell Biol.* 221:e202109144. https://doi.org/10.1083/jcb.202109144

Cornell, C.E., A. Chorlay, D. Krishnamurthy, N.R. Martin, L. Baldauf, and D.A. Fletcher. 2025. Target cell cortical tension regulates macrophage trogocytosis. *Nat. Cell Biol.* 27:2078–2088. https://doi.org/10.1038/s41556-025-01807-6

Coste, B., J. Mathur, M. Schmidt, T.J. Earley, S. Ranade, M.J. Petrus, A.E. Dubin, and A. Patapoutian. 2010. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science*. 330:55–60. https://doi.org/10.1126/science.1193270

Crane, J.D., D.I. Ogborn, C. Cupido, S. Melov, A. Hubbard, J.M. Bourgeois, and M.A. Tarnopolsky. 2012. Massage therapy attenuates inflammatory signaling after exercise-induced muscle damage. *Sci. Transl. Med.* 4:119ra13. https://doi.org/10.1126/scitranslmed.3002882

Crisp, M., Q. Liu, K. Roux, J.B. Rattner, C. Shanahan, B. Burke, P.D. Stahl, and D. Hodzic. 2006. Coupling of the nucleus and cytoplasm: Role of the LINC complex. *J. Cell Biol.* 172:41–53. https://doi.org/10.1083/jcb.200509124

Cunningham, R., and C.G. Hansen. 2022. The Hippo pathway in cancer: YAP/TAZ and TEAD as therapeutic targets in cancer. *Clin. Sci.* 136:197–222. https://doi.org/10.1042/CS20201474

Cunningham, R., S. Jia, K. Purohit, M.N. Fairley, M.K. Maniak, Y. Lin, N.S. Hui, R.E. Graham, A.G. Rossi, J. Cholewa-Waclaw, et al. 2025. Pipeline to evaluate YAP-TEAD inhibitors indicates TEAD inhibition represses *NF2*-mutant mesothelioma. *Life Sci. Alliance*. 8:e202503241. https://doi.org/10.26508/lsa.202503241

Davies, P.F. 1995. Flow-mediated endothelial mechanotransduction. *Physiol. Rev.* 75:519–560. https://doi.org/10.1152/physrev.1995.75.3.519

Dayananda, K.M., I. Singh, N. Mondal, and S. Neelamegham. 2010. von Willebrand factor self-association on platelet GpIbalpha under hydrodynamic shear: Effect on shear-induced platelet activation. *Blood*. 116:3990–3998. https://doi.org/10.1182/blood-2010-02-269266

Decout, A., J.D. Katz, S. Venkatraman, and A. Ablasser. 2021. The cGAS–STING pathway as a therapeutic target in inflammatory diseases. *Nat. Rev. Immunol.* 21:548–569. https://doi.org/10.1038/s41577-021-00524-z

de Jesus, M., A.H. Settle, D. Vorselen, T.K. Gaetjens, M. Galiano, Y. Romin, E. Lee, Y.Y. Wong, T.-M. Fu, E. Santosa, et al. 2024. Single-cell topographical profiling of the immune synapse reveals a biomechanical signature of cytotoxicity. *Sci. Immunol.* 9:eadj2898. https://doi.org/10.1126/sciimmunol.adj2898

Denais, C.M., R.M. Gilbert, P. Isermann, A.L. McGregor, M. te Lindert, B. Weigelin, P.M. Davidson, P. Friedl, K. Wolf, and J. Lammerding. 2016. Nuclear envelope rupture and repair during cancer cell migration. *Science*. 352:353–358. https://doi.org/10.1126/science.aad7297

Deng, W., Y. Xu, W. Chen, D.S. Paul, A.K. Syed, M.A. Dragovich, X. Liang, P. Zakas, M.C. Berndt, J. Di Paola, et al. 2016. Platelet clearance via shear-induced unfolding of a membrane mechanoreceptor. *Nat. Commun.* 7:12863. https://doi.org/10.1038/ncomms12863

Deng, Y., J. Lu, W. Li, A. Wu, X. Zhang, W. Tong, K.K. Ho, L. Qin, H. Song, and K.K. Mak. 2018. Reciprocal inhibition of YAP/TAZ and NF-κB regulates osteoarthritic cartilage degradation. *Nat. Commun.* 9:4564. https://doi.org/10.1038/s41467-018-07022-2

De Silva, N.S., J. Siewiera, C. Alkhoury, G.P.F. Nader, F. Nadalin, K. de Azevedo, M. Couty, H.M. Izquierdo, A. Bhargava, C. Conrad, et al. 2023. Nuclear envelope disruption triggers hallmarks of aging in lung alveolar macrophages. *Nat. Aging*. 3:1251–1268. https://doi.org/10.1038/s43587-023-00488-w

Di, X., X. Gao, L. Peng, J. Ai, X. Jin, S. Qi, H. Li, K. Wang, and D. Luo. 2023. Cellular mechanotransduction in health and diseases: From molecular mechanism to therapeutic targets. *Signal. Transduct. Target. Ther.* 8:282. https://doi.org/10.1038/s41392-023-01501-9

Din, M., S. Paul, S. Ullah, H. Yang, R.-G. Xu, N.A.Z. Abidin, A. Sun, Y.C. Chen, R. Gao, B. Chowdhury, et al. 2024. Multi-parametric thrombus profiling microfluidics detects intensified biomechanical thrombogenesis associated with hypertension and aging. *Nat. Commun.* 15:9067. https://doi.org/10.1038/s41467-024-53069-9

Discher, D.E., P. Janmey, and Y.-L. Wang. 2005. Tissue cells feel and respond to the stiffness of their substrate. *Science*. 310:1139–1143. https://doi.org/10.1126/science.1116995

Diz-Muñoz, A., K. Thurley, S. Chintamen, S.J. Altschuler, L.F. Wu, D.A. Fletcher, and O.D. Weiner. 2016. Membrane tension acts through PLD2 and mTORC2 to limit actin network assembly during neutrophil migration. *PLoS Biol.* 14:e1002474. https://doi.org/10.1371/journal.pbio.1002474

Druso, J.E., and C. Fischbach. 2018. Biophysical properties of extracellular matrix: Linking obesity and cancer. *Trends Cancer*. 4:271–273. https://doi.org/10.1016/j.trecan.2018.02.001

Du, H., J.M. Bartleson, S. Butenko, V. Alonso, W.F. Liu, D.A. Winer, and M.J. Butte. 2023. Tuning immunity through tissue mechanotransduction. *Nat. Rev. Immunol.* 23:174–188. https://doi.org/10.1038/s41577-022-00761-w

Dudek, M., D.R.J. Pathiranage, B. Bano-Otalora, A. Paszek, N. Rogers, C.F. Gonçalves, C. Lawless, D. Wang, Z. Luo, L. Yang, et al. 2023. Mechanical loading and hyperosmolarity as a daily resetting cue for skeletal circadian clocks. *Nat. Commun.* 14:7237. https://doi.org/10.1038/s41467-023-42056-1

Dupont, S. 2025. Mechano-metabolism on the rise. *Curr. Opin. Cell Biol.* 95:102529. https://doi.org/10.1016/j.ceb.2025.102529

Dupont, S., and S.A. Wickström. 2022. Mechanical regulation of chromatin and transcription. *Nat. Rev. Genet.* 23:624–643. https://doi.org/10.1038/s41576-022-00493-6

Dupont, S., L. Morsut, M. Aragona, E. Enzo, S. Giulitti, M. Cordenonsi, F. Zanconato, J. Le Digabel, M. Forcato, S. Bicciato, et al. 2011. Role of YAP/TAZ in mechanotransduction. *Nature*. 474:179–183. https://doi.org/10.1038/nature10137

Dutta, B., R. Goswami, and S.O. Rahaman. 2020. TRPV4 plays a role in matrix stiffness-induced macrophage polarization. *Front. Immunol.* 11:570195. https://doi.org/10.3389/fimmu.2020.570195

D'Aldebert, E., N. Cenac, P. Rousset, L. Martin, C. Rolland, K. Chapman, J. Selves, L. Alric, J.-P. Vinel, and N. Vergnolle. 2011. Transient receptor potential vanilloid 4 activated inflammatory signals by intestinal epithelial cells and colitis in mice. *Gastroenterology*. 140:275–285. https://doi.org/10.1053/j.gastro.2010.09.045

Eby, S.F., B.A. Cloud, J.E. Brandenburg, H. Giambini, P. Song, S. Chen, N.K. LeBrasseur, and K.-N. An. 2015. Shear wave elastography of passive skeletal muscle stiffness: Influences of sex and age throughout adulthood. *Clin. Biomech.* 30:22–27. https://doi.org/10.1016/j.clinbiomech.2014.11.011

Eisenhoffer, G.T., P.D. Loftus, M. Yoshigi, H. Otsuna, C.-B. Chien, P.A. Morcos, and J. Rosenblatt. 2012. Crowding induces live cell extrusion to maintain homeostatic cell numbers in epithelia. *Nature*. 484:546–549. https://doi.org/10.1038/nature10999

Ekpenyong, A.E., N. Toepfner, C. Fiddler, M. Herbig, W. Li, G. Cojoc, C. Summers, J. Guck, and E.R. Chilvers. 2017. Mechanical deformation induces depolarization of neutrophils. *Sci. Adv.* 3:e1602536. https://doi.org/10.1126/sciadv.1602536

Elosegui-Artola, A., I. Andreu, A.E.M. Beedle, A. Lezamiz, M. Uroz, A.J. Kosmalska, R. Oria, J.Z. Kechagia, P. Rico-Lastres, A.-L. Le Roux, et al. 2017. Force triggers YAP nuclear entry by regulating transport across nuclear pores. *Cell*. 171:1397–1410.e14. https://doi.org/10.1016/j.cell.2017.10.008

Engler, A.J., S. Sen, H.L. Sweeney, and D.E. Discher. 2006. Matrix elasticity directs stem cell lineage specification. *Cell*. 126:677–689. https://doi.org/10.1016/j.cell.2006.06.044

Engler, A.J., C. Carag-Krieger, C.P. Johnson, M. Raab, H.-Y. Tang, D.W. Speicher, J.W. Sanger, J.M. Sanger, and D.E. Discher. 2008. Embryonic cardiomyocytes beat best on a matrix with heart-like elasticity: Scar-like rigidity inhibits beating. *J. Cell Sci.* 121:3794–3802. https://doi.org/10.1242/jcs.029678

Enyedi, B., S. Kala, T. Nikolich-Zugich, and P. Niethammer. 2013. Tissue damage detection by osmotic surveillance. *Nat. Cell Biol.* 15:1123–1130. https://doi.org/10.1038/ncb2818

Enyedi, B., M. Jelcic, and P. Niethammer. 2016. The cell nucleus serves as a mechanotransducer of tissue damage-induced inflammation. *Cell*. 165:1160–1170. https://doi.org/10.1016/j.cell.2016.04.016

Erdogmus, S., U. Storch, L. Danner, J. Becker, M. Winter, N. Ziegler, A. Wirth, S. Offermanns, C. Hoffmann, T. Gudermann, and M. Mederos y Schnitzler. 2019. Helix 8 is the essential structural motif of mechanosensitive GPCRs. *Nat. Commun.* 10:5784. https://doi.org/10.1038/s41467-019-13722-0

Everaerts, W., X. Zhen, D. Ghosh, J. Vriens, T. Gevaert, J.P. Gilbert, N.J. Hayward, C.R. McNamara, F. Xue, M.M. Moran, et al. 2010. Inhibition of the cation channel TRPV4 improves bladder function in mice and rats with cyclophosphamide-induced cystitis. *Proc. Natl. Acad. Sci. USA*. 107:19084–19089. https://doi.org/10.1073/pnas.1005333107

Ezzo, M., K. Spindler, J.B. Wang, D. Lee, G. Pecoraro, J. Cowen, P. Pakshir, and B. Hinz. 2024. Acute contact with profibrotic macrophages mechanically activates fibroblasts via αvβ3 integrin–mediated engagement of Piezo1. *Sci. Adv.* 10:eadp4726. https://doi.org/10.1126/sciadv.adp4726

Fan, W., K. Adebowale, L. Váncza, Y. Li, M.F. Rabbi, K. Kunimoto, D. Chen, G. Mozes, D.K.-C. Chiu, Y. Li, et al. 2024. Matrix viscoelasticity promotes liver cancer progression in the pre-cirrhotic liver. *Nature*. 626:635–642. https://doi.org/10.1038/s41586-023-06991-9

Feng, Y., Y. Liang, X. Zhu, M. Wang, Y. Gui, Q. Lu, M. Gu, X. Xue, X. Sun, W. He, et al. 2018. The signaling protein Wnt5a promotes TGFβ1-mediated macrophage polarization and kidney fibrosis by inducing the transcriptional regulators Yap/Taz. *J. Biol. Chem.* 293:19290–19302. https://doi.org/10.1074/jbc.RA118.005457

Fernando, A.J., F. Rossi, D. Docherty, A. Popravko, L. Masters, B. Houston, R. Gupta, K. Dhaliwal, and A.G. Rossi. 2025. Rapid autofluorescence flow cytometric analysis of agonist-induced neutrophil and eosinophil polarization reveals novel insights into 5-oxo-ETE-mediated granulocyte activation. *J. Inflamm.* 22:47. https://doi.org/10.1186/s12950-025-00472-8

Ferrucci, L., and E. Fabbri. 2018. Inflammageing: Chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat. Rev. Cardiol.* 15:505–522. https://doi.org/10.1038/s41569-018-0064-2

Fish, A., and A. Kulkarni. 2024. Flow-induced shear stress primes NLRP3 inflammasome activation in macrophages via Piezo1. *ACS Appl. Mater. Interfaces*. 16:4505–4518. https://doi.org/10.1021/acsami.3c18645

Fish, A., J. Forster, V. Malik, and A. Kulkarni. 2025. Shear-stress initiates signal two of NLRP3 inflammasome activation in LPS-primed macrophages through Piezo1. *ACS Appl. Mater. Interfaces*. 17:7363–7376. https://doi.org/10.1021/acsami.4c18845

Fiuza-Luces, C., P.L. Valenzuela, B.G. Gálvez, M. Ramírez, A. López-Soto, R.J. Simpson, and A. Lucia. 2024. The effect of physical exercise on anticancer immunity. *Nat. Rev. Immunol.* 24:282–293. https://doi.org/10.1038/s41577-023-00943-0

Fleming, I., B. Fisslthaler, M. Dixit, and R. Busse. 2005. Role of PECAM-1 in the shear-stress-induced activation of Akt and the endothelial nitric oxide synthase (eNOS) in endothelial cells. *J. Cell Sci.* 118:4103–4111. https://doi.org/10.1242/jcs.02541

Franceschi, C., M. Bonafè, S. Valensin, F. Olivieri, M. De Luca, E. Ottaviani, and G. De Benedictis. 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann. N. Y. Acad. Sci.* 908:244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x

François, J., A. Kandasamy, Y.-T. Yeh, A. Schwartz, C. Ayala, R. Meili, S. Chien, J.C. Lasheras, and J.C. Del Álamo. 2021. The interplay between matrix deformation and the coordination of turning events governs directed neutrophil migration in 3D matrices. *Sci. Adv.* 7:eabf3882. https://doi.org/10.1126/sciadv.abf3882

Freed, L.E., R. Langer, I. Martin, N.R. Pellis, and G. Vunjak-Novakovic. 1997. Tissue engineering of cartilage in space. *Proc. Natl. Acad. Sci. USA*. 94:13885–13890. https://doi.org/10.1073/pnas.94.25.13885

Freedman, B.R., C. Hwang, S. Talbot, B. Hibler, S. Matoori, and D.J. Mooney. 2023. Breakthrough treatments for accelerated wound healing. *Sci. Adv.* 9:eade7007. https://doi.org/10.1126/sciadv.ade7007

Friedrich, E.E., Z. Hong, S. Xiong, M. Zhong, A. Di, J. Rehman, Y.A. Komarova, and A.B. Malik. 2019. Endothelial cell Piezo1 mediates pressure-induced lung vascular hyperpermeability via disruption of adherens junctions. *Proc. Natl. Acad. Sci. USA*. 116:12980–12985. https://doi.org/10.1073/pnas.1902165116

Frittoli, E., A. Palamidessi, F. Iannelli, F. Zanardi, S. Villa, L. Barzaghi, H. Abdo, V. Cancila, G.V. Beznoussenko, G. Della Chiara, et al. 2023. Tissue fluidification promotes a cGAS–STING cytosolic DNA response in invasive breast cancer. *Nat. Mater.* 22:644–655. https://doi.org/10.1038/s41563-022-01431-x

Fu, T., D.P. Sullivan, A.M. Gonzalez, M.E. Haynes, P.J. Dalal, N.S. Rutledge, A.L. Tierney, J.A. Yescas, E.W. Weber, and W.A. Muller. 2023. Mechanotransduction via endothelial adhesion molecule CD31 initiates transmigration and reveals a role for VEGFR2 in diapedesis. *Immunity*. 56:2311–2324.e6. https://doi.org/10.1016/j.immuni.2023.08.001

Fu, B., J. Shen, X. Zou, N. Sun, Z. Zhang, Z. Liu, C. Zeng, H. Liu, and W. Huang. 2024. Matrix stiffening promotes chondrocyte senescence and the osteoarthritis development through downregulating HDAC3. *Bone Res.* 12:32. https://doi.org/10.1038/s41413-024-00333-9

Fukuoka, S., N. Adachi, E. Ouchi, H. Ikemoto, T. Okumo, F. Ishikawa, H. Onda, and M. Sunagawa. 2025. Mechanoreceptor Piezo1 channel-mediated interleukin expression in conjunctival epithelial cells: Linking mechanical stress to ocular inflammation. *Ocul. Surf.* 36:56–68. https://doi.org/10.1016/j.jtos.2025.01.001

Furman, D., J. Campisi, E. Verdin, P. Carrera-Bastos, S. Targ, C. Franceschi, L. Ferrucci, D.W. Gilroy, A. Fasano, G.W. Miller, et al. 2019. Chronic inflammation in the etiology of disease across the life span. *Nat. Med.* 25:1822–1832. https://doi.org/10.1038/s41591-019-0675-0

Fusilier, Z., A. Clément, F. Simon, I. Calvente, R. Jean-Marie, M. Mathieu, V. Calmettes, F. Piastra-Facon, Y. Quintana-Perez, J.G. Clement, et al. 2026. Macrophages restrict tumor immune infiltration by controlling collagen topography. *Sci. Immunol.* 11:eadw8291. https://doi.org/10.1126/sciimmunol.adw8291

Gaertner, F., Z. Ahmad, G. Rosenberger, S. Fan, L. Nicolai, B. Busch, G. Yavuz, M. Luckner, H. Ishikawa-Ankerhold, R. Hennel, et al. 2017. Migrating platelets are mechano-scavengers that collect and bundle bacteria. *Cell*. 171:1368–1382.e23. https://doi.org/10.1016/j.cell.2017.11.001

Gaertner, F., P. Reis-Rodrigues, I. de Vries, M. Hons, J. Aguilera, M. Riedl, A. Leithner, S. Tasciyan, A. Kopf, J. Merrin, et al. 2022. WASp triggers mechanosensitive actin patches to facilitate immune cell migration in dense tissues. *Dev. Cell*. 57:47–62.e9. https://doi.org/10.1016/j.devcel.2021.11.024

Gao, W., X. Zhang, W. Hu, J. Han, X. Liu, Y. Zhang, and M. Long. 2025. Neutrophils exhibit flexible migration strategies and trail formation mechanisms on varying adhesive substrates. *Biomaterials*. 314:122881. https://doi.org/10.1016/j.biomaterials.2024.122881

García-Arcos, J.M., J. Ziegler, S. Grigolon, L. Reymond, G. Shajepal, C.J. Cattin, A. Lomakin, D.J. Müller, V. Ruprecht, S. Wieser, et al. 2024. Rigidity

percolation and active advection synergize in the actomyosin cortex to drive amoeboid cell motility. *Dev. Cell*. 59:2990–3007.e7. https://doi.org/10.1016/j.devcel.2024.06.023

Gelashvili, Z., Z. Shen, Y. Ma, M. Jelcic, and P. Niethammer. 2026. Zebrafish macrophages convert physical wound signals into rapid vascular permeabilization. *Nat. Commun.* 17:1807. https://doi.org/10.1038/s41467-026-68520-2

Geng, J., Y. Shi, J. Zhang, B. Yang, P. Wang, W. Yuan, H. Zhao, J. Li, F. Qin, L. Hong, et al. 2021. TLR4 signalling via Piezo1 engages and enhances the macrophage mediated host response during bacterial infection. *Nat. Commun.* 12:3519. https://doi.org/10.1038/s41467-021-23683-y

Georges, P.C., J.-J. Hui, Z. Gombos, M.E. McCormick, A.Y. Wang, M. Uemura, R. Mick, P.A. Janmey, E.E. Furth, and R.G. Wells. 2007. Increased stiffness of the rat liver precedes matrix deposition: Implications for fibrosis. *Am. J. Physiol. Gastrointest. Liver Physiol.* 293:G1147–G1154. https://doi.org/10.1152/ajpgi.00032.2007

Glück, S., B. Guey, M.F. Gulen, K. Wolter, T.-W. Kang, N.A. Schmacke, A. Bridgeman, J. Rehwinkel, L. Zender, and A. Ablasser. 2017. Innate immune sensing of cytosolic chromatin fragments through cGAS promotes senescence. *Nat. Cell Biol.* 19:1061–1070. https://doi.org/10.1038/ncb3586

Goetz, J.G., E. Steed, R.R. Ferreira, S. Roth, C. Ramspacher, F. Boselli, G. Charvin, M. Liebling, C. Wyart, Y. Schwab, and J. Vermot. 2014. Endothelial cilia mediate low flow sensing during zebrafish vascular development. *Cell Rep.* 6:799–808. https://doi.org/10.1016/j.celrep.2014.01.032

Golo, M., P.L.H. Newman, D. Kempe, and M. Biro. 2024. Mechanoimmunology in the solid tumor microenvironment. *Biochem. Soc. Trans.* 52:1489–1502. https://doi.org/10.1042/BST20231427

Gordon, W.R., B. Zimmerman, L. He, L.J. Miles, J. Huang, K. Tiyanont, D.G. McArthur, J.C. Aster, N. Perrimon, J.J. Loparo, and S.C. Blacklow. 2015. Mechanical allostery: Evidence for a force requirement in the proteolytic activation of notch. *Dev. Cell*. 33:729–736. https://doi.org/10.1016/j.devcel.2015.05.004

Gossett, D.R., H.T.K. Tse, S.A. Lee, Y. Ying, A.G. Lindgren, O.O. Yang, J. Rao, A.T. Clark, and D. Di Carlo. 2012. Hydrodynamic stretching of single cells for large population mechanical phenotyping. *Proc. Natl. Acad. Sci. USA*. 109:7630–7635. https://doi.org/10.1073/pnas.1200107109

Grainge, C.L., L.C.K. Lau, J.A. Ward, V. Dulay, G. Lahiff, S. Wilson, S. Holgate, D.E. Davies, and P.H. Howarth. 2011. Effect of bronchoconstriction on airway remodeling in asthma. *N. Engl. J. Med.* 364:2006–2015. https://doi.org/10.1056/NEJMoa1014350

Gray, D.T., A. Gutierrez, Y. Jami-Alahmadi, V. Pandey, L. Pan, Y. Zhang, J.A. Wohlschlegel, R.A. McDevitt, and L.M. De Biase. 2025. Midbrain extracellular matrix and microglia are associated with cognition in aging mice. *Nat. Commun.* 16:11319. https://doi.org/10.1038/s41467-025-66434-z

Greener, J.G., S.M. Kandathil, L. Moffat, and D.T. Jones. 2022. A guide to machine learning for biologists. *Nat. Rev. Mol. Cell Biol.* 23:40–55. https://doi.org/10.1038/s41580-021-00407-0

Greuter, T., U. Yaqoob, C. Gan, N. Jalan-Sakrikar, E. Kostallari, J. Lu, J. Gao, L. Sun, M. Liu, T.S. Sehrawat, et al. 2022. Mechanotransduction-induced glycolysis epigenetically regulates a CXCL1-dominant angiocrine signaling program in liver sinusoidal endothelial cells in vitro and in vivo. *J. Hepatol.* 77:723–734. https://doi.org/10.1016/j.jhep.2022.03.029

van Grinsven, E., A.K. Mukherjee, and I.A. Udalova. 2026. Shaping neutrophil morphology and function: The importance of a segmented nucleus. *Nat. Rev. Immunol.* 26:269–283. https://doi.org/10.1038/s41577-025-01237-3

Gu, Y., T. Forostyan, R. Sabbadini, and J. Rosenblatt. 2011. Epithelial cell extrusion requires the sphingosine-1-phosphate receptor 2 pathway. *J. Cell Biol.* 193:667–676. https://doi.org/10.1083/jcb.201010075

Gu, Y., P. Xu, Y. Wu, C. Li, J. Shen, X. Cheng, Y. Wang, L.W. Zhang, Y. Wang, and M. Gao. 2024. Mechanotransduction-piloted whole-cell vaccines for spatiotemporal modulation of postoperative antitumor immunity. *ACS Nano*. 18:28675–28690. https://doi.org/10.1021/acsnano.4c06215

Guck, J., S. Schinkinger, B. Lincoln, F. Wottawah, S. Ebert, M. Romeyke, D. Lenz, H.M. Erickson, R. Ananthakrishnan, D. Mitchell, et al. 2005. Optical deformability as an inherent cell marker for testing malignant transformation and metastatic competence. *Biophys. J.* 88:3689–3698. https://doi.org/10.1529/biophysj.104.045476

Gudipaty, S.A., J. Lindblom, P.D. Loftus, M.J. Redd, K. Edes, C.F. Davey, V. Krishnegowda, and J. Rosenblatt. 2017. Mechanical stretch triggers rapid epithelial cell division through Piezo1. *Nature*. 543:118–121. https://doi.org/10.1038/nature21407

Guharay, F., and F. Sachs. 1984. Stretch-activated single ion channel currents in tissue-cultured embryonic chick skeletal muscle. *J. Physiol.* 352:685–701. https://doi.org/10.1113/jphysiol.1984.sp015317

Gui, Y., W. Li, J.-J. Liu, Y. Wang, C. Jones, R. Bansal, S.M. Mallari, H.W. Shaffer, Y. Yu, H. Fu, et al. 2026. Early-activated extracellular matrix proteins shape the metabolic and spatial dynamics of the kidney fibrotic microenvironment. *Nat. Metab.* 8:604–623. https://doi.org/10.1038/s42255-026-01458-3

Guilluy, C., L.D. Osborne, L. Van Landeghem, L. Sharek, R. Superfine, R. Garcia-Mata, and K. Burridge. 2014. Isolated nuclei adapt to force and reveal a mechanotransduction pathway in the nucleus. *Nat. Cell Biol.* 16:376–381. https://doi.org/10.1038/ncb2927

Guimarães, C.F., L. Gasperini, A.P. Marques, and R.L. Reis. 2020. The stiffness of living tissues and its implications for tissue engineering. *Nat. Rev. Mater.* 5:351–370. https://doi.org/10.1038/s41578-019-0169-1

Gulen, M.F., N. Samson, A. Keller, M. Schwabenland, C. Liu, S. Glück, V.V. Thacker, L. Favre, B. Mangeat, L.J. Kroese, et al. 2023. cGAS–STING drives ageing-related inflammation and neurodegeneration. *Nature*. 620:374–380. https://doi.org/10.1038/s41586-023-06373-1

Györfi, A.-H., A.-E. Matei, M. Fuchs, C. Liang, A.R. Rigau, X. Hong, H. Zhu, M. Luber, C. Bergmann, C. Dees, et al. 2021. Engrailed 1 coordinates cytoskeletal reorganization to induce myofibroblast differentiation. *J. Exp. Med.* 218:e20201916. https://doi.org/10.1084/jem.20201916

Hagenbeek, T.J., J.D. Webster, N.M. Kljavin, M.T. Chang, T. Pham, H.-J. Lee, C. Klijn, A.G. Cai, K. Totpal, B. Ravishankar, et al. 2018. The Hippo pathway effector TAZ induces TEAD-dependent liver inflammation and tumors. *Sci. Signal.* 11:eaaj1757. https://doi.org/10.1126/scisignal.aaj1757

Hahn, C., and M.A. Schwartz. 2009. Mechanotransduction in vascular physiology and atherogenesis. *Nat. Rev. Mol. Cell Biol.* 10:53–62. https://doi.org/10.1038/nrm2596

Hahn, A.K., R.A. Rawle, B. Bothner, E.B. Prado Lopes, T.M. Griffin, and R.K. June. 2022. *In vivo* mechanotransduction: Effect of acute exercise on the metabolomic profiles of mouse synovial fluid. *Osteoarthr. Cartil. Open*. 4:100228. https://doi.org/10.1016/j.ocarto.2021.100228

Hamanaka, K., M.-Y. Jian, D.S. Weber, D.F. Alvarez, M.I. Townsley, A.B. Al-Mehdi, J.A. King, W. Liedtke, and J.C. Parker. 2007. TRPV4 initiates the acute calcium-dependent permeability increase during ventilator-induced lung injury in isolated mouse lungs. *Am. J. Physiol. Lung Cell Mol. Physiol.* 293:L923–L932. https://doi.org/10.1152/ajplung.00221.2007

Hansen, C.G., E. Shvets, G. Howard, K. Riento, and B.J. Nichols. 2013. Deletion of cavin genes reveals tissue-specific mechanisms for morphogenesis of endothelial caveolae. *Nat. Commun.* 4:1831. https://doi.org/10.1038/ncomms2808

Hansen, C.E., D. Hollaus, A. Kamermans, and H.E. de Vries. 2024. Tension at the gate: Sensing mechanical forces at the blood–brain barrier in health and disease. *J. Neuroinflammation*. 21:325. https://doi.org/10.1186/s12974-024-03321-2

Hao, Y., S. Hao, E. Andersen-Nissen, W.M. Mauck, S. Zheng, A. Butler, M.J. Lee, A.J. Wilk, C. Darby, M. Zager, et al. 2021. Integrated analysis of multimodal single-cell data. *Cell*. 184:3573–3587.e29. https://doi.org/10.1016/j.cell.2021.04.048

Harada, T., J. Swift, J. Irianto, J.-W. Shin, K.R. Spinler, A. Athirasala, R. Diegmiller, P.C.D.P. Dingal, I.L. Ivanovska, and D.E. Discher. 2014. Nuclear lamin stiffness is a barrier to 3D migration, but softness can limit survival. *J. Cell Biol.* 204:669–682. https://doi.org/10.1083/jcb.201308029

He, Y., S. Yang, P. Liu, K. Li, K. Jin, R. Becker, J. Zhang, C. Lin, J. Xia, Z. Ma, et al. 2023. Acoustofluidic interfaces for the mechanobiological secretome of MSCs. *Nat. Commun.* 14:7639. https://doi.org/10.1038/s41467-023-43239-6

Henderson, N.C., F. Rieder, and T.A. Wynn. 2020. Fibrosis: From mechanisms to medicines. *Nature*. 587:555–566. https://doi.org/10.1038/s41586-020-2938-9

Hodgkinson, T., D.C. Kelly, C.M. Curtin, and F.J. O'Brien. 2022. Mechanosignalling in cartilage: An emerging target for the treatment of osteoarthritis. *Nat. Rev. Rheumatol.* 18:67–84. https://doi.org/10.1038/s41584-021-00724-w

Hoijman, E., H.-M. Häkkinen, Q. Tolosa-Ramon, S. Jiménez-Delgado, C. Wyatt, M. Miret-Cuesta, M. Irimia, A. Callan-Jones, S. Wieser, and V. Ruprecht. 2021. Cooperative epithelial phagocytosis enables error correction in the early embryo. *Nature*. 590:618–623. https://doi.org/10.1038/s41586-021-03200-3

Hong, J., C. Ge, P. Jothikumar, Z. Yuan, B. Liu, K. Bai, K. Li, W. Rittase, M. Shinzawa, Y. Zhang, et al. 2018. A TCR mechanotransduction signaling

loop induces negative selection in the thymus. *Nat. Immunol.* 19: 1379–1390. https://doi.org/10.1038/s41590-018-0259-z

Hong, S.-G., J. Shin, S.Y. Choi, J.C. Powers, B.M. Meister, J. Sayoc, J.S. Son, R. Tierney, F.A. Recchia, M.D. Brown, et al. 2022. Flow pattern–dependent mitochondrial dynamics regulates the metabolic profile and inflammatory state of endothelial cells. *JCI Insight*. 7:e159286. https://doi.org/10.1172/jci.insight.159286

Hong, S.-G., J.W. Ashby, J.P. Kennelly, M. Wu, M. Steel, E. Chattopadhyay, R. Foreman, P. Tontonoz, E.J. Tarling, P. Turowski, et al. 2024. Mechanosensitive membrane domains regulate calcium entry in arterial endothelial cells to protect against inflammation. *J. Clin. Invest.* 134: e175057. https://doi.org/10.1172/JCI175057

Horsnell, H.L., R.J. Tetley, H. De Belly, S. Makris, L.J. Millward, A.C. Benjamin, L.A. Heeringa, C.M. de Winde, E.K. Paluch, Y. Mao, and S.E. Acton. 2022. Lymph node homeostasis and adaptation to immune challenge resolved by fibroblast network mechanics. *Nat. Immunol.* 23:1169–1182. https://doi.org/10.1038/s41590-022-01272-5

Horton, P.D., A. Syed, M. Winkler, A.B. Vaidya, M. Rariden, N. Arora, Y. Zhou, M. Kobayashi, M. Yoshimoto, H.J. Lee, et al. 2026. Mechanometabolism instructs hematopoietic stem cell specification. *J. Exp. Med.* 223: e20250607. https://doi.org/10.1084/jem.20250607

Houk, A.R., A. Jilkine, C.O. Mejean, R. Boltyanskiy, E.R. Dufresne, S.B. Angenent, S.J. Altschuler, L.F. Wu, and O.D. Weiner. 2012. Membrane tension maintains cell polarity by confining signals to the leading edge during neutrophil migration. *Cell*. 148:175–188. https://doi.org/10.1016/j.cell.2011.10.050

Hsiai, T.K., S.K. Cho, P.K. Wong, M. Ing, A. Salazar, A. Sevanian, M. Navab, L.L. Demer, and C.-M. Ho. 2003. Monocyte recruitment to endothelial cells in response to oscillatory shear stress. *FASEB J.* 17:1648–1657. https://doi.org/10.1096/fj.02-1064com

Hu, Y., H. Li, W. Wang, F. Sun, C. Wu, W. Chen, and Z. Liu. 2023. Molecular force imaging reveals that integrin-dependent mechanical checkpoint regulates Fcγ-receptor-mediated phagocytosis in macrophages. *Nano Lett.* 23:5562–5572. https://doi.org/10.1021/acs.nanolett.3c00957

Huang, H., L. Xiao, L. Fang, M. Lei, Z. Liu, S. Gao, Q. Lei, J. Lei, R. Wei, Y. Lei, et al. 2025. Static topographical cue combined with dynamic fluid stimulation enhances the macrophage extracellular vesicle yield and therapeutic potential for bone defects. *ACS Nano*. 19:8667–8691. https://doi.org/10.1021/acsnano.4c15201

Hudspeth, A.J., and D.P. Corey. 1977. Sensitivity, polarity, and conductance change in the response of vertebrate hair cells to controlled mechanical stimuli. *Proc. Natl. Acad. Sci. USA*. 74:2407–2411. https://doi.org/10.1073/pnas.74.6.2407

Huh, D., B.D. Matthews, A. Mammoto, M. Montoya-Zavala, H.Y. Hsin, and D.E. Ingber. 2010. Reconstituting organ-level lung functions on a chip. *Science*. 328:1662–1668. https://doi.org/10.1126/science.1188302

Huh, D., D.C. Leslie, B.D. Matthews, J.P. Fraser, S. Jurek, G.A. Hamilton, K.S. Thorneloe, M.A. McAlexander, and D.E. Ingber. 2012. A human disease model of drug toxicity–induced pulmonary edema in a lung-on-a-chip microdevice. *Sci. Transl. Med.* 4:159ra147. https://doi.org/10.1126/scitranslmed.3004249

Hui, Y., X. Yi, D. Wibowo, G. Yang, A.P.J. Middelberg, H. Gao, and C.-X. Zhao. 2020. Nanoparticle elasticity regulates phagocytosis and cancer cell uptake. *Sci. Adv.* 6:eaaz4316. https://doi.org/10.1126/sciadv.aaz4316

Hurrell, B.P., S. Shen, X. Li, Y. Sakano, M.H. Kazemi, C. Quach, P. Shafiei-Jahani, K. Sakano, H. Ghiasi, and O. Akbari. 2024. Piezo1 channels restrain ILC2s and regulate the development of airway hyperreactivity. *J. Exp. Med.* 221:e20231835. https://doi.org/10.1084/jem.20231835

Huse, M. 2017. Mechanical forces in the immune system. *Nat. Rev. Immunol.* 17:679–690. https://doi.org/10.1038/nri.2017.74

Huse, M. 2025. Mechanoregulation of lymphocyte cytotoxicity. *Nat. Rev. Immunol.* 25:680–695. https://doi.org/10.1038/s41577-025-01173-2

Iliopoulou, M., A.T. Bajur, H.C.W. McArthur, M. Gabai, C. Coyle, F. Ajao, R. Köchl, A.P. Cope, and K.M. Spillane. 2024. Extracellular matrix rigidity modulates physical properties of subcapsular sinus macrophage-B cell immune synapses. *Biophys. J.* 123:2282–2300. https://doi.org/10.1016/j.bpj.2023.10.010

Incio, J., H. Liu, P. Suboj, S.M. Chin, I.X. Chen, M. Pinter, M.R. Ng, H.T. Nia, J. Grahovac, S. Kao, et al. 2016. Obesity-induced inflammation and desmoplasia promote pancreatic cancer progression and resistance to chemotherapy. *Cancer Discov.* 6:852–869. https://doi.org/10.1158/2159-8290.CD-15-1177

Ingber, D.E. 2022. Human organs-on-chips for disease modelling, drug development and personalized medicine. *Nat. Rev. Genet.* 23:467–491. https://doi.org/10.1038/s41576-022-00466-9

Jacot, J.G., A.D. McCulloch, and J.H. Omens. 2008. Substrate stiffness affects the functional maturation of neonatal rat ventricular myocytes. *Biophys. J.* 95:3479–3487. https://doi.org/10.1529/biophysj.107.124545

Jain, N., and V. Vogel. 2018. Spatial confinement downsizes the inflammatory response of macrophages. *Nat. Mater.* 17:1134–1144. https://doi.org/10.1038/s41563-018-0190-6

Jain, N., K.V. Iyer, A. Kumar, and G.V. Shivashankar. 2013. Cell geometric constraints induce modular gene-expression patterns via redistribution of HDAC3 regulated by actomyosin contractility. *Proc. Natl. Acad. Sci. USA*. 110:11349–11354. https://doi.org/10.1073/pnas.1300801110

Jansen, L.E., N.P. Birch, J.D. Schiffman, A.J. Crosby, and S.R. Peyton. 2015. Mechanics of intact bone marrow. *J. Mech. Behav. Biomed. Mater.* 50: 299–307. https://doi.org/10.1016/j.jmbbm.2015.06.023

Jaumouillé, V., A.X. Cartagena-Rivera, and C.M. Waterman. 2019. Coupling of β2 integrins to actin by a mechanosensitive molecular clutch drives complement receptor-mediated phagocytosis. *Nat. Cell Biol.* 21: 1357–1369. https://doi.org/10.1038/s41556-019-0414-2

Ji, M., S. Dong, S. Lu, H. Liang, Y. Lin, C. Luo, H. Zheng, Y. Shu, Z. Zhang, X. Jin, et al. 2024. Mechano-YAP/TAZ-regulated smooth muscle cells are an important source of Wnt signalling for gut regeneration. *Clin. Transl. Med.* 14:e70005. https://doi.org/10.1002/ctm2.70005

Jia, Y., J. Hu, K. An, Q. Zhao, Y. Dang, H. Liu, Z. Wei, S. Geng, and F. Xu. 2023. Hydrogel dressing integrating FAK inhibition and ROS scavenging for mechano-chemical treatment of atopic dermatitis. *Nat. Commun.* 14: 2478. https://doi.org/10.1038/s41467-023-38209-x

Jiang, T., X.-Y. Tang, Y. Mao, Y.-Q. Zhou, J.-J. Wang, R.-M. Li, X.-R. Xie, H.-M. Zhang, B. Fang, N.-J. Ouyang, and G.-H. Tang. 2023. Matrix mechanics regulate the polarization state of bone marrow-derived neutrophils through the JAK1/STAT3 signaling pathway. *Acta Biomater.* 168:159–173. https://doi.org/10.1016/j.actbio.2023.07.012

Jiang, X., S. Sellami, J. Kessler, M. Bachmann, F. Noulet, B. Russo, N.C. Brembilla, G. Kaya, A.I. Ivanov, M.S. Shutova, et al. 2026. Inflammation drives TGFβ1 activation via the αvβ6 integrin-mechanotransduction pathway in human skin. *iScience*. 29:115052. https://doi.org/10.1016/j.isci.2026.115052

Jiménez-Gracia, L., D. Maspero, S. Aguilar-Fernández, F. Craighero, M. Boulougouri, M. Ruiz, D. Marchese, G. Caratù, J. Liñares-Blanco, M. Berasategi, et al. 2026. Interpretable inflammation landscape of circulating immune cells. *Nat. Med.* 32:633–644. https://doi.org/10.1038/s41591-025-04126-3

Jin, S., M.V. Plikus, and Q. Nie. 2025. CellChat for systematic analysis of cell–cell communication from single-cell transcriptomics. *Nat. Protoc.* 20: 180–219. https://doi.org/10.1038/s41596-024-01045-4

Jongstra-Bilen, J., M. Haidari, S.-N. Zhu, M. Chen, D. Guha, and M.I. Cybulsky. 2006. Low-grade chronic inflammation in regions of the normal mouse arterial intima predisposed to atherosclerosis. *J. Exp. Med.* 203: 2073–2083. https://doi.org/10.1084/jem.20060245

Ju, L., Y. Chen, L. Xue, X. Du, and C. Zhu. 2016. Cooperative unfolding of distinctive mechanoreceptor domains transduces force into signals. *Elife*. 5:e15447. https://doi.org/10.7554/eLife.15447

Ju, L., J.D. McFadyen, S. Al-Daher, I. Alwis, Y. Chen, L.L. Tønnesen, S. Maiocchi, B. Coulter, A.C. Calkin, E.I. Felner, et al. 2018. Compression force sensing regulates integrin $\alpha_{IIb}\beta_3$ adhesive function on diabetic platelets. *Nat. Commun.* 9:1087. https://doi.org/10.1038/s41467-018-03430-6

Jung, W.-H., E. Humann, J.M. Price, Y. Binenbaum, A. Haseki, S. Iyer, and D.J. Mooney. 2025. Matrix viscoelasticity regulates dendritic cell migration and immune priming. *bioRxiv*. https://doi.org/10.1101/2025.09.28.678961 (Preprint posted September 30, 2025).

Kalukula, Y., G. Ciccone, D. Mohammed, A. Procès, M. Versaevel, A. Deridoux, L. Ergot, Z. Barbier, M. Mansy, R. Aucouturier, et al. 2025. Unlocking the therapeutic potential of cellular mechanobiology. *Sci. Adv.* 11: eaea6817. https://doi.org/10.1126/sciadv.aea6817

Karling, T., and H. Weavers. 2025. Immune cells adapt to confined environments in vivo to optimise nuclear plasticity for migration. *EMBO Rep.* 26: 1238–1268. https://doi.org/10.1038/s44319-025-00381-0

Kaur, A., B.L. Ecker, S.M. Douglass, C.H. Kugel, M.R. Webster, F.V. Almeida, R. Somasundaram, J. Hayden, E. Ban, H. Ahmadzadeh, et al. 2019. Remodeling of the collagen matrix in aging skin promotes melanoma metastasis and affects immune cell motility. *Cancer Discov.* 9:64–81. https://doi.org/10.1158/2159-8290.CD-18-0193

Kawanami, O., V.J. Ferrans, J.D. Fulmer, and R.G. Crystal. 1979. Ultrastructure of pulmonary mast cells in patients with fibrotic lung disorders. *Lab. Invest.* 40:717–734.

Keshavanarayana, P., R. Aparicio-Yuste, F. Spill, M.J. Gomez-Benito, and E.E. Bastounis. 2025. Leveraging computational modeling to explore epithelial and endothelial cell monolayer mechanobiology. *Trends Cell Biol.* 35:799–813. https://doi.org/10.1016/j.tcb.2024.12.014

Khan, K.M., and A. Scott. 2009. Mechanotherapy: How physical therapists' prescription of exercise promotes tissue repair. *Br. J. Sports Med.* 43: 247–252. https://doi.org/10.1136/bjsm.2008.054239

Khanmohammadi, M., H. Danish, N.C. Sekar, S.A. Suarez, C. Chheang, K. Peter, K. Khoshmanesh, and S. Baratchi. 2024. Cyclic stretch enhances neutrophil extracellular trap formation. *BMC Biol.* 22:209. https://doi.org/10.1186/s12915-024-02009-6

Khanmohammadi, M., Y. Mirzaalikhan, and S. Baratchi. 2025a. Immunity in motion: The role of mechanics in macrophage biology. *Cell Chem. Biol.* 32:1442–1457. https://doi.org/10.1016/j.chembiol.2025.11.004

Khanmohammadi, M., Y. Mirzaalikhan, H. Danish, T. Torquato, and S. Baratchi. 2025b. Biomechanic regulation of neutrophil extracellular traps in the cardiovascular system. *Trends Immunol.* 46:690–703. https://doi.org/10.1016/j.it.2025.08.001

Kılıç, A., A. Ameli, J.-A. Park, A.T. Kho, K. Tantisira, M. Santolini, F. Cheng, J.A. Mitchel, M. McGill, M.J. O'Sullivan, et al. 2020. Mechanical forces induce an asthma gene signature in healthy airway epithelial cells. *Sci. Rep.* 10:966. https://doi.org/10.1038/s41598-020-57755-8

Kim, J.-H., G. Lee, Y. Won, M. Lee, J.-S. Kwak, C.-H. Chun, and J.-S. Chun. 2015. Matrix cross-linking–mediated mechanotransduction promotes posttraumatic osteoarthritis. *Proc. Natl. Acad. Sci. USA.* 112:9424–9429. https://doi.org/10.1073/pnas.1505700112

Kim, H.J., H. Li, J.J. Collins, and D.E. Ingber. 2016. Contributions of microbiome and mechanical deformation to intestinal bacterial overgrowth and inflammation in a human gut-on-a-chip. *Proc. Natl. Acad. Sci. USA.* 113:E7–E15. https://doi.org/10.1073/pnas.1522193112

Knaus, U.G., R.A. Clark, W.M. Nauseef, M.C. Dinauer, T.L. Leto, and V. Jaquet. 2024. Challenging the role of a NOX4-Piezo1 axis in neutrophil bactericidal function. *Immunity*. 57:1716–1718. https://doi.org/10.1016/j.immuni.2024.07.012

Knodler, L.A., S.M. Crowley, H.P. Sham, H. Yang, M. Wrande, C. Ma, R.K. Ernst, O. Steele-Mortimer, J. Celli, and B.A. Vallance. 2014. Noncanonical inflammasome activation of caspase-4/caspase-11 mediates epithelial defenses against enteric bacterial pathogens. *Cell Host Microbe*. 16:249–256. https://doi.org/10.1016/j.chom.2014.07.002

Konig, S., V. Jayarajan, S. Wray, R. Kamm, and E. Moeendarbary. 2025. Mechanobiology of the blood-brain barrier during development, disease and ageing. *Nat. Commun.* 16:7233. https://doi.org/10.1038/s41467-025-61888-7

Kopf, A., J. Renkawitz, R. Hauschild, I. Girkontaite, K. Tedford, J. Merrin, O. Thorn-Seshold, D. Trauner, H. Häcker, K.-D. Fischer, et al. 2020. Microtubules control cellular shape and coherence in amoeboid migrating cells. *J. Cell Biol.* 219:e201907154. https://doi.org/10.1083/jcb.201907154

Krausgruber, T., N. Fortelny, V. Fife-Gernedl, M. Senekowitsch, L.C. Schuster, A. Lercher, A. Nemc, C. Schmidl, A.F. Rendeiro, A. Bergthaler, and C. Bock. 2020. Structural cells are key regulators of organ-specific immune responses. *Nature*. 583:296–302. https://doi.org/10.1038/s41586-020-2424-4

Kroll, J., R. Hauschild, A. Kuznetcov, K. Stefanowski, M.D. Hermann, J. Merrin, L. Shafeek, A. Müller-Taubenberger, and J. Renkawitz. 2023. Adaptive pathfinding by nucleokinesis during amoeboid migration. *EMBO J.* 42:e114557. https://doi.org/10.15252/embj.2023114557

Kubánková, M., B. Hohberger, J. Hoffmanns, J. Fürst, M. Herrmann, J. Guck, and M. Kräter. 2021. Physical phenotype of blood cells is altered in COVID-19. *Biophys. J.* 120:2838–2847. https://doi.org/10.1016/j.bpj.2021.05.025

Lam, W.A., O. Chaudhuri, A. Crow, K.D. Webster, T.-D. Li, A. Kita, J. Huang, and D.A. Fletcher. 2011. Mechanics and contraction dynamics of single platelets and implications for clot stiffening. *Nat. Mater.* 10:61–66. https://doi.org/10.1038/nmat2903

Lammerding, J., P.C. Schulze, T. Takahashi, S. Kozlov, T. Sullivan, R.D. Kamm, C.L. Stewart, and R.T. Lee. 2004. Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. *J. Clin. Invest.* 113: 370–378. https://doi.org/10.1172/JCI19670

Lämmermann, T., B.L. Bader, S.J. Monkley, T. Worbs, R. Wedlich-Söldner, K. Hirsch, M. Keller, R. Förster, D.R. Critchley, R. Fässler, and M. Sixt. 2008. Rapid leukocyte migration by integrin-independent flowing and squeezing. *Nature*. 453:51–55. https://doi.org/10.1038/nature06887

Lämmermann, T., J. Renkawitz, X. Wu, K. Hirsch, C. Brakebusch, and M. Sixt. 2009. Cdc42-dependent leading edge coordination is essential for interstitial dendritic cell migration. *Blood*. 113:5703–5710. https://doi.org/10.1182/blood-2008-11-191882

Lampi, M.C., and C.A. Reinhart-King. 2018. Targeting extracellular matrix stiffness to attenuate disease: From molecular mechanisms to clinical trials. *Sci. Transl. Med.* 10:eaao0475. https://doi.org/10.1126/scitranslmed.aao0475

Lan, Y., J. Lu, S. Zhang, C. Jie, C. Chen, C. Xiao, C. Qin, and D. Cheng. 2024. Piezo1-mediated mechanotransduction contributes to disturbed flow-induced atherosclerotic endothelial inflammation. *J. Am. Heart Assoc.* 13: e035558. https://doi.org/10.1161/JAHA.123.035558

Langston, P.K., J. Vijaya Raghavan, C. Benoist, and D. Mathis. 2026. Piezo1-dependent activation of stromal cells ignites muscle inflammation in exercise and injury and is associated with inflammaging. *Nat. Immunol.* 27:543–555. https://doi.org/10.1038/s41590-026-02435-4

Lasch, M., E.C. Kleinert, S. Meister, K. Kumaraswami, J.-I. Buchheim, T. Grantzow, T. Lautz, S. Salpisti, S. Fischer, K. Troidl, et al. 2019. Extracellular RNA released due to shear stress controls natural bypass growth by mediating mechanotransduction in mice. *Blood*. 134:1469–1479. https://doi.org/10.1182/blood.2019001392

Lee, W., H.A. Leddy, Y. Chen, S.H. Lee, N.A. Zelenski, A.L. McNulty, J. Wu, K.N. Beicker, J. Coles, S. Zauscher, et al. 2014. Synergy between Piezo1 and Piezo2 channels confers high-strain mechanosensitivity to articular cartilage. *Proc. Natl. Acad. Sci. USA.* 111:E5114–E5122. https://doi.org/10.1073/pnas.1414298111

Lee, H., L. Gu, D.J. Mooney, M.E. Levenston, and O. Chaudhuri. 2017. Mechanical confinement regulates cartilage matrix formation by chondrocytes. *Nat. Mater.* 16:1243–1251. https://doi.org/10.1038/nmat4993

Lee, H.-P., R. Stowers, and O. Chaudhuri. 2019. Volume expansion and TRPV4 activation regulate stem cell fate in three-dimensional microenvironments. *Nat. Commun.* 10:529. https://doi.org/10.1038/s41467-019-08465-x

Lee, W., R.J. Nims, A. Savadipour, Q. Zhang, H.A. Leddy, F. Liu, A.L. McNulty, Y. Chen, F. Guilak, and W.B. Liedtke. 2021. Inflammatory signaling sensitizes Piezo1 mechanotransduction in articular chondrocytes as a pathogenic feed-forward mechanism in osteoarthritis. *Proc. Natl. Acad. Sci. USA.* 118:e2001611118. https://doi.org/10.1073/pnas.2001611118

Lee, T., E.H.Y. Cheung, K.C.M. Lee, D.M.D. Siu, M.C.K. Lo, E.Y. Lam, R. Goswami, S. Girardo, K. Kim, F. Reichel, et al. 2025. High-throughput multimodal optofluidic biophysical imaging cytometry. *Lab. Chip*. 25: 5329–5341. https://doi.org/10.1039/D5LC00381D

Lee, Y., X. Wu, A. Narayanan, S. Chakraborty, C.L. Heaps, and M. Muthuchamy. 2026. Exercise training ameliorates myocardial dysfunction through fibronectin-mediated mechanotransduction in a swine model of ischemic heart disease. *Am. J. Physiol. Heart Circ. Physiol.* 330: H31–H45. https://doi.org/10.1152/ajpheart.00133.2025

Leithner, A., L.M. Altenburger, R. Hauschild, F.P. Assen, K. Rottner, T.E.B. Stradal, A. Diz-Muñoz, J.V. Stein, and M. Sixt. 2021. Dendritic cell actin dynamics control contact duration and priming efficiency at the immunological synapse. *J. Cell Biol.* 220:e202006081. https://doi.org/10.1083/jcb.202006081

Leung, V.Y.-f., J. Shen, V.W. Wong, J. Abrigo, G.L. Wong, A.M. Chim, S.H. Chu, A.W. Chan, P.C. Choi, A.T. Ahuja, et al. 2013. Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: Comparison of shear-wave elastography and transient elastography with liver biopsy correlation. *Radiology*. 269:910–918. https://doi.org/10.1148/radiol.13130128

Leung, C.M., P. de Haan, K. Ronaldson-Bouchard, G.-A. Kim, J. Ko, H.S. Rho, Z. Chen, P. Habibovic, N.L. Jeon, S. Takayama, et al. 2022. A guide to the organ-on-a-chip. *Nat. Rev. Methods Primers*. 2:33. https://doi.org/10.1038/s43586-022-00118-6

Leyva-Castillo, J.-M., C. Galand, C. Kam, O. Burton, M. Gurish, M.A. Musser, J.D. Goldsmith, E. Hait, S. Nurko, F. Brombacher, et al. 2019. Mechanical skin injury promotes food anaphylaxis by driving intestinal mast cell expansion. *Immunity*. 50:1262–1275.e4. https://doi.org/10.1016/j.immuni.2019.03.023

Li, D., and M. Wu. 2021. Pattern recognition receptors in health and diseases. *Signal. Transduct. Target. Ther.* 6:291. https://doi.org/10.1038/s41392-021-00687-0

Li, J., B. Hou, S. Tumova, K. Muraki, A. Bruns, M.J. Ludlow, A. Sedo, A.J. Hyman, L. McKeown, R.S. Young, et al. 2014. Piezo1 integration of vascular architecture with physiological force. *Nature*. 515:279–282. https://doi.org/10.1038/nature13701

Li, X., C. Li, W. Zhang, Y. Wang, P. Qian, and H. Huang. 2023. Inflammation and aging: Signaling pathways and intervention therapies. *Signal.*

Transduct. Target. Ther. 8:239. https://doi.org/10.1038/s41392-023-01502-8

Li, J., J. Zhu, O. Gray, D.R. Sobreira, D. Wu, R.-T. Huang, B. Miao, N.J. Sakabe, M.D. Krause, M.U. Kaikkonen, et al. 2024a. Mechanosensitive super-enhancers regulate genes linked to atherosclerosis in endothelial cells. *J. Cell Biol.* 223:e202211125. https://doi.org/10.1083/jcb.202211125

Li, M., J. Roeder, J. Blázquez-Prieto, S. Schulz, J. Naujox, J. Falivene, L. Erfinanda, W. Liedtke, G.M. Albaiceta, W.M. Kuebler, and L. Michalick. 2024b. Calcium-activated potassium channels as amplifiers of TRPV4-mediated pulmonary edema formation in male mice. *Anesthesiology*. 141: 913–928. https://doi.org/10.1097/ALN.0000000000005171

Li, Z., J. Tang, L. Zhou, J. Mao, W. Wang, Z. Huang, L. Zhang, J. Wu, X. Jiang, Z. Ding, et al. 2025. MicroSphere 3D structures delay tissue senescence through mechanotransduction. *ACS Nano*. 19:2695–2714. https://doi.org/10.1021/acsnano.4c14874

Li, W., L.N. Tu, L. Hsieh, J.R. Smith, Y.-T. Yeh, A. Sinyagin, E.G.B. Evans, M. Ghassemian, A. Timms, K. Charette, et al. 2026. A shear stress-responsive pathway in monocytes drives cardiopulmonary bypass-induced inflammation via spectrin/RAF1/store-operated calcium entry. *Cell Rep.* 45:116903. https://doi.org/10.1016/j.celrep.2025.116903

Liao, Y., L. Yuan, T.R. Sornapudi, M. Land, R. Gupta, and G.V. Shivashankar. 2026. Chromatin accessibility regulates age-dependent nuclear mechanotransduction. *Proc. Natl. Acad. Sci. USA*. 123:e2522217123. https://doi.org/10.1073/pnas.2522217123

Lim, M., S. Park, Y.H. Joo, S.E. Kim, M.H. Ham, T. Kim, K. Kwak, S.J. Kim, J.C. Lee, S.H. Park, and H.Y. Kim. 2025. Piezo1-mediated mechanotransduction regulates the translational activity, function and lung pathogenicity of group 2 innate lymphoid cells. *Signal. Transduct. Target. Ther.* 10:269. https://doi.org/10.1038/s41392-025-02350-4

Lin, Y.-M., F. Li, and X.-Z. Shi. 2014. Mechanical stress is a pro-inflammatory stimulus in the gut: In vitro, in vivo and ex vivo evidence. *PLoS One*. 9: e106242. https://doi.org/10.1371/journal.pone.0106242

Liu, F., J.D. Mih, B.S. Shea, A.T. Kho, A.S. Sharif, A.M. Tager, and D.J. Tschumperlin. 2010. Feedback amplification of fibrosis through matrix stiffening and COX-2 suppression. *J. Cell Biol.* 190:693–706. https://doi.org/10.1083/jcb.201004082

Liu, F., D. Lagares, K.M. Choi, L. Stopfer, A. Marinković, V. Vrbanac, C.K. Probst, S.E. Hiemer, T.H. Sisson, J.C. Horowitz, et al. 2015a. Mechanosignaling through YAP and TAZ drives fibroblast activation and fibrosis. *Am. J. Physiol. Lung Cell Mol. Physiol.* 308:L344–L357. https://doi.org/10.1152/ajplung.00300.2014

Liu, Y.-J., M. Le Berre, F. Lautenschlaeger, P. Maiuri, A. Callan-Jones, M. Heuzé, T. Takaki, R. Voituriez, and M. Piel. 2015b. Confinement and low adhesion induce fast amoeboid migration of slow mesenchymal cells. *Cell*. 160:659–672. https://doi.org/10.1016/j.cell.2015.01.007

Liu, W., K. Ma, S.H. Kwon, R. Garg, Y.R. Patta, T. Fujiwara, and G.C. Gurtner. 2017. The abnormal architecture of healed diabetic ulcers is the result of FAK degradation by calpain 1. *J. Invest. Dermatol.* 137:1155–1165. https://doi.org/10.1016/j.jid.2016.11.039

Liu, M., M. Yan, H. Lv, B. Wang, X. Lv, H. Zhang, S. Xiang, J. Du, T. Liu, Y. Tian, et al. 2020. Macrophage K63-linked ubiquitination of YAP promotes its nuclear localization and exacerbates atherosclerosis. *Cell Rep.* 32:107990. https://doi.org/10.1016/j.celrep.2020.107990

Liu, Y., T. Zhang, H. Zhang, J. Li, N. Zhou, R. Fiskesund, J. Chen, J. Lv, J. Ma, H. Zhang, et al. 2021. Cell softness prevents cytolytic T-cell killing of tumor-repopulating cells. *Cancer Res.* 81:476–488. https://doi.org/10.1158/0008-5472.CAN-20-2569

Liu, Q., D. Wang, X. Yang, F. Ma, W. Han, J. Hu, and Q. Mei. 2023. The mechanosensitive ion channel PIEZO1 in intestinal epithelial cells mediates inflammation through the NOD-like receptor 3 pathway in Crohn's disease. *Inflamm. Bowel Dis.* 29:103–115. https://doi.org/10.1093/ibd/izac152

Liu, Z., Y.-R. Li, Y. Yang, Y. Zhu, W. Yuan, T. Hoffman, Y. Wu, E. Zhu, J. Zarubova, J. Shen, et al. 2024. Viscoelastic synthetic antigen-presenting cells for augmenting the potency of cancer therapies. *Nat. Biomed. Eng.* 8:1615–1633. https://doi.org/10.1038/s41551-024-01272-w

Liu, Y., J. Zhang, Y. Zhao, F. Fang, S. Zhang, Q. An, J. Zhuang, F. Xu, and F. Li. 2025. Mechanotransduction activates microglia and impairs phagocytosis in stiff amyloid-β plaques. *Adv. Sci.* 12:e03389. https://doi.org/10.1002/advs.202503389

Liu, Z., G. Chen, M.-S. Jo, V. Vogel, J. Chen, J.A. Rogers, and S. Li. 2026. Mechanomedicine. *Nat. Rev. Bioeng.* 4:216–235. https://doi.org/10.1038/s44222-025-00391-6

Liu-Chittenden, Y., B. Huang, J.S. Shim, Q. Chen, S.-J. Lee, R.A. Anders, J.O. Liu, and D. Pan. 2012. Genetic and pharmacological disruption of the TEAD–YAP complex suppresses the oncogenic activity of YAP. *Genes Dev.* 26:1300–1305. https://doi.org/10.1101/gad.192856.112

Lomakin, A.J., C.J. Cattin, D. Cuvelier, Z. Alraies, M. Molina, G.P.F. Nader, N. Srivastava, P.J. Sáez, J.M. Garcia-Arcos, I.Y. Zhitnyak, et al. 2020. The nucleus acts as a ruler tailoring cell responses to spatial constraints. *Science*. 370:eaba2894. https://doi.org/10.1126/science.aba2894

López-Otín, C., M.A. Blasco, L. Partridge, M. Serrano, and G. Kroemer. 2023. Hallmarks of aging: An expanding universe. *Cell*. 186:243–278. https://doi.org/10.1016/j.cell.2022.11.001

Lu, Z., Z. Zhang, Z. Xu, A. Abdulraouf, W. Zhou, and J. Cao. 2026. Organism-wide cellular dynamics and epigenomic remodeling in mammalian aging. *Science*. 391:eadw6273. https://doi.org/10.1126/science.adw6273

Luo, J., A. Qian, L.K. Oetjen, W. Yu, P. Yang, J. Feng, Z. Xie, S. Liu, S. Yin, D. Dryn, et al. 2018. TRPV4 channel signaling in macrophages promotes gastrointestinal motility via direct effects on smooth muscle cells. *Immunity*. 49:107–119.e4. https://doi.org/10.1016/j.immuni.2018.04.021

Luo, S., X. Zhao, J. Jiang, B. Deng, S. Liu, H. Xu, Q. Tan, Y. Chen, Z. Zhang, X. Pan, et al. 2023. Piezo1 specific deletion in macrophage protects the progression of liver fibrosis in mice. *Theranostics*. 13:5418–5434. https://doi.org/10.7150/thno.86103

Luo, J., R. Huang, Y. Tu, S. Zheng, X. Zhang, Q. Luo, and G. Song. 2026. Nuclear envelope rupture and DNA damage driven by high pressure are mediated by F-actin and induce hepatocyte inflammation via cGAS-STING. *Int. Immunopharmacol.* 168:115841. https://doi.org/10.1016/j.intimp.2025.115841

Luu, T.U., S.C. Gott, B.W.K. Woo, M.P. Rao, and W.F. Liu. 2015. Micro- and nanopatterned topographical cues for regulating macrophage cell shape and phenotype. *ACS Appl. Mater. Interfaces*. 7:28665–28672. https://doi.org/10.1021/acsami.5b10589

Ma, K., S.H. Kwon, J. Padmanabhan, D. Duscher, A.A. Trotsyuk, Y. Dong, M. Inayathullah, J. Rajadas, and G.C. Gurtner. 2018. Controlled delivery of a focal adhesion kinase inhibitor results in accelerated wound closure with decreased scar formation. *J. Invest. Dermatol.* 138:2452–2460. https://doi.org/10.1016/j.jid.2018.04.034

Ma, S., A.E. Dubin, Y. Zhang, S.A.R. Mousavi, Y. Wang, A.M. Coombs, M. Loud, I. Andolfo, and A. Patapoutian. 2021. A role of PIEZO1 in iron metabolism in mice and humans. *Cell*. 184:969–982.e13. https://doi.org/10.1016/j.cell.2021.01.024

Ma, M., W. Jiang, and R. Zhou. 2024. DAMPs and DAMP-sensing receptors in inflammation and diseases. *Immunity*. 57:752–771. https://doi.org/10.1016/j.immuni.2024.03.002

Ma, J., N. Xie, Z. Wang, X. Liang, Y. Han, Q. Zhao, M. Wang, H. Lu, W. Kou, W. Alazawi, et al. 2026. Liver stiffness rises early in MASLD and drives inflammation, lipid dysmetabolism, and fibrosis via piezo1–YAP mechanotransduction. *Adv. Sci.* 13:e19109. https://doi.org/10.1002/advs.202519109

Mack, J.J., T.S. Mosqueiro, B.J. Archer, W.M. Jones, H. Sunshine, G.C. Faas, A. Briot, R.L. Aragón, T. Su, M.C. Romay, et al. 2017. NOTCH1 is a mechanosensor in adult arteries. *Nat. Commun.* 8:1620. https://doi.org/10.1038/s41467-017-01741-8

Maione, A.G., A. Smith, O. Kashpur, V. Yanez, E. Knight, D.J. Mooney, A. Veves, M. Tomic-Canic, and J.A. Garlick. 2016. Altered ECM deposition by diabetic foot ulcer-derived fibroblasts implicates fibronectin in chronic wound repair. *Wound Repair Regen.* 24:630–643. https://doi.org/10.1111/wrr.12437

Maiques, O., M.C. Sallan, R. Laddach, P. Pandya, A. Varela, E. Crosas-Molist, J. Barcelo, O. Courbot, Y. Liu, V. Graziani, et al. 2025. Matrix mechanosensing at the invasive front induces a cytoskeletal and transcriptional memory supporting metastasis. *Nat. Commun.* 16:1394. https://doi.org/10.1038/s41467-025-56299-7

Maiuri, P., J.-F. Rupprecht, S. Wieser, V. Ruprecht, O. Bénichou, N. Carpi, M. Coppey, S. De Beco, N. Gov, C.-P. Heisenberg, et al. 2015. Actin flows mediate a universal coupling between cell speed and cell persistence. *Cell*. 161:374–386. https://doi.org/10.1016/j.cell.2015.01.056

Mammadova-Bach, E., T. Gudermann, and A. Braun. 2023. Platelet mechanotransduction: Regulatory cross talk between mechanosensitive receptors and calcium channels. *Arterioscler. Thromb. Vasc. Biol.* 43: 1339–1348. https://doi.org/10.1161/ATVBAHA.123.318341

Manwaring-Mueller, M., H. Du, T.R. Valentino, M. Fuentealba, A. Chebykin, F. Wu, D. Furman, and D.A. Winer. 2026. The case for space as a model of accelerated aging. *Nat. Aging*. 6:752–769. https://doi.org/10.1038/s43587-026-01105-2

Martinez, V.G., V. Pankova, L. Krasny, T. Singh, S. Makris, I.J. White, A.C. Benjamin, S. Dertschnig, H.L. Horsnell, J. Kriston-Vizi, et al. 2019. Fibroblastic reticular cells control conduit matrix deposition during

lymph node expansion. *Cell Rep.* 29:2810–2822.e5. https://doi.org/10.1016/j.celrep.2019.10.103

Martínez-Sánchez, L.D.C., P.A. Ngo, R. Pradhan, L.-S. Becker, D. Boehringer, D. Soteriou, M. Kubankova, C. Schweitzer, T. Koch, V. Thonn, et al. 2023. Epithelial RAC1-dependent cytoskeleton dynamics controls cell mechanics, cell shedding and barrier integrity in intestinal inflammation. *Gut*. 72:275–294. https://doi.org/10.1136/gutjnl-2021-325520

Mascharak, S., H.E. desJardins-Park, M.F. Davitt, M. Griffin, M.R. Borrelli, A.L. Moore, K. Chen, B. Duoto, M. Chinta, D.S. Foster, et al. 2021. Preventing *Engrailed-1* activation in fibroblasts yields wound regeneration without scarring. *Science*. 372:eaba2374. https://doi.org/10.1126/science.aba2374

Mascharak, S., J.L. Guo, M. Griffin, C.E. Berry, D.C. Wan, and M.T. Longaker. 2024. Modelling and targeting mechanical forces in organ fibrosis. *Nat. Rev. Bioeng.* 2:305–323. https://doi.org/10.1038/s44222-023-00144-3

Mascharak, S., M. Griffin, H.E. Talbott, J.L. Guo, J. Parker, A.G. Morgan, C. Valencia, M.M. Kuhnert, D.J. Li, N.E. Liang, et al. 2025. Inhibiting mechanotransduction prevents scarring and yields regeneration in a large animal model. *Sci. Transl. Med.* 17:eadt6387. https://doi.org/10.1126/scitranslmed.adt6387

Masters, T.A., B. Pontes, V. Viasnoff, Y. Li, and N.C. Gauthier. 2013. Plasma membrane tension orchestrates membrane trafficking, cytoskeletal remodeling, and biochemical signaling during phagocytosis. *Proc. Natl. Acad. Sci. USA*. 110:11875–11880. https://doi.org/10.1073/pnas.1301766110

McCormick, B., H.E. Craig, J.Y. Chu, L.M. Carlin, M. Canel, F. Wollweber, M. Toivakka, M. Michael, A.L. Astier, L. Norton, et al. 2019. A negative feedback loop regulates integrin inactivation and promotes neutrophil recruitment to inflammatory sites. *J. Immunol.* 203:1579–1588. https://doi.org/10.4049/jimmunol.1900443

McNamara, S.L., B.R. Seo, B.R. Freedman, E.B. Roloson, J.T. Alvarez, C.T. O'Neill, H.H. Vandenburgh, C.J. Walsh, and D.J. Mooney. 2023. Anti-inflammatory therapy enables robot-actuated regeneration of aged muscle. *Sci. Robot.* 8:eadd9369. https://doi.org/10.1126/scirobotics.add9369

McQuattie-Pimentel, A.C., Z. Ren, N. Joshi, S. Watanabe, T. Stoeger, M. Chi, Z. Lu, L. Sichizya, R.P. Aillon, C.-I. Chen, et al. 2021. The lung microenvironment shapes a dysfunctional response of alveolar macrophages in aging. *J. Clin. Invest.* 131:e140299. https://doi.org/10.1172/JCI140299

McWhorter, F.Y., T. Wang, P. Nguyen, T. Chung, and W.F. Liu. 2013. Modulation of macrophage phenotype by cell shape. *Proc. Natl. Acad. Sci. USA*. 110:17253–17258. https://doi.org/10.1073/pnas.1308887110

Mehl, J.L., A. Earle, J. Lammerding, M. Mhlanga, V. Vogel, and N. Jain. 2022. Blockage of lamin-A/C loss diminishes the pro-inflammatory macrophage response. *iScience*. 25:105528. https://doi.org/10.1016/j.isci.2022.105528

Mehta, V., K.-L. Pang, D. Rozbesky, K. Nather, A. Keen, D. Lachowski, Y. Kong, D. Karia, M. Ameismeier, J. Huang, et al. 2020. The guidance receptor plexin D1 is a mechanosensor in endothelial cells. *Nature*. 578:290–295. https://doi.org/10.1038/s41586-020-1979-4

Mehta, V., K.-L. Pang, C.S. Givens, Z. Chen, J. Huang, D.T. Sweet, H. Jo, J.S. Reader, and E. Tzima. 2021. Mechanical forces regulate endothelial-to-mesenchymal transition and atherosclerosis via an Alk5-Shc mechanotransduction pathway. *Sci. Adv.* 7:eabg5060. https://doi.org/10.1126/sciadv.abg5060

Meizlish, M.L., Y. Kimura, S.D. Pope, R. Matta, C. Kim, N.H. Philip, L. Meyaard, A. Gonzalez, and R. Medzhitov. 2024. Mechanosensing regulates tissue repair program in macrophages. *Sci. Adv.* 10:eadk6906. https://doi.org/10.1126/sciadv.adk6906

Mejía-Ramírez, E., P.I. Picazo, B. Walter, S. Montserrat-Vazquez, F. Affuso, S. Wieser, F. Pezzano, L. Reymond, J. Castillo-Robles, F. Matteini, et al. 2025. Targeting RhoA nuclear mechanoactivity rejuvenates aged hematopoietic stem cells. *Nat. Aging*. 6:68–87. https://doi.org/10.1038/s43587-025-01014-w

Meli, V.S., H. Atcha, P.K. Veerasubramanian, R.R. Nagalla, T.U. Luu, E.Y. Chen, C.F. Guerrero-Juarez, K. Yamaga, W. Pandori, J.Y. Hsieh, et al. 2020. YAP-mediated mechanotransduction tunes the macrophage inflammatory response. *Sci. Adv.* 6:eabb8471. https://doi.org/10.1126/sciadv.abb8471

Meng, Z., T. Moroishi, V. Mottier-Pavie, S.W. Plouffe, C.G. Hansen, A.W. Hong, H.W. Park, J.-S. Mo, W. Lu, S. Lu, et al. 2015. MAP4K family kinases act in parallel to MST1/2 to activate LATS1/2 in the Hippo pathway. *Nat. Commun.* 6:8357. https://doi.org/10.1038/ncomms9357

Meng, K.P., F.S. Majedi, T.J. Thauland, and M.J. Butte. 2020. Mechanosensing through YAP controls T cell activation and metabolism. *J. Exp. Med.* 217:e20200053. https://doi.org/10.1084/jem.20200053

Mercado-Perez, A., and A. Beyder. 2022. Gut feelings: Mechanosensing in the gastrointestinal tract. *Nat. Rev. Gastroenterol. Hepatol.* 19:283–296. https://doi.org/10.1038/s41575-021-00561-y

Merino-Cortés, S.V., S.R. Gardeta, S. Roman-Garcia, A. Martínez-Riaño, J. Pineau, R. Liebana, I. Merida, A.-M.L. Dumenil, P. Pierobon, J. Husson, et al. 2020. Diacylglycerol kinase ζ promotes actin cytoskeleton remodeling and mechanical forces at the B cell immune synapse. *Sci. Signal.* 13:eaaw8214. https://doi.org/10.1126/scisignal.aaw8214

Mia, M.M., D.M. Cibi, S.A.B. Abdul Ghani, W. Song, N. Tee, S. Ghosh, J. Mao, E.N. Olson, and M.K. Singh. 2020. YAP/TAZ deficiency reprograms macrophage phenotype and improves infarct healing and cardiac function after myocardial infarction. *PLoS Biol.* 18:e3000941. https://doi.org/10.1371/journal.pbio.3000941

Mia, M.M., S.A.B.A. Ghani, D.M. Cibi, H. Bogireddi, U. Nilanthi, A. Selvan, W.S.F. Wong, and M.K. Singh. 2025. YAP/TAZ are crucial regulators of macrophage-mediated pulmonary inflammation and fibrosis after bleomycin-induced injury. *Eur. Respir. J.* 65:2301544. https://doi.org/10.1183/13993003.01544-2023

Miao, S., X. Dai, X. Li, Z. Chen, Y. Wang, T. Ye, Y. Ying, Y. Yu, A. Wu, H. Song, et al. 2025. Endothelial mechanosensitive transcription factor BHLHE40 induced by Piezo1 suppresses endothelial ferroptosis and inflammation via SLC7A11. *Cell Death Discov.* 12:47. https://doi.org/10.1038/s41420-025-02909-8

Michalick, L., L. Erfinanda, U. Weichelt, M. van der Giet, W. Liedtke, and W.M. Kuebler. 2017. Transient receptor potential vanilloid 4 and serum glucocorticoid–regulated kinase 1 are critical mediators of lung injury in overventilated mice in vivo. *Anesthesiology*. 126:300–311. https://doi.org/10.1097/ALN.0000000000001443

Misharin, A.V., L. Morales-Nebreda, P.A. Reyfman, C.M. Cuda, J.M. Walter, A.C. McQuattie-Pimentel, C.-I. Chen, K.R. Anekalla, N. Joshi, K.J.N. Williams, et al. 2017. Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span. *J. Exp. Med.* 214:2387–2404. https://doi.org/10.1084/jem.20162152

Mittelheisser, V., V. Gensbittel, L. Bonati, W. Li, L. Tang, and J.G. Goetz. 2024. Evidence and therapeutic implications of biomechanically regulated immunosurveillance in cancer and other diseases. *Nat. Nanotechnol.* 19:281–297. https://doi.org/10.1038/s41565-023-01535-8

Mitten, E.K., and G. Baffy. 2022. Mechanotransduction in the pathogenesis of non-alcoholic fatty liver disease. *J. Hepatol.* 77:1642–1656. https://doi.org/10.1016/j.jhep.2022.08.028

Moreau, H.D., C. Blanch-Mercader, R. Attia, M. Maurin, Z. Alraies, D. Sanséau, O. Malbec, M.-G. Delgado, P. Bousso, J.-F. Joanny, et al. 2019. Macropinocytosis overcomes directional bias in dendritic cells due to hydraulic resistance and facilitates space exploration. *Dev. Cell*. 49:171–188.e5. https://doi.org/10.1016/j.devcel.2019.03.024

Moretti, L., J. Stalfort, T.H. Barker, and D. Abebayehu. 2022. The interplay of fibroblasts, the extracellular matrix, and inflammation in scar formation. *J. Biol. Chem.* 298:101530. https://doi.org/10.1016/j.jbc.2021.101530

Morgan, E.F., G.U. Unnikrisnan, and A.I. Hussein. 2018. Bone mechanical properties in healthy and diseased states. *Annu. Rev. Biomed. Eng.* 20:119–143. https://doi.org/10.1146/annurev-bioeng-062117-121139

Morikis, V.A., S. Chase, T. Wun, E.L. Chaikof, J.L. Magnani, and S.I. Simon. 2017. Selectin catch-bonds mechanotransduce integrin activation and neutrophil arrest on inflamed endothelium under shear flow. *Blood*. 130:2101–2110. https://doi.org/10.1182/blood-2017-05-783027

Morikis, V.A., E. Masadeh, and S.I. Simon. 2020. Tensile force transmitted through LFA-1 bonds mechanoregulate neutrophil inflammatory response. *J. Leukoc. Biol.* 108:1815–1828. https://doi.org/10.1002/JLB.3A0520-100RR

Mukhopadhyay, A., V. Natarajan, Y. Komarova, and A.B. Malik. 2024a. Neutrophils meet their fate in endothelial adherens junctions. *Immunity*. 57:1719–1720. https://doi.org/10.1016/j.immuni.2024.07.015

Mukhopadhyay, A., Y. Tsukasaki, W.C. Chan, J.P. Le, M.L. Kwok, J. Zhou, V. Natarajan, N. Mostafazadeh, M. Maienschein-Cline, I. Papautsky, et al. 2024b. trans-Endothelial neutrophil migration activates bactericidal function via Piezo1 mechanosensing. *Immunity*. 57:52–67.e10. https://doi.org/10.1016/j.immuni.2023.11.007

Murphy, M.C., J. Huston, C.R. Jack, K.J. Glaser, A. Manduca, J.P. Felmlee, and R.L. Ehman. 2011. Decreased brain stiffness in Alzheimer's disease determined by magnetic resonance elastography. *J. Magn. Reson. Imaging*. 34:494–498. https://doi.org/10.1002/jmri.22707

Mwase, C., W. Deng, H.J. Kim, J.A. Mitchel, T.-K. Phung, M.J. O'Sullivan, J.A. Mathews, J. Crosby, C.E. Turner, A.L. Haber, and J.-A. Park. 2025. Hic-5 drives epithelial mechanotransduction promoting a feed-forward cycle of bronchoconstriction. *Nat. Commun.* 17:516. https://doi.org/10.1038/s41467-025-67210-9

Najibi, A.J., R.S. Lane, M.C. Sobral, G. Bovone, S. Kang, B.R. Freedman, J. Gutierrez Estupinan, A. Elosegui-Artola, C.M. Tringides, M.O. Dellacherie, et al. 2024. Durable lymph-node expansion is associated with the efficacy of therapeutic vaccination. *Nat. Biomed. Eng.* 8:1226–1242. https://doi.org/10.1038/s41551-024-01209-3

Nakasaki, M., Y. Hwang, Y. Xie, S. Kataria, R. Gund, E.Y. Hajam, R. Samuel, R. George, D. Danda, M.J. Paul, T. Nakamura, et al. 2015. The matrix protein Fibulin-5 is at the interface of tissue stiffness and inflammation in fibrosis. *Nat. Commun.* 6:8574. https://doi.org/10.1038/ncomms9574

Natkanski, E., W.-Y. Lee, B. Mistry, A. Casal, J.E. Molloy, and P. Tolar. 2013. B cells use mechanical energy to discriminate antigen affinities. *Science*. 340:1587–1590. https://doi.org/10.1126/science.1237572

Nava, M.M., Y.A. Miroshnikova, L.C. Biggs, D.B. Whitefield, F. Metge, J. Boucas, H. Vihinen, E. Jokitalo, X. Li, J.M. García Arcos, et al. 2020. Heterochromatin-driven nuclear softening protects the genome against mechanical stress-induced damage. *Cell*. 181:800–817.e22. https://doi.org/10.1016/j.cell.2020.03.052

Nayak, P.S., Y. Wang, T. Najrana, L.M. Priolo, M. Rios, S.K. Shaw, and J. Sanchez-Esteban. 2015. Mechanotransduction via TRPV4 regulates inflammation and differentiation in fetal mouse distal lung epithelial cells. *Respir. Res.* 16:60. https://doi.org/10.1186/s12931-015-0224-4

Nazari, B., L.M. Rice, G. Stifano, A.M.S. Barron, Y.M. Wang, T. Korndorf, J. Lee, J. Bhawan, R. Lafyatis, and J.L. Browning. 2016. Altered dermal fibroblasts in systemic sclerosis display podoplanin and CD90. *Am. J. Pathol.* 186:2650–2664. https://doi.org/10.1016/j.ajpath.2016.06.020

Nesbitt, W.S., E. Westein, F.J. Tovar-Lopez, E. Tolouei, A. Mitchell, J. Fu, J. Carberry, A. Fouras, and S.P. Jackson. 2009. A shear gradient–dependent platelet aggregation mechanism drives thrombus formation. *Nat. Med.* 15:665–673. https://doi.org/10.1038/nm.1955

Netea, M.G., F. Balkwill, M. Chonchol, F. Cominelli, M.Y. Donath, E.J. Giamarellos-Bourboulis, D. Golenbock, M.S. Gresnigt, M.T. Heneka, H.M. Hoffman, et al. 2017. A guiding map for inflammation. *Nat. Immunol.* 18:826–831. https://doi.org/10.1038/ni.3790

Nguyen, T.T., D. Ding, W.R. Wolter, R.L. Pérez, M.M. Champion, K.V. Mahasenan, D. Hesek, M. Lee, V.A. Schroeder, J.I. Jones, et al. 2018. Validation of matrix metalloproteinase-9 (MMP-9) as a novel target for treatment of diabetic foot ulcers in humans and discovery of a potent and selective small-molecule MMP-9 inhibitor that accelerates healing. *J. Med. Chem.* 61:8825–8837. https://doi.org/10.1021/acs.jmedchem.8b01005

Nonomura, K., S.-H. Woo, R.B. Chang, A. Gillich, Z. Qiu, A.G. Francisco, S.S. Ranade, S.D. Liberles, and A. Patapoutian. 2017. Piezo2 senses airway stretch and mediates lung inflation-induced apnoea. *Nature*. 541:176–181. https://doi.org/10.1038/nature20793

Nowell, C.S., P.D. Odermatt, L. Azzolin, S. Hohnel, E.F. Wagner, G.E. Fantner, M.P. Lutolf, Y. Barrandon, S. Piccolo, and F. Radtke. 2016. Chronic inflammation imposes aberrant cell fate in regenerating epithelia through mechanotransduction. *Nat. Cell Biol.* 18:168–180. https://doi.org/10.1038/ncb3290

Olsen, A.L., S.A. Bloomer, E.P. Chan, M.D.A. Gaça, P.C. Georges, B. Sackey, M. Uemura, P.A. Janmey, and R.G. Wells. 2011. Hepatic stellate cells require a stiff environment for myofibroblastic differentiation. *Am. J. Physiol. Gastrointest. Liver Physiol.* 301:G110–G118. https://doi.org/10.1152/ajpgi.00412.2010

Olson, E.N., and A. Nordheim. 2010. Linking actin dynamics and gene transcription to drive cellular motile functions. *Nat. Rev. Mol. Cell Biol.* 11:353–365. https://doi.org/10.1038/nrm2890

Oria, R., K. Jain, and V.M. Weaver. 2025. Exploring the intersection of mechanobiology and artificial intelligence. *Npj Biol. Phys. Mech.* 2:9. https://doi.org/10.1038/s44341-025-00010-w

Otto, O., P. Rosendahl, A. Mietke, S. Golfier, C. Herold, D. Klaue, S. Girardo, S. Pagliara, A. Ekpenyong, A. Jacobi, et al. 2015. Real-time deformability cytometry: On-the-fly cell mechanical phenotyping. *Nat. Methods*. 12:199–202. https://doi.org/10.1038/nmeth.3281

O'Conor, C.J., H.A. Leddy, H.C. Benefield, W.B. Liedtke, and F. Guilak. 2014. TRPV4-mediated mechanotransduction regulates the metabolic response of chondrocytes to dynamic loading. *Proc. Natl. Acad. Sci. USA*. 111:1316–1321. https://doi.org/10.1073/pnas.1319569111

Padmanabhan, J., K. Chen, D. Sivaraj, D. Henn, B.A. Kuehlmann, H.C. Kussie, E.T. Zhao, A. Kahn, C.A. Bonham, T. Dohi, et al. 2023. Allometrically scaling tissue forces drive pathological foreign-body responses to implants via Rac2-activated myeloid cells. *Nat. Biomed. Eng.* 7:1419–1436. https://doi.org/10.1038/s41551-023-01091-5

Pairet, N., S. Mang, G. Fois, M. Keck, M. Kühnbach, J. Gindele, M. Frick, P. Dietl, and D.J. Lamb. 2018. TRPV4 inhibition attenuates stretch-induced inflammatory cellular responses and lung barrier dysfunction during mechanical ventilation. *PLoS One*. 13:e0196055. https://doi.org/10.1371/journal.pone.0196055

Pakshir, P., M. Alizadehgiashi, B. Wong, N.M. Coelho, X. Chen, Z. Gong, V.B. Shenoy, C.A. McCulloch, and B. Hinz. 2019. Dynamic fibroblast contractions attract remote macrophages in fibrillar collagen matrix. *Nat. Commun.* 10:1850. https://doi.org/10.1038/s41467-019-09709-6

Papayannopoulos, V. 2018. Neutrophil extracellular traps in immunity and disease. *Nat. Rev. Immunol.* 18:134–147. https://doi.org/10.1038/nri.2017.105

Park, J.-A., J.M. Drazen, and D.J. Tschumperlin. 2010. The chitinase-like protein YKL-40 is secreted by airway epithelial cells at base line and in response to compressive mechanical stress. *J. Biol. Chem.* 285:29817–29825. https://doi.org/10.1074/jbc.M110.103416

Park, H.W., Y.C. Kim, B. Yu, T. Moroishi, J.-S. Mo, S.W. Plouffe, Z. Meng, K.C. Lin, F.-X. Yu, C.M. Alexander, et al. 2015a. Alternative Wnt signaling activates YAP/TAZ. *Cell*. 162:780–794. https://doi.org/10.1016/j.cell.2015.07.013

Park, J.-A., J.H. Kim, D. Bi, J.A. Mitchel, N.T. Qazvini, K. Tantisira, C.Y. Park, M. McGill, S.-H. Kim, B. Gweon, et al. 2015b. Unjamming and cell shape in the asthmatic airway epithelium. *Nat. Mater.* 14:1040–1048. https://doi.org/10.1038/nmat4357

Park, H., J. Furtado, M. Poulet, M. Chung, S. Yun, S. Lee, W.C. Sessa, C.A. Franco, M.A. Schwartz, and A. Eichmann. 2021. Defective flow-migration coupling causes arteriovenous malformations in hereditary hemorrhagic telangiectasia. *Circulation*. 144:805–822. https://doi.org/10.1161/CIRCULATIONAHA.120.053047

Park, J., S. Jia, D. Salter, P. Bagnaninchi, and C.G. Hansen. 2022. The Hippo pathway drives the cellular response to hydrostatic pressure. *EMBO J.* 41:e108719. https://doi.org/10.15252/embj.2021108719

Park, S.Y., S. Ju, J. Lee, H.-R. Kim, Y. Sub, D.J. Park, S. Park, D. Kwon, H.G. Kang, J.E. Shin, et al. 2025. Noncanonical role of Golgi-associated macrophage TAZ in chronic inflammation and tumorigenesis. *Sci. Adv.* 11:eadq2395. https://doi.org/10.1126/sciadv.adq2395

Parmar, K.M., H.B. Larman, G. Dai, Y. Zhang, E.T. Wang, S.N. Moorthy, J.R. Kratz, Z. Lin, M.K. Jain, M.A. Gimbrone Jr, and G. García-Cardeña. 2005. Integration of flow-dependent endothelial phenotypes by Kruppel-like factor 2. *J. Clin. Invest.* 116:49–58. https://doi.org/10.1172/JCI24787

Patel, N.R., M. Bole, C. Chen, C.C. Hardin, A.T. Kho, J. Mih, L. Deng, J. Butler, D. Tschumperlin, J.J. Fredberg, et al. 2012. Cell elasticity determines macrophage function. *PLoS One*. 7:e41024. https://doi.org/10.1371/journal.pone.0041024

Paul, D., S. Achouri, Y.-Z. Yoon, J. Herre, C.E. Bryant, and P. Cicuta. 2013. Phagocytosis dynamics depends on target shape. *Biophys. J.* 105:1143–1150. https://doi.org/10.1016/j.bpj.2013.07.036

Pearce, M.J., T.M. McIntyre, S.M. Prescott, G.A. Zimmerman, and R.E. Whatley. 1996. Shear stress activates cytosolic phospholipase A2(cPLA2) and MAP kinase in human endothelial cells. *Biochem. Biophys. Res. Commun.* 218:500–504. https://doi.org/10.1006/bbrc.1996.0089

Pellegrinelli, V., J. Heuvingh, O. du Roure, C. Rouault, A. Devulder, C. Klein, M. Lacasa, E. Clément, D. Lacasa, and K. Clément. 2014. Human adipocyte function is impacted by mechanical cues. *J. Pathol.* 233:183–195. https://doi.org/10.1002/path.4347

Pellegrinelli, V., E. Figueroa-Juárez, I. Samuelson, M. U-Din, S. Rodriguez-Fdez, S. Virtue, J. Leggat, C. Çubuk, V.J. Peirce, T. Niemi, et al. 2023. Defective extracellular matrix remodeling in brown adipose tissue is associated with fibro-inflammation and reduced diet-induced thermogenesis. *Cell Rep.* 42:112640. https://doi.org/10.1016/j.celrep.2023.112640

Petzold, T., Z. Zhang, I. Ballesteros, I. Saleh, A. Polzin, M. Thienel, L. Liu, Q. Ul Ain, V. Ehreiser, C. Weber, et al. 2022. Neutrophil "plucking" on megakaryocytes drives platelet production and boosts cardiovascular disease. *Immunity*. 55:2285–2299.e7. https://doi.org/10.1016/j.immuni.2022.10.001

Previtera, M.L., and A. Sengupta. 2015. Substrate stiffness regulates proinflammatory mediator production through TLR4 activity in macrophages. *PLoS One*. 10:e0145813. https://doi.org/10.1371/journal.pone.0145813

Prosser, B.L., C.W. Ward, and W.J. Lederer. 2011. X-ROS signaling: Rapid mechano-chemo transduction in heart. *Science*. 333:1440–1445. https://doi.org/10.1126/science.1202768

Qiao, P., W. Guo, Y. Ke, H. Fang, Y. Zhuang, M. Jiang, J. Zhang, S. Shen, H. Qiao, E. Dang, and G. Wang. 2019. Mechanical stretch exacerbates psoriasis by stimulating keratinocyte proliferation and cytokine production. *J. Invest. Dermatol.* 139:1470–1479. https://doi.org/10.1016/j.jid.2018.12.019

Quan, X., B. Sun, X. Song, and L. Zhang. 2026. Biophysics-informed design of biohybrid microrobots. *Nat. Rev. Bioeng*. https://doi.org/10.1038/s44222-026-00416-8

Raab, M., M. Gentili, H. de Belly, H.-R. Thiam, P. Vargas, A.J. Jimenez, F. Lautenschlaeger, R. Voituriez, A.-M. Lennon-Duménil, N. Manel, and M. Piel. 2016. ESCRT III repairs nuclear envelope ruptures during cell migration to limit DNA damage and cell death. *Science*. 352:359–362. https://doi.org/10.1126/science.aad7611

Rabhi, N., K. Desevin, A.C. Belkina, A. Tilston-Lunel, X. Varelas, M.D. Layne, and S.R. Farmer. 2022. Obesity-induced senescent macrophages activate a fibrotic transcriptional program in adipocyte progenitors. *Life Sci. Alliance.* 5:e202101286. https://doi.org/10.26508/lsa.202101286

Rabodzey, A., P. Alcaide, F.W. Luscinskas, and B. Ladoux. 2008. Mechanical forces induced by the transendothelial migration of human neutrophils. *Biophys. J.* 95:1428–1438. https://doi.org/10.1529/biophysj.107.119156

Ramachandran, P., A. Pellicoro, M.A. Vernon, L. Boulter, R.L. Aucott, A. Ali, S.N. Hartland, V.K. Snowdon, A. Cappon, T.T. Gordon-Walker, et al. 2012. Differential Ly-6C expression identifies the recruited macrophage phenotype, which orchestrates the regression of murine liver fibrosis. *Proc. Natl. Acad. Sci. USA*. 109. E3186–E3195. https://doi.org/10.1073/pnas.1119964109

Ramírez, C.M., X. Zhang, C. Bandyopadhyay, N. Rotllan, M.G. Sugiyama, B. Aryal, X. Liu, S. He, J.R. Kraehling, V. Ulrich, et al. 2019. Caveolin-1 regulates atherogenesis by attenuating low-density lipoprotein transcytosis and vascular inflammation independently of endothelial nitric oxide synthase activation. *Circulation*. 140:225–239. https://doi.org/10.1161/CIRCULATIONAHA.118.038571

Ran, L., T. Ye, E. Erbs, S. Ehl, N. Spassky, I. Sumara, Z. Zhang, and R. Ricci. 2023. KCNN4 links PIEZO-dependent mechanotransduction to NLRP3 inflammasome activation. *Sci. Immunol.* 8:eadf4699. https://doi.org/10.1126/sciimmunol.adf4699

Ranade, S.S., Z. Qiu, S.-H. Woo, S.S. Hur, S.E. Murthy, S.M. Cahalan, J. Xu, J. Mathur, M. Bandell, B. Coste, et al. 2014. Piezo1, a mechanically activated ion channel, is required for vascular development in mice. *Proc. Natl. Acad. Sci. USA*. 111:10347–10352. https://doi.org/10.1073/pnas.1409233111

Rausch, V., and C.G. Hansen. 2020. The Hippo pathway, YAP/TAZ, and the plasma membrane. *Trends Cell Biol.* 30:32–48. https://doi.org/10.1016/j.tcb.2019.10.005

Rausch, V., J.R. Bostrom, J. Park, I.R. Bravo, Y. Feng, D.C. Hay, B.A. Link, and C.G. Hansen. 2019. The Hippo pathway regulates caveolae expression and mediates flow response via caveolae. *Curr. Biol.* 29:242–255.e6. https://doi.org/10.1016/j.cub.2018.11.066

Reis-Rodrigues, P., M.J. Avellaneda, N. Canigova, F. Gaertner, K. Vaahtomeri, M. Riedl, I. de Vries, J. Merrin, R. Hauschild, Y. Fukui, et al. 2025. Migrating immune cells globally coordinate protrusive forces. *Nat. Immunol.* 26:1258–1266. https://doi.org/10.1038/s41590-025-02211-w

Renkawitz, J., K. Schumann, M. Weber, T. Lämmermann, H. Pflicke, M. Piel, J. Polleux, J.P. Spatz, and M. Sixt. 2009. Adaptive force transmission in amoeboid cell migration. *Nat. Cell Biol.* 11:1438–1443. https://doi.org/10.1038/ncb1992

Renkawitz, J., A. Kopf, J. Stopp, I. de Vries, M.K. Driscoll, J. Merrin, R. Hauschild, E.S. Welf, G. Danuser, R. Fiolka, and M. Sixt. 2019. Nuclear positioning facilitates amoeboid migration along the path of least resistance. *Nature*. 568:546–550. https://doi.org/10.1038/s41586-019-1087-5

Renkawitz, J., A. Yesin, J. Kroll, A.T. Cabral, S. D'Annunzio, and H.R. Thiam. 2026. Nuclear mechanobiology rules immune cells' functions: From differentiation to cell trafficking and pathogen killing. *Nucleus*. 17:2590843. https://doi.org/10.1080/19491034.2025.2590843

Reversat, A., F. Gaertner, J. Merrin, J. Stopp, S. Tasciyan, J. Aguilera, I. de Vries, R. Hauschild, M. Hons, M. Piel, et al. 2020. Cellular locomotion using environmental topography. *Nature*. 582:582–585. https://doi.org/10.1038/s41586-020-2283-z

Rollins, K.R., S. Fiaz, I. Datta, and M.A. Morrissey. 2025. Target cell adhesion limits macrophage phagocytosis and promotes trogocytosis. *J. Cell Biol.* 224:e202502034. https://doi.org/10.1083/jcb.202502034

Rosendahl, P., K. Plak, A. Jacobi, M. Kraeter, N. Toepfner, O. Otto, C. Herold, M. Winzi, M. Herbig, Y. Ge, et al. 2018. Real-time fluorescence and deformability cytometry. *Nat. Methods*. 15:355–358. https://doi.org/10.1038/nmeth.4639

Rowat, A.C., D.E. Jaalouk, M. Zwerger, W.L. Ung, I.A. Eydelnant, D.E. Olins, A.L. Olins, H. Herrmann, D.A. Weitz, and J. Lammerding. 2013. Nuclear envelope composition determines the ability of neutrophil-type cells to passage through micron-scale constrictions. *J. Biol. Chem.* 288:8610–8618. https://doi.org/10.1074/jbc.M112.441535

Rupar, M.J., H. Hanson, S. Rogers, B. Botlick, S. Trimmer, and J.J. Hickman. 2024. Modelling the innate immune system in microphysiological systems. *Lab. Chip*. 24:3604–3625. https://doi.org/10.1039/D3LC00812F

Ruprecht, V., S. Wieser, A. Callan-Jones, M. Smutny, H. Morita, K. Sako, V. Barone, M. Ritsch-Marte, M. Sixt, R. Voituriez, and C.-P. Heisenberg. 2015. Cortical contractility triggers a stochastic switch to fast amoeboid cell motility. *Cell*. 160:673–685. https://doi.org/10.1016/j.cell.2015.01.008

Saha, S., J.P. Town, and O.D. Weiner. 2023. Mechanosensitive mTORC2 independently coordinates leading and trailing edge polarity programs during neutrophil migration. *Mol. Biol. Cell*. 34:ar35. https://doi.org/10.1091/mbc.E22-05-0191

Samir, A.E., A.S. Allegretti, Q. Zhu, M. Dhyani, A. Anvari, D.A. Sullivan, C.A. Trottier, S. Dougherty, W.W. Williams, J.L. Babitt, et al. 2015. Shear wave elastography in chronic kidney disease: A pilot experience in native kidneys. *BMC Nephrol.* 16:119. https://doi.org/10.1186/s12882-015-0120-7

Sampietro, M., M. Cellani, and C. Scielzo. 2025. B cell mechanobiology in health and disease: Emerging techniques and insights into therapeutic responses. *FEBS Lett.* 599:2854–2877. https://doi.org/10.1002/1873-3468.70071

Saucerman, J.J., P.M. Tan, K.S. Buchholz, A.D. McCulloch, and J.H. Omens. 2019. Mechanical regulation of gene expression in cardiac myocytes and fibroblasts. *Nat. Rev. Cardiol.* 16:361–378. https://doi.org/10.1038/s41569-019-0155-8

Scheraga, R.G., S. Abraham, K.A. Niese, B.D. Southern, L.M. Grove, R.D. Hite, C. McDonald, T.A. Hamilton, and M.A. Olman. 2016. TRPV4 mechanosensitive ion channel regulates lipopolysaccharide-stimulated macrophage phagocytosis. *J. Immunol.* 196:428–436. https://doi.org/10.4049/jimmunol.1501688

Scheraga, R.G., S. Abraham, L.M. Grove, B.D. Southern, J.F. Crish, A. Perelas, C. McDonald, K. Asosingh, J.D. Hasday, and M.A. Olman. 2020. TRPV4 protects the lung from bacterial pneumonia via MAPK molecular pathway switching. *J. Immunol.* 204:1310–1321. https://doi.org/10.4049/jimmunol.1901033

Schievella, A.R., M.K. Regier, W.L. Smith, and L.-L. Lin. 1995. Calcium-mediated translocation of cytosolic phospholipase A2 to the nuclear envelope and endoplasmic reticulum. *J. Biol. Chem.* 270:30749–30754. https://doi.org/10.1074/jbc.270.51.30749

Schmitt, M.T., J. Kroll, M.J.A. Ruiz-Fernandez, R. Hauschild, S. Ghosh, P. Kameritsch, J. Merrin, J. Schmid, K. Stefanowski, A.W. Thomae, et al. 2025. Protecting centrosomes from fracturing enables efficient cell navigation. *Sci. Adv.* 11:eadx4047. https://doi.org/10.1126/sciadv.adx4047

Segel, M., B. Neumann, M.F.E. Hill, I.P. Weber, C. Viscomi, C. Zhao, A. Young, C.C. Agley, A.J. Thompson, G.A. Gonzalez, et al. 2019. Niche stiffness underlies the ageing of central nervous system progenitor cells. *Nature*. 573:130–134. https://doi.org/10.1038/s41586-019-1484-9

Sellin, M.E., A.A. Müller, B. Felmy, T. Dolowschiak, M. Diard, A. Tardivel, K.M. Maslowski, and W.-D. Hardt. 2014. Epithelium-intrinsic NAIP/NLRC4 inflammasome drives infected enterocyte expulsion to restrict *Salmonella* replication in the intestinal mucosa. *Cell Host Microbe*. 16:237–248. https://doi.org/10.1016/j.chom.2014.07.001

SenBanerjee, S., Z. Lin, G.B. Atkins, D.M. Greif, R.M. Rao, A. Kumar, M.W. Feinberg, Z. Chen, D.I. Simon, F.W. Luscinskas, et al. 2004. KLF2 is a novel transcriptional regulator of endothelial proinflammatory activation. *J. Exp. Med.* 199:1305–1315. https://doi.org/10.1084/jem.20031132

Seo, B.R., P. Bhardwaj, S. Choi, J. Gonzalez, R.C. Andresen Eguiluz, K. Wang, S. Mohanan, P.G. Morris, B. Du, X.K. Zhou, et al. 2015. Obesity-dependent changes in interstitial ECM mechanics promote breast tumorigenesis. *Sci. Transl. Med.* 7:301ra130. https://doi.org/10.1126/scitranslmed.3010467

Seo, B.R., C.J. Payne, S.L. McNamara, B.R. Freedman, B.J. Kwee, S. Nam, I. de Lázaro, M. Darnell, J.T. Alvarez, M.O. Dellacherie, et al. 2021. Skeletal muscle regeneration with robotic actuation–mediated clearance of neutrophils. *Sci. Transl. Med.* 13:eabe8868. https://doi.org/10.1126/scitranslmed.abe8868

Serhan, N., N.S. Abdullah, N. Gheziel, A. Loste, R. Ekren, E. Labit, A.-A. Gonzalez, G. Oliva, P. Tarot, C. Petitfils, et al. 2025. Maternal stress triggers early-life eczema through fetal mast cell programming. *Nature*. 646:161–170. https://doi.org/10.1038/s41586-025-09419-8

Şerifoğlu, N., G. Allavena, B. Lopes-Bastos, M. Marzullo, A. Marques, P. Colibert, P. Bousounis, E. Trompouki, and M.G. Ferreira. 2025. cGAS-STING are responsible for premature aging of telomerase-deficient zebrafish. *EMBO J.* 44:4666–4680. https://doi.org/10.1038/s44318-025-00482-5

Settle, A.H., B.Y. Winer, M.M. de Jesus, L. Seeman, Z. Wang, E. Chan, Y. Romin, Z. Li, M.M. Miele, R.C. Hendrickson, et al. 2024. β2 integrins impose a mechanical checkpoint on macrophage phagocytosis. *Nat. Commun.* 15:8182. https://doi.org/10.1038/s41467-024-52453-9

Shaka, X., C. Aitken, V. Mehta, B. Tardajos-Ayllon, J. Serbanovic-Canic, J. Zhu, B. Miao, E. Tzima, P. Evans, Y. Fang, and M.A. Schwartz. 2024. Controversy in mechanotransduction – the role of endothelial cell–cell junctions in fluid shear stress sensing. *J. Cell Sci.* 137:jcs262348. https://doi.org/10.1242/jcs.262348

Shang, T., L. Zhao, S. Ying, L. Su, Y. Yang, J. Liu, Y. Wang, J. Xue, C. Cheng, Y. Wu, et al. 2026. Shear stress governs hematopoietic stem cell fate to promote inflammation-induced aging. *Nat. Aging*. 6:88–107. https://doi.org/10.1038/s43587-025-01039-1

Shen, B., X. Zhao, K.A. O'Brien, A. Stojanovic-Terpo, M.K. Delaney, K. Kim, J. Cho, S.C.-T. Lam, and X. Du. 2013. A directional switch of integrin signalling and a new anti-thrombotic strategy. *Nature*. 503:131–135. https://doi.org/10.1038/nature12613

Shen, B., A. Tasdogan, J.M. Ubellacker, J. Zhang, E.D. Nosyreva, L. Du, M.M. Murphy, S. Hu, Y. Yi, N. Kara, et al. 2021. A mechanosensitive peri-arteriolar niche for osteogenesis and lymphopoiesis. *Nature*. 591:438–444. https://doi.org/10.1038/s41586-021-03298-5

Shen, Z., Z. Gelashvili, and P. Niethammer. 2026. Endoplasmic reticulum disruption stimulates nuclear membrane mechanotransduction. *Nat. Cell Biol.* 28:125–134. https://doi.org/10.1038/s41556-025-01820-9

Shi, G., Z. Chang, P. Zhang, X. Zou, X. Zheng, X. Liu, J. Yan, H. Xu, Z. Tian, N. Zhang, et al. 2024. Heterogeneous stiffness of the bone marrow microenvironment regulates the fate decision of haematopoietic stem and progenitor cells. *Cell Prolif.* 57:e13715. https://doi.org/10.1111/cpr.13715

Shi, Y., B. Yang, Y. Linghu, Y. Liu, H. Li, Y. Xing, B. Wu, Y. Gao, L. Liao, Y. Zheng, et al. 2025. Piezo1 senses hyphae and initiates host defense against pathogenic fungi. *Cell Rep.* 44:115839. https://doi.org/10.1016/j.celrep.2025.115839

Shimbori, C., C. Upagupta, P.-S. Bellaye, E.A. Ayaub, S. Sato, T. Yanagihara, Q. Zhou, A. Ognjanovic, K. Ask, J. Gauldie, et al. 2019. Mechanical stress-induced mast cell degranulation activates TGF-β1 signalling pathway in pulmonary fibrosis. *Thorax*. 74:455–465. https://doi.org/10.1136/thoraxjnl-2018-211516

Shindo, K., S. Aishima, K. Ohuchida, K. Fujiwara, M. Fujino, Y. Mizuuchi, M. Hattori, K. Mizumoto, M. Tanaka, and Y. Oda. 2013. Podoplanin expression in cancer-associated fibroblasts enhances tumor progression of invasive ductal carcinoma of the pancreas. *Mol. Cancer*. 12:168. https://doi.org/10.1186/1476-4598-12-168

Shiraishi, K., P.P. Shah, M.P. Morley, C. Loebel, G.T. Santini, J. Katzen, M.C. Basil, S.M. Lin, J.D. Planer, E. Cantu, et al. 2023. Biophysical forces mediated by respiration maintain lung alveolar epithelial cell fate. *Cell*. 186:1478–1492.e15. https://doi.org/10.1016/j.cell.2023.02.010

Shutova, M.S., J. Borowczyk, B. Russo, S. Sellami, J. Drukala, M. Wolnicki, N.C. Brembilla, G. Kaya, A.I. Ivanov, and W.-H. Boehncke. 2023. Inflammation modulates intercellular adhesion and mechanotransduction in human epidermis via ROCK2. *iScience*. 26:106195. https://doi.org/10.1016/j.isci.2023.106195

Sicard, D., A.J. Haak, K.M. Choi, A.R. Craig, L.E. Fredenburgh, and D.J. Tschumperlin. 2018. Aging and anatomical variations in lung tissue stiffness. *Am. J. Physiol. Lung Cell Mol. Physiol.* 314:L946–L955. https://doi.org/10.1152/ajplung.00415.2017

Singh, T., K.A. Jacobs, W.J. Polacheck, and M.L. Kutys. 2026. The Notch1 intracellular domain orchestrates mechanotransduction of fluid shear stress. *Life Sci. Alliance*. 9:e202503599. https://doi.org/10.26508/lsa.202503599

Sinha, B., D. Köster, R. Ruez, P. Gonnord, M. Bastiani, D. Abankwa, R.V. Stan, G. Butler-Browne, B. Vedie, L. Johannes, et al. 2011. Cells respond to mechanical stress by rapid disassembly of caveolae. *Cell*. 144:402–413. https://doi.org/10.1016/j.cell.2010.12.031

Sladitschek-Martens, H.L., A. Guarnieri, G. Brumana, F. Zanconato, G. Battilana, R.L. Xiccato, T. Panciera, M. Forcato, S. Bicciato, V. Guzzardo, et al. 2022. YAP/TAZ activity in stromal cells prevents ageing by controlling cGAS–STING. *Nature*. 607:790–798. https://doi.org/10.1038/s41586-022-04924-6

Solarz, J., C. Soukaseum, S. Frémont, S. Eymieux, C. Nabli, C. Repérant, E. Rossi, J.-C. Bordet, C.V. Denis, P. Mangin, et al. 2025. F-actin disassembly by the oxidoreductase MICAL1 promotes mechano-dependent VWF-GPIbα interaction in platelets. *Nat. Commun.* 16:7375. https://doi.org/10.1038/s41467-025-62487-2

Solis, A.G., P. Bielecki, H.R. Steach, L. Sharma, C.C.D. Harman, S. Yun, M.R. de Zoete, J.N. Warnock, S.D.F. To, A.G. York, et al. 2019. Mechanosensation of cyclical force by PIEZO1 is essential for innate immunity. *Nature*. 573:69–74. https://doi.org/10.1038/s41586-019-1485-8

Song, K., H. Kwon, C. Han, W. Chen, J. Zhang, W. Ma, S. Dash, C.R. Gandhi, and T. Wu. 2020. Yes-associated protein in kupffer cells enhances the production of proinflammatory cytokines and promotes the development of nonalcoholic steatohepatitis. *Hepatology*. 72:72–87. https://doi.org/10.1002/hep.30990

Song, Y., H. Na, S.E. Lee, Y.M. Kim, J. Moon, T.W. Nam, Y. Ji, Y. Jin, J.H. Park, S.C. Cho, et al. 2024. Dysfunctional adipocytes promote tumor progression through YAP/TAZ-dependent cancer-associated adipocyte transformation. *Nat. Commun.* 15:4052. https://doi.org/10.1038/s41467-024-48179-3

Song, Z., Y. Cui, L. Xin, R. Xiao, J. Feng, C. Li, Z. Yin, H. Wang, Q. Li, M. Wang, et al. 2025. Mechano-oncogenic cytoskeletal remodeling drives leukemic transformation with mitochondrial vesicle-mediated STING activation. *Cell Stem Cell*. 32:581–597.e11. https://doi.org/10.1016/j.stem.2025.01.013

Sorokin, L. 2026. Biochemical signals from the extracellular matrix in inflammation and tumour immunology. *Nat. Rev. Immunol.* 26:350–366. https://doi.org/10.1038/s41577-025-01248-0

Sosale, N.G., T. Rouhiparkouhi, A.M. Bradshaw, R. Dimova, R. Lipowsky, and D.E. Discher. 2015. Cell rigidity and shape override CD47's "self"-signaling in phagocytosis by hyperactivating myosin-II. *Blood*. 125:542–552. https://doi.org/10.1182/blood-2014-06-585299

Soteriou, D., M. Kubánková, C. Schweitzer, R. López-Posadas, R. Pradhan, O.-M. Thoma, A.-H. Györfi, A.-E. Matei, M. Waldner, J.H.W. Distler, et al. 2023. Rapid single-cell physical phenotyping of mechanically dissociated tissue biopsies. *Nat. Biomed. Eng.* 7:1392–1403. https://doi.org/10.1038/s41551-023-01015-3

Spillane, K.M., and P. Tolar. 2017. B cell antigen extraction is regulated by physical properties of antigen-presenting cells. *J. Cell Biol.* 216:217–230. https://doi.org/10.1083/jcb.201607064

Sprenkeler, E.G.G., A.T.J. Tool, S.S.V. Henriet, R. van Bruggen, and T.W. Kuijpers. 2022. Formation of neutrophil extracellular traps requires actin cytoskeleton rearrangements. *Blood*. 139:3166–3180. https://doi.org/10.1182/blood.2021013565

Springer, N.L., N.M. Iyengar, R. Bareja, A. Verma, M.S. Jochelson, D.D. Giri, X.K. Zhou, O. Elemento, A.J. Dannenberg, and C. Fischbach. 2019. Obesity-associated extracellular matrix remodeling promotes a macrophage phenotype similar to tumor-associated macrophages. *Am. J. Pathol.* 189:2019–2035. https://doi.org/10.1016/j.ajpath.2019.06.005

Sridharan, R., B. Cavanagh, A.R. Cameron, D.J. Kelly, and F.J. O'Brien. 2019. Material stiffness influences the polarization state, function and migration mode of macrophages. *Acta Biomater.* 89:47–59. https://doi.org/10.1016/j.actbio.2019.02.048

Stephens, A.D., E.J. Banigan, S.A. Adam, R.D. Goldman, and J.F. Marko. 2017. Chromatin and lamin A determine two different mechanical response regimes of the cell nucleus. *Mol. Biol. Cell*. 28:1984–1996. https://doi.org/10.1091/mbc.e16-09-0653

Stephens, A.D., P.Z. Liu, E.J. Banigan, L.M. Almassalha, V. Backman, S.A. Adam, R.D. Goldman, and J.F. Marko. 2018. Chromatin histone modifications and rigidity affect nuclear morphology independent of lamins. *Mol. Biol. Cell*. 29:220–233. https://doi.org/10.1091/mbc.E17-06-0410

Stephens, A.D., P.Z. Liu, V. Kandula, H. Chen, L.M. Almassalha, C. Herman, V. Backman, T. O'Halloran, S.A. Adam, R.D. Goldman, et al. 2019. Physicochemical mechanotransduction alters nuclear shape and mechanics via heterochromatin formation. *Mol. Biol. Cell*. 30:2320–2330. https://doi.org/10.1091/mbc.E19-05-0286

Stewart, D.C., D. Berrie, J. Li, X. Liu, C. Rickerson, D. Mkoji, A. Iqbal, S. Tan, A.L. Doty, S.C. Glover, and C.S. Simmons. 2018. Quantitative assessment of intestinal stiffness and associations with fibrosis in human inflammatory bowel disease. *PLoS One*. 13:e0200377. https://doi.org/10.1371/journal.pone.0200377

Suchyna, T.M., J.H. Johnson, K. Hamer, J.F. Leykam, D.A. Gage, H.F. Clemo, C.M. Baumgarten, and F. Sachs. 2000. Identification of a peptide toxin

from *Grammostola spatulata* spider venom that blocks cation-selective stretch-activated channels. *J. Gen. Physiol.* 115:583–598. https://doi.org/10.1085/jgp.115.5.583

Sun, K., J. Tordjman, K. Clément, and P.E. Scherer. 2013. Fibrosis and adipose tissue dysfunction. *Cell Metab.* 18:470–477. https://doi.org/10.1016/j.cmet.2013.06.016

Sun, M., S. Mao, C. Wu, X. Zhao, C. Guo, J. Hu, S. Xu, F. Zheng, G. Zhu, H. Tao, et al. 2024. Piezo1-mediated neurogenic inflammatory cascade exacerbates ventricular remodeling after myocardial infarction. *Circulation*. 149:1516–1533. https://doi.org/10.1161/CIRCULATIONAHA.123.065390

Sun, L., Y. Wang, T. Kan, H. Wang, J. Cui, L. Wang, C. Liu, H. Li, Z. Yu, and M. Yan. 2025. Elevated expression of Piezo1 activates the cGAS-STING pathway in chondrocytes by releasing mitochondrial DNA. *Osteoarthritis Cartilage*. 33:601–615. https://doi.org/10.1016/j.joca.2025.02.778

Sutherland, T.E., D.P. Dyer, and J.E. Allen. 2023. The extracellular matrix and the immune system: A mutually dependent relationship. *Science*. 379:379. https://doi.org/10.1126/science.abp8964

Swiatlowska, P., B. Sit, Z. Feng, E. Marhuenda, I. Xanthis, S. Zingaro, M. Ward, X. Zhou, Q. Xiao, C. Shanahan, et al. 2022. Pressure and stiffness sensing together regulate vascular smooth muscle cell phenotype switching. *Sci. Adv.* 8:eabm3471. https://doi.org/10.1126/sciadv.abm3471

Swiatlowska, P., W. Tipping, E. Marhuenda, P. Severi, V. Fomin, Z. Yang, Q. Xiao, D. Graham, C. Shanahan, and T. Iskratsch. 2024. Hypertensive pressure mechanosensing alone triggers lipid droplet accumulation and transdifferentiation of vascular smooth muscle cells to foam cells. *Adv. Sci.* 11:e2308686. https://doi.org/10.1002/advs.202308686

Swift, J., I.L. Ivanovska, A. Buxboim, T. Harada, P.C.D.P. Dingal, J. Pinter, J.D. Pajerowski, K.R. Spinler, J.-W. Shin, M. Tewari, et al. 2013. Nuclear lamin-A scales with tissue stiffness and enhances matrix-directed differentiation. *Science*. 341:341. https://doi.org/10.1126/science.1240104

Tamargo, I.A., K.I. Baek, Y. Kim, C. Park, and H. Jo. 2023. Flow-induced reprogramming of endothelial cells in atherosclerosis. *Nat. Rev. Cardiol.* 20:738–753. https://doi.org/10.1038/s41569-023-00883-1

Tamzalit, F., M.S. Wang, W. Jin, M. Tello-Lafoz, V. Boyko, J.M. Heddleston, C.T. Black, L.C. Kam, and M. Huse. 2019. Interfacial actin protrusions mechanically enhance killing by cytotoxic T cells. *Sci. Immunol.* 4:eaav5445. https://doi.org/10.1126/sciimmunol.aav5445

Tanaka, K., M. Chen, A. Prendergast, Z. Zhuang, A. Nasiri, D. Joshi, J. Hintzen, M. Chung, A. Kumar, A. Mani, et al. 2024. Latrophilin-2 mediates fluid shear stress mechanotransduction at endothelial junctions. *EMBO J.* 43:3175–3191. https://doi.org/10.1038/s44318-024-00142-0

Tatulian, S.A. 2001. Toward understanding interfacial activation of secretory phospholipase A2 (PLA2): Membrane surface properties and membrane-induced structural changes in the enzyme contribute synergistically to PLA2 activation. *Biophys. J.* 80:789–800. https://doi.org/10.1016/S0006-3495(01)76058-4

Tello-Lafoz, M., K. Srpan, E.E. Sanchez, J. Hu, J. Remsik, Y. Romin, A. Calò, D. Hoen, U. Bhanot, L. Morris, et al. 2021. Cytotoxic lymphocytes target characteristic biophysical vulnerabilities in cancer. *Immunity*. 54:1037–1054.e7. https://doi.org/10.1016/j.immuni.2021.02.020

Tharp, K.M., R. Higuchi-Sanabria, G.A. Timblin, B. Ford, C. Garzon-Coral, C. Schneider, J.M. Muncie, C. Stashko, J.R. Daniele, A.S. Moore, et al. 2021. Adhesion-mediated mechanosignaling forces mitohormesis. *Cell Metab.* 33:1322–1341.e13. https://doi.org/10.1016/j.cmet.2021.04.017

Theocharidis, G., H. Yuk, H. Roh, L. Wang, I. Mezghani, J. Wu, A. Kafanas, M. Contreras, B. Sumpio, Z. Li, et al. 2022. A strain-programmed patch for the healing of diabetic wounds. *Nat. Biomed. Eng.* 6:1118–1133. https://doi.org/10.1038/s41551-022-00905-2

Thiam, H.-R., P. Vargas, N. Carpi, C.L. Crespo, M. Raab, E. Terriac, M.C. King, J. Jacobelli, A.S. Alberts, T. Stradal, et al. 2016. Perinuclear Arp2/3-driven actin polymerization enables nuclear deformation to facilitate cell migration through complex environments. *Nat. Commun.* 7:10997. https://doi.org/10.1038/ncomms10997

Thiam, H.R., S.L. Wong, R. Qiu, M. Kittisopikul, A. Vahabikashi, A.E. Goldman, R.D. Goldman, D.D. Wagner, and C.M. Waterman. 2020. NETosis proceeds by cytoskeleton and endomembrane disassembly and PAD4-mediated chromatin decondensation and nuclear envelope rupture. *Proc. Natl. Acad. Sci. USA*. 117:7326–7337. https://doi.org/10.1073/pnas.1909546117

Thorneloe, K.S., M. Cheung, W. Bao, H. Alsaid, S. Lenhard, M.-Y. Jian, M. Costell, K. Maniscalco-Hauk, J.A. Krawiec, A. Olzinski, et al. 2012. An orally active TRPV4 channel blocker prevents and resolves pulmonary edema induced by heart failure. *Sci. Transl. Med.* 4:159ra148. https://doi.org/10.1126/scitranslmed.3004276

Timmons, B., M. Akins, and M. Mahendroo. 2010. Cervical remodeling during pregnancy and parturition. *Trends Endocrinol. Metab.* 21:353–361. https://doi.org/10.1016/j.tem.2010.01.011

Toepfner, N., C. Herold, O. Otto, P. Rosendahl, A. Jacobi, M. Kräter, J. Stächele, L. Menschner, M. Herbig, L. Ciuffreda, et al. 2018. Detection of human disease conditions by single-cell morpho-rheological phenotyping of blood. *Elife*. 7:e29213. https://doi.org/10.7554/eLife.29213

Tomaskovic, I., C. Prieto-Garcia, M. Boskovic, M. Glumac, T.-L. Tsai, T. Mosler, R. Kazi, R. Rathore, J. Andrade, M. Hoffmann, et al. 2026. DNA-protein cross-links promote cGAS-STING–driven premature aging and embryonic lethality. *Science*. 391:391. https://doi.org/10.1126/science.adx9445

Trepat, X., L. Deng, S.S. An, D. Navajas, D.J. Tschumperlin, W.T. Gerthoffer, J.P. Butler, and J.J. Fredberg. 2007. Universal physical responses to stretch in the living cell. *Nature*. 447:592–595. https://doi.org/10.1038/nature05824

Tschumperlin, D.J., G. Dai, I.V. Maly, T. Kikuchi, L.H. Laiho, A.K. McVittie, K.J. Haley, C.M. Lilly, P.T.C. So, D.A. Lauffenburger, et al. 2004. Mechanotransduction through growth-factor shedding into the extracellular space. *Nature*. 429:83–86. https://doi.org/10.1038/nature02543

Tse, H.T.K., D.R. Gossett, Y.S. Moon, M. Masaeli, M. Sohsman, Y. Ying, K. Mislick, R.P. Adams, J. Rao, and D. Di Carlo. 2013. Quantitative diagnosis of malignant pleural effusions by single-cell mechanophenotyping. *Sci. Transl. Med.* 5:212ra163. https://doi.org/10.1126/scitranslmed.3006559

Tzima, E., M. Irani-Tehrani, W.B. Kiosses, E. Dejana, D.A. Schultz, B. Engelhardt, G. Cao, H. DeLisser, and M.A. Schwartz. 2005. A mechanosensory complex that mediates the endothelial cell response to fluid shear stress. *Nature*. 437:426–431. https://doi.org/10.1038/nature03952

Ullrich, K.A.-M., J. Derdau, C. Baltes, A. Battistella, G. Rosso, S. Uderhardt, L. Lou Schulze, L.-J. Liu, M. Dedden, M. Spocinska, et al. 2023. IL-3 receptor signalling suppresses chronic intestinal inflammation by controlling mechanobiology and tissue egress of regulatory T cells. *Gut*. 72:2081–2094. https://doi.org/10.1136/gutjnl-2023-329818

Urbanska, M., H.E. Muñoz, J. Shaw Bagnall, O. Otto, S.R. Manalis, D. Di Carlo, and J. Guck. 2020. A comparison of microfluidic methods for high-throughput cell deformability measurements. *Nat. Methods*. 17:587–593. https://doi.org/10.1038/s41592-020-0818-8

Valanarasu, J.M.J., H. Xu, N. Usuyama, C. Kim, C. Wong, P. Argaw, R. Ben Shimol, A. Crabtree, K. Matlock, A.Q. Bartlett, et al. 2026. Multimodal AI generates virtual population for tumor microenvironment modeling. *Cell*. 189:386–400.e19. https://doi.org/10.1016/j.cell.2025.11.016

Vargas, P., P. Maiuri, M. Bretou, B.J. Sáez, P. Pierobon, M. Maurin, M. Chabaud, D. Lankar, D. Obino, E. Terriac, et al. 2016. Innate control of actin nucleation determinens two distinct migration behaviours in dendritic cells. *Nat. Cell Biol.* 18:43–53. https://doi.org/10.1038/ncb3284

Veerappan, A., N.J. O'Connor, J. Brazin, A.C. Reid, A. Jung, D. McGee, B. Summers, D. Branch-Elliman, B. Stiles, S. Worgall, et al. 2013. Mast cells: A pivotal role in pulmonary fibrosis. *DNA Cell Biol.* 32:206–218. https://doi.org/10.1089/dna.2013.2005

Venturini, V., F. Pezzano, F. Català Castro, H.-M. Häkkinen, S. Jiménez-Delgado, M. Colomer-Rosell, M. Marro, Q. Tolosa-Ramon, S. Paz-López, M.A. Valverde, et al. 2020. The nucleus measures shape changes for cellular proprioception to control dynamic cell behavior. *Science*. 370:eaba2644. https://doi.org/10.1126/science.aba2644

Vining, K.H., and D.J. Mooney. 2017. Mechanical forces direct stem cell behaviour in development and regeneration. *Nat. Rev. Mol. Cell Biol.* 18:728–742. https://doi.org/10.1038/nrm.2017.108

Vining, K.H., A.E. Marneth, K. Adu-Berchie, J.M. Grolman, C.M. Tringides, Y. Liu, W.J. Wong, O. Pozdnyakova, M. Severgnini, A. Stafford, et al. 2022. Mechanical checkpoint regulates monocyte differentiation in fibrotic niches. *Nat. Mater.* 21:939–950. https://doi.org/10.1038/s41563-022-01293-3

Vlahakis, N.E., M.A. Schroeder, A.H. Limper, and R.D. Hubmayr. 1999. Stretch induces cytokine release by alveolar epithelial cells in vitro. *Am. J. Physiol. Lung Cell Mol. Physiol.* 277:L167–L173. https://doi.org/10.1152/ajplung.1999.277.1.L167

Vorselen, D., Y. Wang, M.M. de Jesus, P.K. Shah, M.J. Footer, M. Huse, W. Cai, and J.A. Theriot. 2020. Microparticle traction force microscopy reveals subcellular force exertion patterns in immune cell–target interactions. *Nat. Commun.* 11:20. https://doi.org/10.1038/s41467-019-13804-z

Vorselen, D., S.R. Barger, Y. Wang, W. Cai, J.A. Theriot, N.C. Gauthier, and M. Krendel. 2021. Phagocytic 'teeth' and myosin-II 'jaw' power target constriction during phagocytosis. *Elife*. 10:e68627. https://doi.org/10.7554/eLife.68627

Walzik, D., N. Joisten, A.J. Metcalfe, S. Proschinger, A. Schenk, C. Wenzel, A.L. Henneberg, M. Schneider, S. Calderazzo, A. Groll, et al. 2026. Acute

exercise rewires the proteomic landscape of human immune cells. *Nat. Commun.* 17:130. https://doi.org/10.1038/s41467-025-68101-9
Wang, N., J.P. Butler, and D.E. Ingber. 1993. Mechanotransduction across the cell surface and through the cytoskeleton. *Science*. 260:1124–1127. https://doi.org/10.1126/science.7684161
Wang, K.-C., Y.-T. Yeh, P. Nguyen, E. Limqueco, J. Lopez, S. Thorossian, K.-L. Guan, Y.-S.J. Li, and S. Chien. 2016a. Flow-dependent YAP/TAZ activities regulate endothelial phenotypes and atherosclerosis. *Proc. Natl. Acad. Sci. USA*. 113:11525–11530. https://doi.org/10.1073/pnas.1613121113
Wang, L., J.-Y. Luo, B. Li, X.Y. Tian, L.-J. Chen, Y. Huang, J. Liu, D. Deng, C.W. Lau, S. Wan, et al. 2016b. Integrin-YAP/TAZ-JNK cascade mediates atheroprotective effect of unidirectional shear flow. *Nature*. 540: 579–582. https://doi.org/10.1038/nature20602
Wang, X., Z. Zheng, J.M. Caviglia, K.E. Corey, T.M. Herfel, B. Cai, R. Masia, R.T. Chung, J.H. Lefkowitch, R.F. Schwabe, and I. Tabas. 2016c. Hepatocyte TAZ/WWTR1 promotes inflammation and fibrosis in nonalcoholic steatohepatitis. *Cell Metab.* 24:848–862. https://doi.org/10.1016/j.cmet.2016.09.016
Wang, S., F. Xie, F. Chu, Z. Zhang, B. Yang, T. Dai, L. Gao, L. Wang, L. Ling, J. Jia, et al. 2017. YAP antagonizes innate antiviral immunity and is targeted for lysosomal degradation through IKKε-mediated phosphorylation. *Nat. Immunol.* 18:733–743. https://doi.org/10.1038/ni.3744
Wang, J., H.-J. Chen, T. Hang, Y. Yu, G. Liu, G. He, S. Xiao, B. Yang, C. Yang, F. Liu, et al. 2018. Physical activation of innate immunity by spiky particles. *Nat. Nanotechnol.* 13:1078–1086. https://doi.org/10.1038/s41565-018-0274-0
Wang, S., S. Cao, M. Arhatte, D. Li, Y. Shi, S. Kurz, J. Hu, L. Wang, J. Shao, A. Atzberger, et al. 2020a. Adipocyte Piezo1 mediates obesogenic adipogenesis through the FGF1/FGFR1 signaling pathway in mice. *Nat. Commun.* 11:2303. https://doi.org/10.1038/s41467-020-16026-w
Wang, X., M. Hossain, A. Bogoslowski, P. Kubes, and D. Irimia. 2020b. Chemotaxing neutrophils enter alternate branches at capillary bifurcations. *Nat. Commun.* 11:2385. https://doi.org/10.1038/s41467-020-15476-6
Wang, D., Y. Zhang, X. Xu, J. Wu, Y. Peng, J. Li, R. Luo, L. Huang, L. Liu, S. Yu, et al. 2021. YAP promotes the activation of NLRP3 inflammasome via blocking K27-linked polyubiquitination of NLRP3. *Nat. Commun.* 12: 2674. https://doi.org/10.1038/s41467-021-22987-3
Wang, M.S., Y. Hu, E.E. Sanchez, X. Xie, N.H. Roy, M. de Jesus, B.Y. Winer, E.A. Zale, W. Jin, C. Sachar, et al. 2022a. Mechanically active integrins target lytic secretion at the immune synapse to facilitate cellular cytotoxicity. *Nat. Commun.* 13:3222. https://doi.org/10.1038/s41467-022-30809-3
Wang, S., B. Wang, Y. Shi, T. Möller, R.I. Stegmeyer, B. Strilic, T. Li, Z. Yuan, C. Wang, N. Wettschureck, et al. 2022b. Mechanosensation by endothelial PIEZO1 is required for leukocyte diapedesis. *Blood*. 140:171–183. https://doi.org/10.1182/blood.2021014614
Wang, Y., H. Yang, A. Jia, Y. Wang, Q. Yang, Y. Dong, Y. Hou, Y. Cao, L. Dong, Y. Bi, and G. Liu. 2022c. Dendritic cell Piezo1 directs the differentiation of TH1 and Treg cells in cancer. *Elife*. 11:e79957. https://doi.org/10.7554/eLife.79957
Wang, Y., T. Chu, X. Pan, Y. Bian, and J. Li. 2023. Escin ameliorates inflammation via inhibiting mechanical stretch and chemically induced Piezo1 activation in vascular endothelial cells. *Eur. J. Pharmacol.* 956:175951. https://doi.org/10.1016/j.ejphar.2023.175951
Wang, Y., J. Wang, J. Zhang, Y. Wang, Y. Wang, H. Kang, W. Zhao, W. Bai, N. Miao, and J. Wang. 2024. Stiffness sensing via Piezo1 enhances macrophage efferocytosis and promotes the resolution of liver fibrosis. *Sci. Adv.* 10:eadj3289. https://doi.org/10.1126/sciadv.adj3289
Wang, B., J. Liu, Q. Wang, M. Arhatte, L.Y. Cheong, E. Glogowska, X. Jiang, S.K. Chung, L. Jin, Q. Hu, et al. 2025a. Piezo1 activation suppresses bone marrow adipogenesis to prevent osteoporosis by inhibiting a mechanoinflammatory autocrine loop. *Signal. Transduct. Target. Ther.* 10:357. https://doi.org/10.1038/s41392-025-02455-w
Wang, J., W. Zhao, W. Bai, D. Dong, H. Wang, X. Qi, A. Thanabalasuriar, Y. Ye, T. Xu, H. Li, et al. 2025b. PIEZO1 mediates mechanical reprogramming of neutrophils for proangiogenic specialization in the lung. *J. Clin. Invest.* 135:e183796. https://doi.org/10.1172/JCI183796
Wang, Z., Y. Elbanna, I. Godet, S. Gan, L. Peters, G. Lampe, Y. Chen, J. Xavier, M. Huse, and J. Massagué. 2026. TGFβ induces an atypical EMT to evade immune mechanosurveillance in lung adenocarcinoma dormant metastasis. *Nat. Cancer*. 7:131–149. https://doi.org/10.1038/s43018-025-01094-y
Ward, N.A., H. Prendeville, E.J. Wallace, P. Shokrani, L. Trask, R. Dillon, R. Beatty, E.T. Roche, G.P. Duffy, and E.B. Dolan. 2025. Mechanotherapy: Modulating immune cell function in tissue regeneration and fibrosis. *Acta Biomater.* 205:34–53. https://doi.org/10.1016/j.actbio.2025.08.048
Warnatsch, A., M. Ioannou, Q. Wang, and V. Papayannopoulos. 2015. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. *Science*. 349:316–320. https://doi.org/10.1126/science.aaa8064
Weber, J., S. Rajan, C. Schremmer, Y.-K. Chao, G. Krasteva-Christ, M. Kannler, A.Ö. Yildirim, M. Brosien, J. Schredelseker, N. Weissmann, et al. 2020. TRPV4 channels are essential for alveolar epithelial barrier function as protection from lung edema. *JCI Insight*. 5:e134464. https://doi.org/10.1172/jci.insight.134464
Wehner, S., B.M. Buchholz, S. Schuchtrup, A. Rocke, N. Schaefer, M. Lysson, A. Hirner, and J.C. Kalff. 2010. Mechanical strain and TLR4 synergistically induce cell-specific inflammatory gene expression in intestinal smooth muscle cells and peritoneal macrophages. *Am. J. Physiol. Gastrointest. Liver Physiol.* 299:G1187–G1197. https://doi.org/10.1152/ajpgi.00452.2009
Wenqiang, D., A. Novin, Y. Liu, J. Afzal, Y. Suhail, S. Liu, N.R. Gavin, J.R. Jorgensen, C.M. Morosky, R. Figueroa, et al. 2024. Scar matrix drives Piezo1 mediated stromal inflammation leading to placenta accreta spectrum. *Nat. Commun.* 15:8379. https://doi.org/10.1038/s41467-024-52351-0
Winer, D.A., H. Du, J. Kim, V. Chang, M. Burke, S. Winer, S.V. Costes, J.-P. Frippiat, C. Sams, A.M. Paul, et al. 2026. Astroimmunology: The effects of spaceflight and its associated stressors on the immune system. *Nat. Rev. Immunol.* 26:189–212. https://doi.org/10.1038/s41577-025-01226-6
Wipff, P.-J., D.B. Rifkin, J.-J. Meister, and B. Hinz. 2007. Myofibroblast contraction activates latent TGF-β1 from the extracellular matrix. *J. Cell Biol.* 179:1311–1323. https://doi.org/10.1083/jcb.200704042
Wishart, A.L., S.J. Conner, J.R. Guarin, J.P. Fatherree, Y. Peng, R.A. McGinn, R. Crews, S.P. Naber, M. Hunter, A.S. Greenberg, and M.J. Oudin. 2020. Decellularized extracellular matrix scaffolds identify full-length collagen VI as a driver of breast cancer cell invasion in obesity and metastasis. *Sci. Adv.* 6:eabc3175. https://doi.org/10.1126/sciadv.abc3175
Wong, V.W., K.C. Rustad, S. Akaishi, M. Sorkin, J.P. Glotzbach, M. Januszyk, E.R. Nelson, K. Levi, J. Paterno, I.N. Vial, et al. 2012. Focal adhesion kinase links mechanical force to skin fibrosis via inflammatory signaling. *Nat. Med.* 18:148–152. https://doi.org/10.1038/nm.2574
Wong, V.W., R.K. Garg, M. Sorkin, K.C. Rustad, S. Akaishi, K. Levi, E.R. Nelson, M. Tran, R. Rennert, W. Liu, et al. 2014. Loss of keratinocyte focal adhesion kinase stimulates dermal proteolysis through upregulation of MMP9 in wound healing. *Ann. Surg.* 260:1138–1146. https://doi.org/10.1097/SLA.0000000000000219
Wong, N.R., J. Mohan, B.J. Kopecky, S. Guo, L. Du, J. Leid, G. Feng, I. Lokshina, O. Dmytrenko, H. Luehmann, et al. 2021. Resident cardiac macrophages mediate adaptive myocardial remodeling. *Immunity*. 54:2072–2088.e7. https://doi.org/10.1016/j.immuni.2021.07.003
Worthen, G.S., B. Schwab, E.L. Elson, and G.P. Downey. 1989. Mechanics of stimulated neutrophils: Cell stiffening induces retention in capillaries. *Science*. 245:183–186. https://doi.org/10.1126/science.2749255
Wu, J., Z. Yan, D.E. Schwartz, J. Yu, A.B. Malik, and G. Hu. 2013. Activation of NLRP3 inflammasome in alveolar macrophages contributes to mechanical stretch-induced lung inflammation and injury. *J. Immunol.* 190: 3590–3599. https://doi.org/10.4049/jimmunol.1200860
Wu, J., Y. Chen, Z. Liao, H. Liu, S. Zhang, D. Zhong, X. Qiu, T. Chen, D. Su, X. Ke, et al. 2022. Self-amplifying loop of NF-κB and periostin initiated by PIEZO1 accelerates mechano-induced senescence of nucleus pulposus cells and intervertebral disc degeneration. *Mol. Ther.* 30:3241–3256. https://doi.org/10.1016/j.ymthe.2022.05.021
Wu, F., H. Du, E. Overbey, J. Kim, P. Makhijani, N. Martin, C.A. Lerner, K. Nguyen, J. Baechle, T.R. Valentino, et al. 2024a. Single-cell analysis identifies conserved features of immune dysfunction in simulated microgravity and spaceflight. *Nat. Commun.* 15:4795. https://doi.org/10.1038/s41467-023-42013-y
Wu, P., A.Y. Hsu, T. Peng, W. Zhao, F. Liu, Z. Zhang, L. Ghimire, A. Balasubramanian, X. Xie, J. Li, et al. 2024b. The effect of transient, constricted migration on neutrophil intracellular bacteria-killing capability. *Immunity*. 57:1713–1715. https://doi.org/10.1016/j.immuni.2024.07.008
Wu, Y., Y. Song, J. Soto, T. Hoffman, X. Lin, A. Zhang, S. Chen, R.N. Massad, X. Han, D. Qi, et al. 2025. Viscoelastic extracellular matrix enhances epigenetic remodeling and cellular plasticity. *Nat. Commun.* 16:4054. https://doi.org/10.1038/s41467-025-59190-7
Xie, Y., D. Chen, K. Jiang, L. Song, N. Qian, Y. Du, Y. Yang, F. Wang, and T. Chen. 2022. Hair shaft miniaturization causes stem cell depletion through mechanosensory signals mediated by a Piezo1-calcium-TNF-α axis. *Cell Stem Cell*. 29:70–85.e6. https://doi.org/10.1016/j.stem.2021.09.009
Xie, W., X. Yu, Q. Yang, N. Ke, P. Wang, H. Kong, X. Wu, P. Ma, L. Chen, J. Yang, et al. 2025a. The immunomechanical checkpoint PYK2 governs

monocyte-to-macrophage differentiation in pancreatic cancer. *Cancer Discov.* 15:1740–1765. https://doi.org/10.1158/2159-8290.CD-24-1712

Xie, Z., L. Rose, J. Feng, Y. Zhao, Y. Lu, H. Kane, T.J. Hibberd, X. Hu, Z. Wang, K. Zang, et al. 2025b. Enteric neuronal Piezo1 maintains mechanical and immunological homeostasis by sensing force. *Cell.* 188:2417–2432.e19. https://doi.org/10.1016/j.cell.2025.02.031

Xu, J., J. Mathur, E. Vessières, S. Hammack, K. Nonomura, J. Favre, L. Grimaud, M. Petrus, A. Francisco, J. Li, et al. 2018. GPR68 senses flow and is essential for vascular physiology. *Cell.* 173:762–775.e16. https://doi.org/10.1016/j.cell.2018.03.076

Xu, Y., L. Ying, J.K. Lang, B. Hinz, and R. Zhao. 2024. Modeling mechanical activation of macrophages during pulmonary fibrogenesis for targeted anti-fibrosis therapy. *Sci. Adv.* 10:eadj9559. https://doi.org/10.1126/sciadv.adj9559

Xu, X., D. Wang, B. Ni, H. Xu, Z. Wu, T. He, Y. Zhang, X. Hao, G. Ding, X. Zhang, et al. 2025a. Inhibiting the REV-ERBα expression protects against mechanical overloading-induced cartilage clock disruption and osteoarthritis progression. *J. Orthop. Translat.* 53:112–125. https://doi.org/10.1016/j.jot.2025.06.005

Xu, X., L. Wang, X. Bi, T. Cao, M. Gao, B. Hu, J. Zhong, C. Ji, R. Sun, C. Sun, et al. 2025b. Targeted silencing of Engrailed-1 reprograms profibrotic fibroblast lineage for scarless wound healing. *Mol. Ther.* 33:4889–4903. https://doi.org/10.1016/j.ymthe.2025.07.031

Xue, Y., E. Winnicki, Z. Zhang, I. Lopez, S. Wang, C. Kirby, S.S. Lee, A. Li, C. Lee, H. Minsky, et al. 2025. The mechanotransducer Piezo1 coordinates metabolism and inflammation to promote skin growth. *Nat. Commun.* 16:6876. https://doi.org/10.1038/s41467-025-62270-3

Yamada, S., R. Yasukuni, Y. Bessho, Y. Fujita, Y. Hosokawa, and T. Matsui. 2025. Mechanochemical mechanism underlying intercellular Ca2+ wave propagation and its crucial role in apoptotic cell extrusion. *Nat. Commun.* 16:9887. https://doi.org/10.1038/s41467-025-65474-9

Yamaguchi, N., and H. Knaut. 2022. Focal adhesion-mediated cell anchoring and migration: From *in vitro* to *in vivo*. *Development*. 149:dev200647. https://doi.org/10.1242/dev.200647

Yang, X.-C., and F. Sachs. 1989. Block of stretch-activated ion channels in *Xenopus* oocytes by gadolinium and calcium ions. *Science*. 243:1068–1071. https://doi.org/10.1126/science.2466333

Yang, Z., Y. Zhao, X. Zhang, L. Huang, K. Wang, J. Sun, N. Chen, W. Yin, S. Chen, H. Zhi, et al. 2024. Nano-mechanical immunoengineering: Nanoparticle elasticity reprograms tumor-associated macrophages via Piezo1. *ACS Nano*. 18:21221–21235. https://doi.org/10.1021/acsnano.4c04614

Yang, K., R. Zhong, K. Li, J. Mai, P. Liu, Y. He, J. Rich, Y. Chen, J. Wang, Z. Ma, et al. 2026. Precision acoustofluidics for high-throughput mechanobiology in suspension cells. *Sci. Adv.* 12:eady1136. https://doi.org/10.1126/sciadv.ady1136

Yi, J., Y. Wang, H. Sui, Z. Chen, T. Ye, Y. Zhong, J. Qian, B. Wu, J. Huang, T. Tian, et al. 2025. Elastin-derived extracellular matrix fragments drive aging through innate immune activation. *Nat. Aging.* 5:2380–2398. https://doi.org/10.1038/s43587-025-00961-8

Yu, J., S. Bergaya, T. Murata, I.F. Alp, M.P. Bauer, M.I. Lin, M. Drab, T. V Kurzchalia, R. V Stan, and W.C. Sessa. 2006. Direct evidence for the role of caveolin-1 and caveolae in mechanotransduction and remodeling of blood vessels. *J. Clin. Invest.* 116:1284–1291. https://doi.org/10.1172/JCI27100

Yu, X., J. Tan, and S.L. Diamond. 2018. Hemodynamic force triggers rapid NETosis within sterile thrombotic occlusions. *J. Thromb. Haemost.* 16:316–329. https://doi.org/10.1111/jth.13907

Yu, H., Z. Liu, H. Guo, X. Hu, Y. Wang, X. Cheng, L.W. Zhang, and Y. Wang. 2024. Mechanoimmune-driven backpack sustains dendritic cell maturation for synergistic tumor radiotherapy. *ACS Nano*. 18:23741–23756. https://doi.org/10.1021/acsnano.4c08701

Yu, X., V. Mukwaya, L. Wang, W. Zhao, S. Mann, and H. Dou. 2025. Mechanocrosstalk between living and artificial cells. *Nat. Commun.* 16:8582. https://doi.org/10.1038/s41467-025-63581-1

Yuan, P., Q. Hu, X. He, Y. Long, X. Song, F. Wu, Y. He, and X. Zhou. 2020. Laminar flow inhibits the Hippo/YAP pathway via autophagy and SIRT1-mediated deacetylation against atherosclerosis. *Cell Death Dis.* 11:141. https://doi.org/10.1038/s41419-020-2343-1

Zak, A., S.V. Merino-Cortés, A. Sadoun, F. Mustapha, A. Babataheri, S. Dogniaux, S. Dupré-Crochet, E. Hudik, H.-T. He, A.I. Barakat, et al. 2021. Rapid viscoelastic changes are a hallmark of early leukocyte activation. *Biophys. J.* 120:1692–1704. https://doi.org/10.1016/j.bpj.2021.02.042

Zepp, J.A., M.P. Morley, C. Loebel, M.M. Kremp, F.N. Chaudhry, M.C. Basil, J.P. Leach, D.C. Liberti, T.K. Niethamer, Y. Ying, et al. 2021. Genomic, epigenomic, and biophysical cues controlling the emergence of the lung alveolus. *Science*. 371:eabc3172. https://doi.org/10.1126/science.abc3172

Zhang, H., S.K. Ramakrishnan, D. Triner, B. Centofanti, D. Maitra, B. Győrffy, J.S. Sebolt-Leopold, M.K. Dame, J. Varani, D.E. Brenner, et al. 2015. Tumor-selective proteotoxicity of verteporfin inhibits colon cancer progression independently of YAP1. *Sci. Signal.* 8:ra98. https://doi.org/10.1126/scisignal.aac5418

Zhang, H., C.K. Tsui, G. Garcia, L.K. Joe, H. Wu, A. Maruichi, W. Fan, S. Pandovski, P.H. Yoon, B.M. Webster, et al. 2024a. The extracellular matrix integrates mitochondrial homeostasis. *Cell.* 187:4289–4304.e26. https://doi.org/10.1016/j.cell.2024.05.057

Zhang, J., W. Chen, K. Song, K. Song, J. Kolls, and T. Wu. 2024b. YAP activation in liver macrophages via depletion of MST1/MST2 enhances liver inflammation and fibrosis in MASLD. *FASEB J.* 38:e70026. https://doi.org/10.1096/fj.202400813RR

Zhang, J., J. Li, Y. Hou, Y. Lin, H. Zhao, Y. Shi, K. Chen, C. Nian, J. Tang, L. Pan, et al. 2024c. Osr2 functions as a biomechanical checkpoint to aggravate CD8+ T cell exhaustion in tumor. *Cell.* 187:3409–3426.e24. https://doi.org/10.1016/j.cell.2024.04.023

Zhang, Y., S.A. Kini, S.A. Mishkanian, O. Yarishkin, R. Luo, S.H. Seradj, V.H. Leung, Y. Wang, M.R. Servín-Vences, W.T. Keenan, et al. 2025. PIEZO channels link mechanical forces to uterine contractions in parturition. *Science*. 390:eady3045. https://doi.org/10.1126/science.ady3045

Zhang, L., X. Gui, R. Hou, L. Jia, S. Xia, X. Zhang, Y. Fu, Q.-F. Meng, Q. Luo, X. Shi, et al. 2026. Single-cell multiomics uncovers an endothelial mechanosensitive PIEZO1-IL-33 axis driving pulmonary fibrosis. *Nat. Commun.* 17:2655. https://doi.org/10.1038/s41467-026-70193-w

Zhao, Z., X. Chen, A.M. Dowbaj, A. Sljukic, K. Bratlie, L. Lin, E.L.S. Fong, G.M. Balachander, Z. Chen, A. Soragni, et al. 2022. Organoids. *Nat. Rev. Methods Primers*. 2:94. https://doi.org/10.1038/s43586-022-00174-y

Zhao, Y., M. Simon, A. Seluanov, and V. Gorbunova. 2023. DNA damage and repair in age-related inflammation. *Nat. Rev. Immunol.* 23:75–89. https://doi.org/10.1038/s41577-022-00751-y

Zhen, G., Q. Guo, Y. Li, C. Wu, S. Zhu, R. Wang, X.E. Guo, B.C. Kim, J. Huang, Y. Hu, et al. 2021. Mechanical stress determines the configuration of TGFβ activation in articular cartilage. *Nat. Commun.* 12:1706. https://doi.org/10.1038/s41467-021-21948-0

Zhong, G., S. Su, J. Li, H. Zhao, D. Hu, J. Chen, S. Li, Y. Lin, L. Wen, X. Lin, et al. 2023. Activation of Piezo1 promotes osteogenic differentiation of aortic valve interstitial cell through YAP-dependent glutaminolysis. *Sci. Adv.* 9:eadg0478. https://doi.org/10.1126/sciadv.adg0478

Zhou, X., W. Li, S. Wang, P. Zhang, Q. Wang, J. Xiao, C. Zhang, X. Zheng, X. Xu, S. Xue, et al. 2019. YAP aggravates inflammatory bowel disease by regulating M1/M2 macrophage polarization and gut microbial homeostasis. *Cell Rep.* 27:1176–1189.e5. https://doi.org/10.1016/j.celrep.2019.03.028

Zhou, X., R.A. Franklin, M. Adler, T.S. Carter, E. Condiff, T.S. Adams, S.D. Pope, N.H. Philip, M.L. Meizlish, N. Kaminski, and R. Medzhitov. 2022. Microenvironmental sensing by fibroblasts controls macrophage population size. *Proc. Natl. Acad. Sci. USA*. 119:e2205360119. https://doi.org/10.1073/pnas.2205360119

Zhou, Y., D. Wang, L. Zhou, N. Zhou, Z. Wang, J. Chen, R. Pang, H. Fu, Q. Huang, F. Dong, et al. 2024. Cell softness renders cytotoxic T lymphocytes and T leukemic cells resistant to perforin-mediated killing. *Nat. Commun.* 15:1405. https://doi.org/10.1038/s41467-024-45750-w

Zhou, F., R.J. Ju, C. Kang, J. Li, A. Yang, A. Libert, Y. Sun, L. Liang, Y. Ai, X. Hu, et al. 2025a. Mechanical confinement induces ferroptosis through mitochondrial dysfunction. *Nat. Commun.* 16:11717. https://doi.org/10.1038/s41467-025-66353-z

Zhou, Y., M. Li, S. Lin, Z. Zhu, Z. Zhuang, S. Cui, L. Chen, R. Zhang, X. Wang, B. Shen, et al. 2025b. Mechanical sensing protein PIEZO1 controls osteoarthritis via glycolysis mediated mesenchymal stem cells-Th17 cells crosstalk. *Cell Death Dis.* 16:231. https://doi.org/10.1038/s41419-025-07577-1

Zhu, Y., H. Liang, X. Liu, J. Wu, C. Yang, T.M. Wong, K.Y.H. Kwan, K.M.C. Cheung, S. Wu, and K.W.K. Yeung. 2021. Regulation of macrophage polarization through surface topography design to facilitate implant-to-bone osteointegration. *Sci. Adv.* 7:eabf6654. https://doi.org/10.1126/sciadv.abf6654

Zhu, Y., T. Wang, Y. Yang, Z. Wang, X. Chen, L. Wang, R. Niu, Z. Sun, C. Zhang, Y. Luo, et al. 2024. Low shear stress exacerbates atherosclerosis by inducing the generation of neutrophil extracellular traps via Piezo1-mediated mechanosensation. *Atherosclerosis*. 391:117473. https://doi.org/10.1016/j.atherosclerosis.2024.117473

Zou, Z., X. Qian, J. Ren, Y. Wang, Y. Liu, A. Luo, M. Guo, H. Tong, R. Li, S. Li, and H. Zhang. 2026. Mechanical activation of PIEZO1 drives AP-1–dependent PTGS2/PGE2 signaling and corneal inflammation. *iScience*. 29:115396. https://doi.org/10.1016/j.isci.2026.115396