

REVIEW

Mechanobiology of inflammation: Pulling the strings of innate immunity

Marcin Krzysztof Maniak¹ , Stephen J. Jenkins¹ , and Carsten Gram Hansen¹ 

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 (Trepap 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- κ B 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.

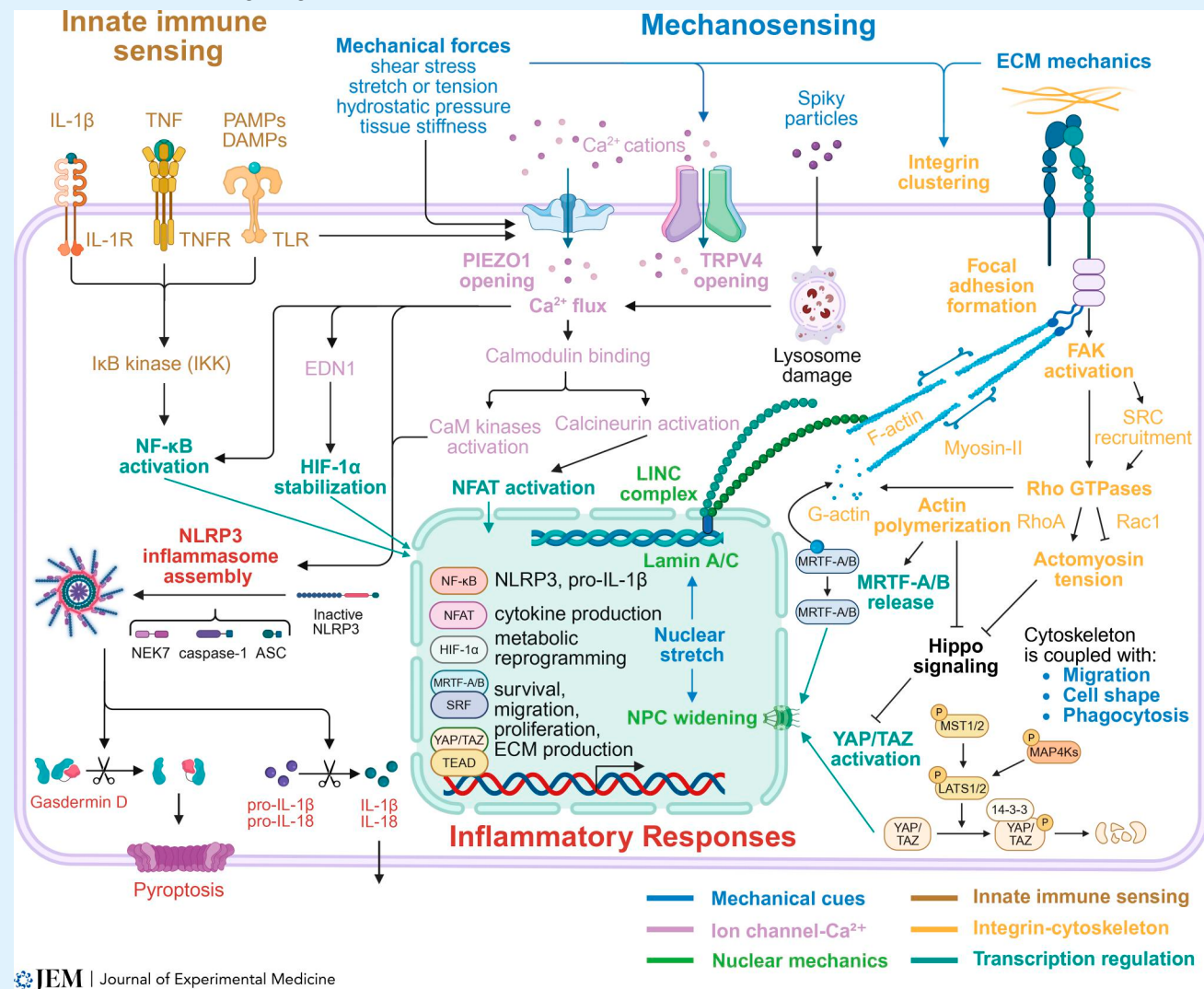
In this review, we take a whole-body perspective on how mechanical forces pull the strings of inflammation. We focus primarily on mammalian innate immunity and begin by examining barrier tissues, such as lungs, gut, and skin, where mechanical stress first interfaces with immunity. We then explore stromal 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

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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 mechano-transduction (Geng et al., 2021). Downstream Ca^{2+} /calmodulin signaling intersects with inflammatory pathways by contributing to NF- κ B and inflammasome activation, linking mechanical stress to pyroptosis and IL-1 β 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- α (HIF-1 α), 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-1 β -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; Eloegui-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

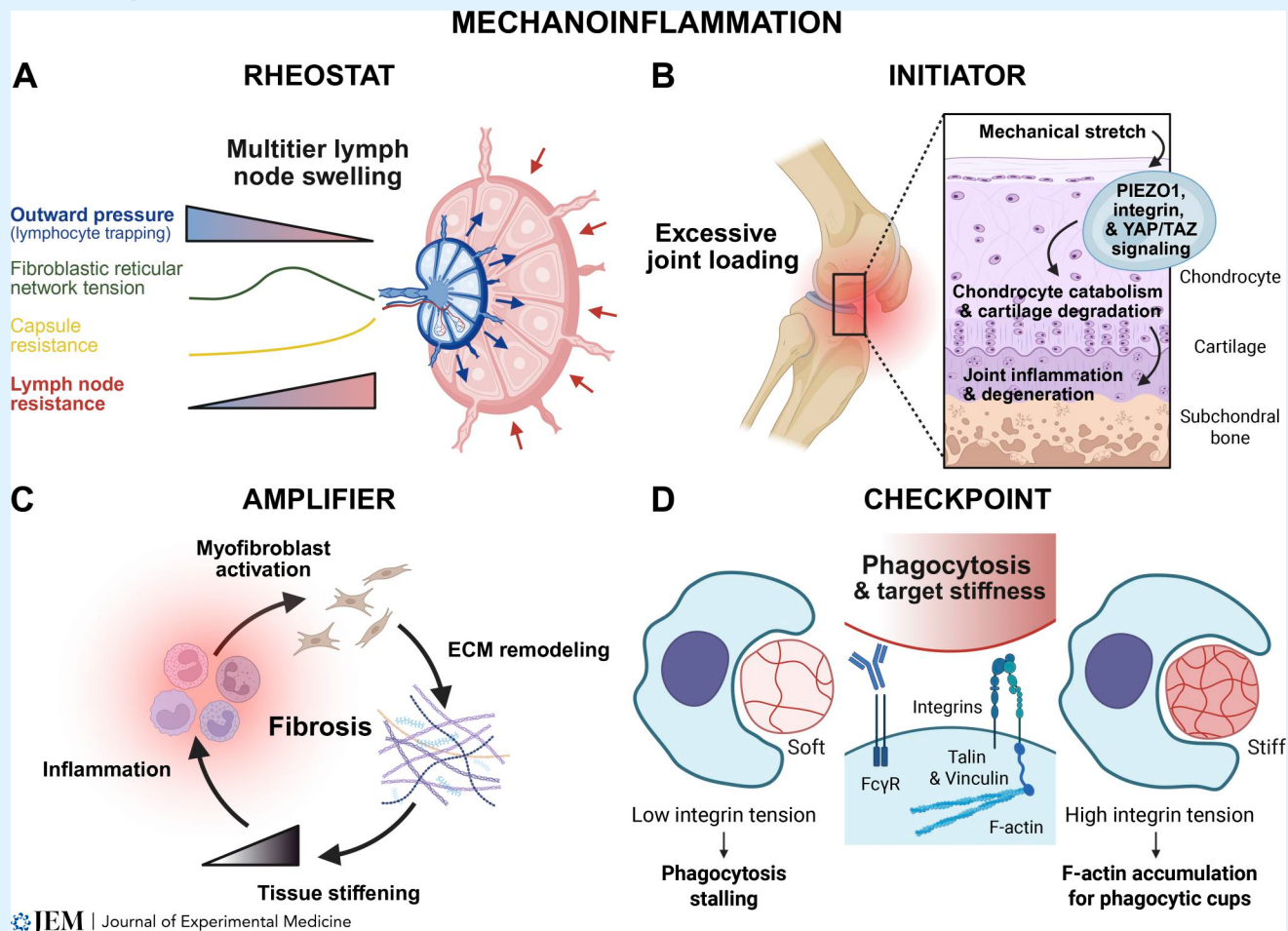
requires cytoskeletal remodeling dependent on RAC1, a member of the Rho GTPase family, to enable cells to deform and separate during shedding (Martínez-Sánchez et al., 2023). Consequently, in *Rac1* knockout mice, cell extrusion stalls, leading to overcrowding, junctional disruption, epithelial leakage, 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- κ B, 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 (Natanski 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-1 β release (Wu et al., 2013). Monocytes and macrophages sense cyclical hydrostatic pressure via PIEZO1, which facilitates Ca²⁺ influx into the cytoplasm, activating a signaling cascade that stabilizes HIF-1 α 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- β 1-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- β 1, 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-1 β , 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- κ B 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-1 α , 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 mechano-regulatory 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.

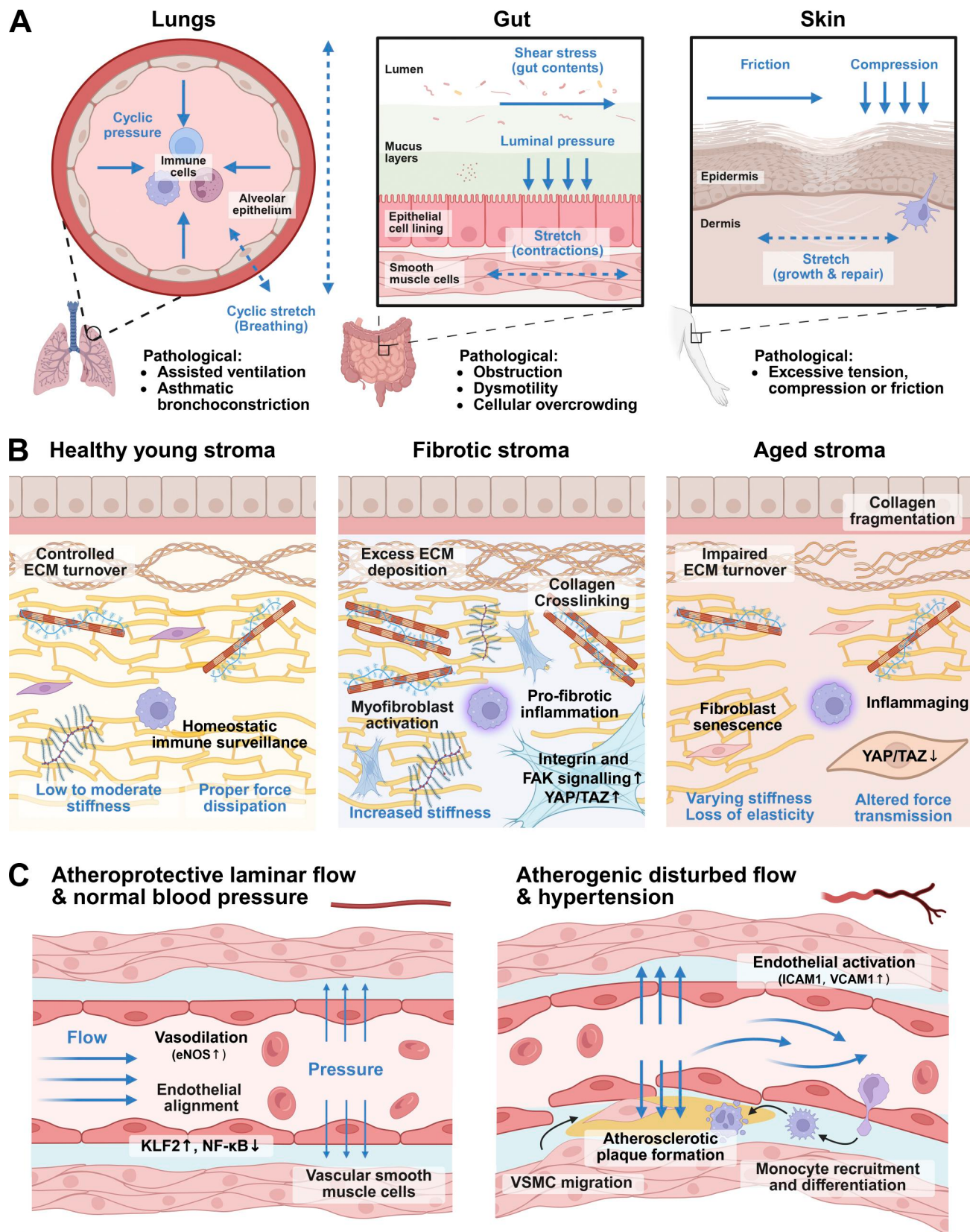
However, age-related ECM cross-linking, stiffening, and viscoelasticity changes disrupt force transmission, impairing immune cell migration and surveillance while promoting inflammation and fibrosis across organs (Lampi and Reinhart-King, 2018; Segel et al., 2019; Sladitschek-Martens et al., 2022; López-Otín 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-1 β , 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-



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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- κ B-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- κ B 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 β 1-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 (Adebawale et al., 2021; Adebawale 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 $\alpha 2\beta 1$ 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- $\beta 1$, 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 *Csfl*, 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 $\alpha v\beta 3$ 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 $\alpha M\beta 2$ - 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-1 α -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- κ B

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'Connor 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, α V-integrin-mediated activation of latent TGF β , 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- κ B, 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- κ B-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- κ B 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, pro-inflammatory 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-1 α 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 *Piezol* 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 mechanobiology 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- β 1 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- κ B 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- κ B 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- κ B, 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- κ B, 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- κ B-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- κ B signaling and downstream inflammatory cytokines such as IL-1 β 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 (Bobbà 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-1 β -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 mechano-transduction 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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