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REVIEW

T-cell mechanobiology: How molecular forces shape immune function

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T cells are central to adaptive immunity, and continuously sense, generate, and respond to mechanical forces. Advances in mechanoimmunology show that T-cell behavior is tightly shaped by the physical properties of their environment, including stiffness, viscoelasticity, ligand arrangement, and tissue topography. T-cell activation depends not only on biochemical signals but also on forces transmitted through the T-cell receptor, coreceptors, and mechanosensitive ion channels, which converge on the cytoskeleton to regulate signaling and effector function. When these mechanical interactions are disrupted, as in cancer, autoimmune diseases, or aging, T-cell function is impaired. Despite recent progress, T-cell mechanobiology remains partially understood, limited by challenges in measuring forces at relevant spatial and temporal scales. Incorporating biophysical principles into the design of immunotherapies may enhance treatment efficacy, specificity, and safety. This review summarizes emerging concepts in T-cell mechanobiology and outlines key challenges and future directions toward integrating mechanical and biochemical regulation of adaptive immunity.

Introduction

T lymphocytes (T cells) are crucial mediators of the adaptive immune response, responsible for recognizing and eliminating infected or malignant cells (Sun et al., 2023). T cells arise from the hematopoietic stem cells in the bone marrow and migrate to the thymus, where they undergo tightly regulated differentiation and selection (Chopp et al., 2023). Following thymic entry, double-negative thymocytes ($CD3^+$, $CD4^-$, $CD8^-$) initiate T-cell receptor (TCR) gene rearrangements, generating a diverse repertoire of αβ TCR heterodimers that provide each T cell with unique antigen specificity. During positive selection in the thymic cortex, cortical epithelial cells present self-peptides on major histocompatibility complex (MHC) molecules (Marx et al., 2021). Thymocytes with TCRs recognizing MHC class II commit to the $CD4^+$ helper lineage, whereas those recognizing MHC class I differentiate into $CD8^+$ cytotoxic T cells. Cells failing to recognize self-MHC die, while those with excessive self-reactivity are eliminated during negative selection in the thymic medulla. A subset of $CD4^+$ thymocytes with intermediate affinity for self-antigens differentiate into thymic regulatory T cells (Tregs), characterized by the expression of the transcription factor FOXP3 (Owen et al., 2019). Together with the peripherally induced Tregs, which arise from conventional $CD4^+$ T cells under tolerogenic conditions in peripheral tissues, these cells maintain immune tolerance and prevent autoimmunity by suppressing excessive immune activation (Ashby and Hogquist, 2024; Chopp et al., 2023).

The resulting naïve single-positive T cells exit the thymus and migrate to secondary lymphoid organs, where they continuously scan antigen-presenting cells (APCs) for cognate peptide–MHC (pMHC) complexes (Fowell and Kim, 2021). Specific TCR engagement and appropriate costimulatory signaling trigger clonal expansion of the matching T-cell clone, producing a large population of effector T cells that mediate the corresponding immune responses: $CD8^+$ T cells eliminate infected or cancerous cells through cytolysis, while $CD4^+$ T cells coordinate the immune response by activating other immune cells (Adams et al., 2020). Following antigen clearance, most effector T cells undergo apoptosis during the contraction phase, while a small subset of cells persists in the circulation and lymphoid tissues as memory T cells, capable of enabling faster and more robust responses upon reexposure to the same antigen (Kaech and Cui, 2012). As such, throughout their lifespan T cells move across multiple tissues and engage in diverse cell–cell interactions (Fig. 1) (Rushdi et al., 2020; Sun et al., 2023).

While biomolecular and biochemical approaches have been instrumental in shaping our current understanding of T-cell biology (Sun et al., 2023), the role of mechanical forces and physical properties has remained comparatively underexplored. This is particularly surprising given the inherently mechanical nature of many T-cell functions: they must actively migrate through crowded tissues, squeeze through narrow endothelial gaps, and form dynamic immunological synapses (ISs) (Fig. 1).

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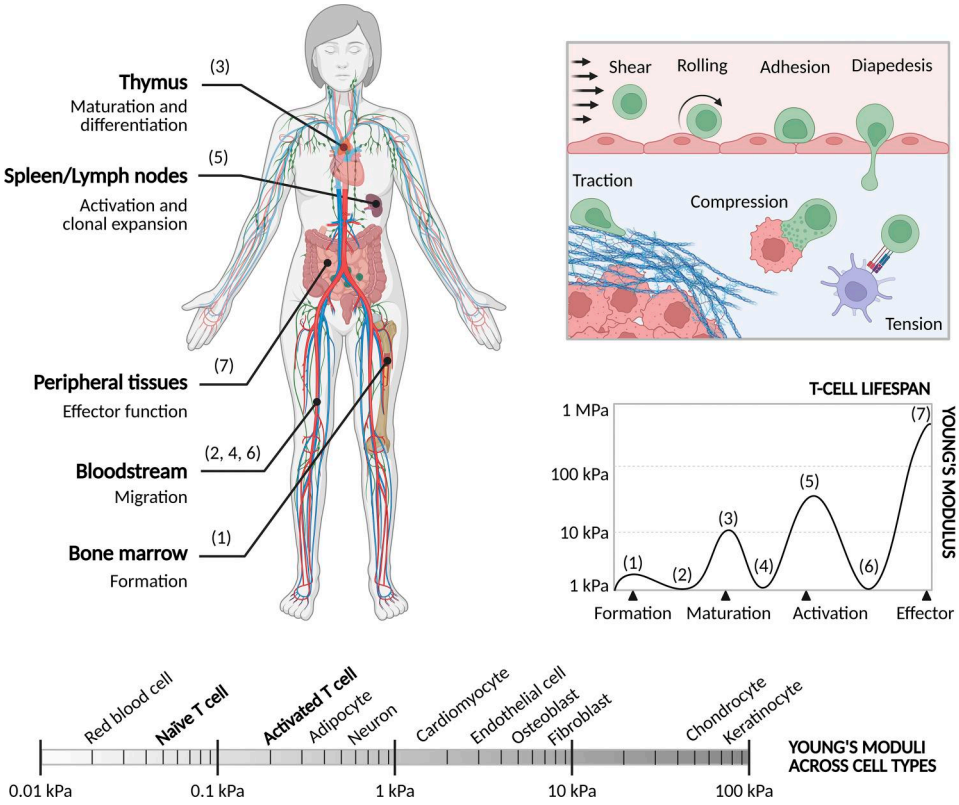

Figure 1. **Mechanical environments across T-cell lifespan.** T cells originate from the hematopoietic stem cells in the bone marrow, mature in the thymus, and circulate through blood and lymphoid organs before migrating to the peripheral tissues to execute effector functions. Along this journey, they encounter a wide range of mechanical conditions, including tissues with distinct stiffness, confined vascular and lymphatic spaces, and dynamic forces during migration and IS formation, which shape their function. Notably, T cells are among the softest cells in the human body, making them particularly sensitive to mechanical changes across tissues.

Emerging research in mechanoimmunology (Box 2) (how physical cues influence immune function) (Pageon et al., 2018) and immunomechanics (Box 2) (how immune cells generate and exert forces) (Mukhopadhyay, 2023) reveals that mechanical factors are integral to T-cell behavior. However, our understanding of these processes remains limited, partly due to the intrinsic biophysical characteristics of T cells, which complicate their experimental manipulation. T cells are small, nonadherent, and spherical, with a large and relatively stiff nuclear core. These features pose significant technical challenges to probe with conventional biophysical tools (Box 1) compared with other eukaryotic cells.

The field is currently guided by several fundamental questions. What are the forces experienced by T cells in vivo, and how do these compare with those measured in vitro? How does the TCR convert mechanical inputs into biochemical signals that determine activation or tolerance? How do mechanical properties of tissues shape T-cell migration, activation, and differentiation? And to what extent can these mechanobiological principles be exploited to improve immunotherapies?

Addressing these questions is important not only for refining our understanding of T-cell biology, but also for translating mechanobiological insights into clinical applications. In this review, we summarize recent advances in T-cell immunomechanics and mechanoimmunology across naïve and activated states, and during migration. We also examine how mechanical properties are altered in disease, particularly in response to tumor microenvironmental changes. Finally, we provide a glimpse of recent research showing how mechanobiology (Box 2) can contribute to new developments in immunotherapy.

Mechanoimmunology and immunomechanics

T cells are not only biochemically driven but also highly mechanosensitive cells, with the capacity to respond to the physical features of the environment that surrounds them (Pathni et al., 2024). Their ability to migrate, scan for antigens, form ISs, and execute effector functions is deeply connected to their intrinsic mechanical properties, as well as mechanosensory and mechanotransduction traits. Interestingly, research in the past decades has shown that these immunomechanical and mechanoimmunological features are not uniform across T-cell types, states, or microenvironments, but vary widely, depending on the conditions (Table 1).

High-speed live-cell super-resolution microscopy has revealed striking differences in the actin cytoskeletal organization and dynamics between Jurkat leukemic T cells and primary mouse and human T cells (Colin-York et al., 2019b). Although the three cell types show comparable calcium signaling upon stimulation, Jurkat cells exhibit a delayed calcium response, reflecting underlying differences in the cytoskeleton. At the IS,

Box 1. **Experimental tools for T-cell mechanobiology**

Quantifying forces sensed and generated by T cells relies on a limited set of high-resolution biophysical tools, each probing distinct force regimes, spatial scales, and aspects of T-cell function.

Atomic force microscopy

AFM consists of using a cantilever to apply or measure forces at the cell surface with pico- to nanonewton sensitivity. In T-cell studies, it is commonly used to quantify cell stiffness, receptor–ligand binding forces (e.g., TCR vs. pMHC), and mechanotransduction responses. AFM enables precise force control and can probe single cells and single-molecule interactions. However, it is inherently low-throughput and typically probes one interaction at a time, limiting its ability to capture the spatiotemporal complexity of the IS. In addition, the cantilever geometry and loading rates can influence measured forces, complicating comparisons across studies (Krieg et al., 2019).

Biomembrane force probe

Biomembrane force probe uses a deformable red blood cell as a force sensor to measure receptor–ligand interactions with high sensitivity and temporal resolution. It has been particularly powerful for characterizing TCR binding kinetics, including catch-bond behavior under force. Its strength lies in resolving fast, single-bond dynamics under well-defined loading conditions. However, similar to AFM, it is low-throughput and focuses on isolated molecular interactions rather than collective cell-scale mechanics. It also requires specialized setups and careful calibration, limiting accessibility (Moldovan et al., 2023).

TFM

TFM measures the forces exerted by cells on deformable substrates by tracking bead displacement within compliant gels. In T cells, it is used to understand how forces are distributed across the IS and how they evolve during activation. It provides spatial maps of cellular traction forces and can be combined with imaging of signaling events. However, its resolution is limited by substrate properties, bead density, and microscopy setting, as well as the assumption of linear elastic behavior of the substrate, which may not reflect physiological ECM conditions. TMF primary captures cell–substrate forces and does not directly measure forces at specific molecular interactions (Zancla et al., 2022).

Optical tweezers

Optical tweezers use highly focused laser beams to trap and manipulate microscopy particles, enabling force measurements in the piconewton range. They are widely used to probe TCR-pMHC interactions, membrane mechanics, and force-dependent signaling. Optical tweezers offer high force precision and dynamic control, making them well suited to study mechanosensitive signaling thresholds. However, they require attachment of beads or ligands to molecules of interest, which can perturb native interactions. As with AFM and biomembrane force probe, experiments are typically low-throughput and focus on simplified systems (Bustamante et al., 2021).

Overall, the features and limitations of these current techniques mean that they are best suited to uncover fundamental mechanistic principles, but less capable of predicting T-cell behavior in vivo.

the actin network is morphologically distinct: primary T cells show dynamic cortical actin undulations (~0.1 Hz), whereas Jurkat cells have a stable cortical network. While both cell types feature lamellipodium and lamellum (Box 2) structures, Jurkat cells lack actin foci.

These architectural differences translate into different force-generation strategies. In primary T cells, filamentous actin (F-actin) flow is driven by myosin II contractility, while Jurkat cells mostly rely on actin nucleation and polymerization. TCR mobility remains robust and is insensitive to the disruption of the two main actin nucleators (formin and Arp2/3) or myosin II, which suggests that TCR mobility can be sustained despite an altered actin architecture, because Jurkat T cells lack negative regulators of TCR signaling like SHIP-1 or PTEN (Colin-York et al., 2019b).

Tissue-resident memory T cells (TRM) demonstrate how the intrinsic mechanical activity supports immune surveillance in complex tissue environments (Ruef et al., 2023). In exocrine glands, TRM continuously scan their environment without external chemotactic cues, only relying on autonomously

Box 2. **Glossary**

- Mechanobiology: study of how mechanical properties and biophysical forces of cells and tissues influence biological processes such as cell signaling, differentiation, migration, and function.
- Mechanoimmunology: subfield of mechanobiology that studies how mechanical cues regulate immune cell function, including antigen recognition, activation, effector function, and migration.
- Immunomechanics: quantitative and physical characterization of mechanical properties and force dynamics within immune cells and their interactions.
- Mechanosensing: a cell's ability to detect and respond to mechanical stimuli through specialized receptors or cytoskeletal components.
- Mechanotransduction: process by which mechanical stimuli are converted into biochemical signals inside the cell.
- Mechanopotentiation: enhancement of cellular signaling or function through mechanical stimulation.
- Mechanogenetic: using mechanical stimulation to control genetic regulation and cellular functions.
- Lamellipodium: broad and flat actin-rich membrane protrusion at the leading edge of a migrating cell that drives forward movement by continuous actin polymerization.
- Lamellum: thicker and more stable actin network (more bundled and contractile actomyosin filaments) located behind the lamellipodium, which provides structural support and connects the lamellipodium to the cell body.
- Actin foci: WASP- and Arp2/3-dependent actin polymerization hubs that form at the T-cell–APC interface, stabilizing the IS.
- Integrin: mechanosensitive transmembrane αβ heterodimeric proteins that mediate cell adhesion and mechanical coupling between the ECM or other cells and the cytoskeleton. T cells mainly express LFA-1 and VLA-4 integrins.
- CAR T-cell therapy: therapy where T cells are engineered to express synthetic CARs that directly recognize tumor surface antigens for targeted cytotoxicity.
- eTCR therapy: therapy where T cells are modified to express eTCRs with enhanced affinity for tumor–pMHC complexes; thus, it is MHC-dependent.

Table 1. **Summary table of mechanical properties measured on living cells**

T-cell subtype	Cell immobilization	Method and specifications	Mechanical properties	Ref.
Jurkat T cells	Microfabricated wells	AFM •Number of cells: 37 •Pyramidal and colloidal (R = 5 µm) indenters •Spring constant: 0.009–0.011 N/m •Setpoint: 800 pN or indentation: 3 µm •Loading rate: 415 nm/s •Curve for fitting: approach •Hertz and liquid droplet models •Poisson's ratio: 0.5	Cell diameter •11.5 ± 1.5 µm Nucleus:cell ratio •55 ± 8% Young's modulus •48 ± 35 Pa Cortical tension •21 ± 13 pN/um	(Rosenbluth et al., 2006)
Lymph node cells of BALB/c mice •Resting •Activated (ConA) •Apoptotic (Dex)	–	AFM •Number of cells: – •Indenter radius <10 nm •Spring constant: 0.01 N/m •Setpoint: – •Loading rate: – •Curve for fitting: – •Hertz model •Poisson's ratio: 0.5	Cell diameter •Resting: 6–8 µm •Activated: 8–10 µm •Apoptotic: 5–7 µm Cell height •Resting: 1–1.5 µm (smooth) •Activated: 1.5–2 µm (rough) •Apoptotic: 0.8–1 µm (rough) Young's modulus •Resting: 11.2 ± 5.9 kPa •Activated: 19.7 ± 4 kPa •Apoptotic: 7.1 ± 4.1 kPa	(Hu et al., 2009)
Jurkat T cells Lymphocyte cells from peripheral vein of healthy volunteer donors	–	AFM •Number of cells: 30–40 per cell type •Indenter radius <10 nm •Spring constant: 0.01 N/m •Setpoint: – •Loading rate: – •Curve for fitting: – •Hertz model •Poisson's ratio: 0.5	Young's modulus before actin depolymerization •Jurkat: 0.23 ± 0.04 kPa •Lymphocyte: 1.24 ± 0.09 kPa Young's modulus after actin depolymerization (20 µg/ml Cyt-B) •Jurkat: 0.51 ± 0.06 kPa •Lymphocyte: 0.34 ± 0.04 kPa	(Cai et al., 2010)
Jurkat T cells Primary $CD4^+$ T cells	200 µg/ml fibronectin	Single microplate assay •Number of cells: eight Jurkat cells; – for primary $CD4^+$ T cells •Compression: 15–20% •Estimation of static Young's modulus from dynamic measurements •Viscoelastic properties three-decade sweep from 0.02- to 6.4-Hz oscillations (power law)	Young's modulus •Jurkat: 90 ± 10 Pa •Primary $CD4^+$ T cells: 85 ± 5 Pa Storage modulus (G'_0) •Jurkat: 80 + 70/-40 Pa •Primary $CD4^+$ T cells: – Loss modulus (G''_0) •Jurkat: 60 ± 10 Pa •Primary $CD4^+$ T cells: –	(Bufi et al., 2015)
Jurkat T cells	0.02% (200 µg/ml) PLL	AFM •Number of cells: – •Colloidal (R = 2.5 µm) indenter •Spring constant: 0.01 N/m •Setpoint: 0.2 nN •Loading rate: – •Curve for fitting: approach •Hertz model •Poisson's ratio: 0.5	Young's modulus •$CD4^-$ cells: 175 ± 18.4 Pa •$CD4^+$ cells: 108.8 ± 9.1 Pa	(Bui and Nguyen, 2016)
Jurkat T cells PWBCs from healthy volunteers	PLL	AFM •Number of cells: 10–15 •Pyramidal (R = 20 nm) indenter •Spring constant: 0.01 N/m •Setpoint: – •Loading rate: – •Curve for fitting: approach •Hertz model •Poisson's ratio: 0.5	Young's modulus •Jurkat at 25°C: 1.37 ± 0.55 and 2.72 ± 0.46 kPa •Jurkat at 37°C: 0.95 ± 0.28 kPa •PWBC at 25°C: 3.17 ± 1.23 kPa •PWBC at 37°C: 2.68 ± 1.24 kPa	(Li et al., 2015)

Table 1. **Summary table of mechanical properties measured on living cells (*Continued*)**

T-cell subtype	Cell immobilization	Method and specifications	Mechanical properties	Ref.
Activated CD8⁺ T cells	Cells allowed to settle at the bottom of the chamber	Micromanipulation •Number of cells: 20 in each sample (diff. donors) •Spherical (R = 25 µm) indenter •Indentation frequency: 50 Hz •Indentation speed: 2 µm/s •Hertz model •Poisson's ratio: 0.5	Rupture force •Day 0: 2.3 ± 0.8 µN •Day 2: 2.6 ± 0.9 µN •Day 4: 4.6 ± 1.6 µN Rupture stress/tension •Day 0: 0.58 ± 0.07 N/m •Day 2: 0.45 ± 0.07 N/m •Day 4: 0.62 ± 0.1 N/m Young's modulus •Day 0 (resting): 58 ± 6.3 kPa •Day 2 (after activation): 43.7 ± 5 kPa •Day 4 (after activation): 43 ± 6.3 kPa	(Du et al., 2017)
3A9m T cells	0.01 and 0.1% PLL 50 ug/ml anti-CD45	AFM •Number of cells: – •Spherical (R = 2.5 µm) indenter •Spring constant: – •Setpoint: 0.5 nN •Loading rate: 2 µm/s •Curve for fitting: approach •Hertz model •Poisson's ratio: 0.5	Young's modulus •Young's modulus values of hundreds of Pa •Circular patterns of anti-CD45 do not affect T-cell mechanics at 37°C •Young's modulus decreases at 37°C compared with 25°C •The smaller the patterned area, the smaller the Young's modulus	(Sadoun et al., 2021)
Jurkat T cells	0.02% (200 µg/ml) PLL	AFM •Number of cells: – •Spherical (R = 2.15 µm) indenter •Spring constant: 0.01 N/m •Setpoint: 0.2 nN •Loading rate: – •Curve for fitting: approach •Hertz model •Poisson's ratio: 0.5	Young's modulus •Nondividing cell: 134.5 ± 2.8 Pa •Interphase: nonsignificant change •Metaphase–telophase: increase •Mitosis: max Young's modulus •End of division: gradual return	(Bui and Nguyen, 2023)

AFM, atomic force microscopy; ConA, concanavalin A; Dex, dexamethasone; Cyt-B, cytochalasin B; PLL, poly-L-lysine; PWBCs, peripheral white blood cells.

generated front-to-back F-actin flow coupled to high cortical actomyosin contractility, which drives amoeboid migration and leading-edge bleb formation. This is triggered by sensing physical confinement and subsequent nuclear deformation, which activates arachidonic acid and calcium pathways to trigger the cytoskeletal flow. Inhibition of these pathways disrupts the scanning and interception of target cells. This mechanically driven strategy allows TRM to scan exocrine glands or tissues with low chemokine levels and limited microbial exposure, but still retaining the chemosensory capabilities for infection response.

Among the different T-cell subsets, Tregs are particularly relevant due to their central role in maintaining immune homeostasis. In cancer, their upregulation suppresses effector antitumor immune responses, allowing cancer cells to evade immune surveillance. In contrast, in autoimmune diseases, they fail to prevent autoreactive T cells from attacking self-tissues (Wang et al., 2025).

Substrate stiffness influences Treg induction, although results depend on the stiffness range. In mouse CD4⁺ T cells, softer polydimethylsiloxane (PDMS) substrates (100 kPa) promote Treg differentiation compared with stiffer ones (Nataraj et al., 2018), and in human cells, increasing stiffness (7.5–140 kPa PA gels) enhances Treg induction via elevated mitochondrial oxidative phosphorylation (OXPHOS) (Shi et al., 2023). Mechanistically, stiffer substrates increase OXPHOS and mitochondrial gene expression, and Treg induction is reduced by ATP synthase inhibition but enhanced by AMPK activation, confirming metabolic dependence. This aligns with the known reliance of Tregs on OXPHOS (Gerriets et al., 2015).

Stiffness also affects the suppressive capacity and stability of Tregs. Softer substrates yield higher Treg numbers, but stiffer substrates generate cells with greater suppressive function, persistence, and epigenetic stability (FOXP3 and CTLA4 hypomethylation) (Shi et al., 2024). Intermediate stiffness (870 kPa) appears optimal, balancing expansion and function. However, T-cell mechanosensing (Box 2) is also dependent on the activating ligand concentration and surface chemistry, highlighting the need for a more complete characterization of the environmental conditions required for stable and suppressive Treg generation.

Despite these advances, key gaps remain unsolved (Huang et al., 2025). The in vivo relevance of mechanically induced Tregs is unclear, and mechanistic pathways linking mechanics, metabolism, and epigenetics are incompletely defined. Moreover, Treg induction depends not only on mechanics by also on

physicochemical cues, as similar outcomes are observed across very different rigidities (Nataraj et al., 2018). Pathways such as YAP (Meng et al., 2020) and p53 (Ebata et al., 2017) signaling may contribute, but require systematic investigation. Overall, evidence suggests that Treg differentiation is governed by a biphasic, mechanometabolic response to stiffness, where soft environments favor expansion and stiff environments enhance function, but in vivo relevance and underlying pathways remain unresolved.

Beyond differences between cell types, T-cell elasticity also undergoes dynamic changes during the cell cycle, as shown in atomic force microscopy (AFM) measurements of Jurkat T cells (Bui and Nguyen, 2023). During interphase, cellular elasticity remains unchanged, but it starts to increase from metaphase to telophase, likely due to the modified surface tension, accumulated actin and myosin, and redistributed organelles after the formation of the cleavage furrow. Intuitively, aberrant divisions display differences in elasticity patterns, likely arising from uneven chromosome segregation.

In addition to nuclear and cytoskeletal structures, or membrane-embedded receptors such as the TCR or integrins, (Box 2) ion channels also act as mechanosensors that transduce mechanical detection to signaling, gene expression, and effector functions. A prominent example is the mechanosensitive ion channel PIEZO1, a key regulator of the antitumor cytotoxic behavior of T cells (Pang et al., 2024). Pharmacological blockade of PIEZO1 enhances tumor cell killing by strengthening T-cell traction forces at the IS. Mechanistically, PIEZO1 activation upregulates the transcription factor GRHL3, which in turn induces the expression of the E3 ubiquitin ligase RNF114. RNF114 then binds to F-actin, promoting its downregulation and reorganization, which ultimately reduces the mechanical traction forces exerted by T cells. This finding reveals a negative regulatory role of PIEZO1 in T-cell mechanics, exposing the ion channel or its downstream effectors as possible targets to enhance the efficacy of cancer immunotherapies by boosting T-cell cytotoxicity through mechanical pathways.

Owing to the presence of several types of mechanosensors, T cells are remarkably sensitive to the mechanical properties of their environment, particularly substrate stiffness and matrix viscoelasticity, which modulate the amplitude, dynamics, and outcome of T-cell function. While early studies suggested that stiffer substrates generally enhance T-cell responses (Saitakis et al., 2017), more recent work shows this relationship is nonlinear. T-cell spreading, proliferation, and IL-2 secretion exhibit a biphasic dependence on stiffness, with optimal responses at intermediate values (Wahl et al., 2019; Yuan et al., 2021). This behavior is TCR-specific: it occurs with anti-CD3 stimulation alone but is abolished when integrin engagement (intracellular adhesion molecule (ICAM)-1/LFA-1) is present, leading instead to a monotonic increase in spreading. Similarly, nonspecific adhesion with poly-L-lysine without anti-CD3 does not reproduce the biphasic response. These findings highlight that T-cell responses to stiffness are not simply linear but biphasic and context-dependent, governed by TCR signaling, integrin engagement, and cytoskeletal dynamics.

However, in physiological tissues, T cells rarely encounter homogeneous substrates. Instead, they navigate through heterogeneous mechanical environments. Recent work showed that T cells exposed to heterogeneous substrates with alternating soft and stiff regions do not average mechanical inputs but rather adopt a response characteristic of the soft regions, giving rise to lower activation with respect to cells on uniformly stiff surfaces (Pandit et al., 2025). This demonstrates that soft regions can dominate T-cell mechanosensing, with important implications for lymphoid tissues and tumor microenvironments (TMEs), where stiffness heterogeneity is common. This finding underscores the need for experimental models that better capture the complexity of in vivo environments, where multiple mechanical, chemical, and spatial factors act simultaneously.

Although the mechanical stiffness of the extracellular matrix (ECM) has been widely studied, most current studies still simplify tissues as purely elastic, overlooking their intrinsic viscoelasticity. In physiological environments, the rate at which mechanical stress relaxes over time profoundly influences T-cell activation and differentiation. For instance, under identical CD3/CD28 stimulation, slow-relaxing matrices promote the expression of both activation and inhibitory markers, whereas fast-relaxing matrices favor memory T-cell marker expression, demonstrating that the temporal dimension of mechanical feedback is a key determinant of the functional outcome (Adu-Berchie et al., 2023). In line with these observations, synthetic viscoelastic alginate-based beads with rapid stress relaxation dynamics (unlike the purely elastic polystyrene Dynabeads) were shown to enhance cytotoxic function, increasing expression of CD69 (an early activation marker), perforin, granzyme B, and interferon-γ, expanding the $CD8^+$ population, and reducing the proportion of Tregs (Liu et al., 2024b). While promising, these results should be interpreted with caution, as differences in ligand presentation, bead chemistry, or activation strength may also contribute to the observed effects.

Beyond temporal mechanical properties, spatial features of the activating interface, such as geometry and topography, also shape T-cell responses. Micro- and nanoscale geometries have been shown to play a crucial role in T-cell behavior, although isolating the specific contribution of geometry from stiffness and ligand density remains challenging. For example, PDMS microbeads with a modulus of 7.3 MPa functionalized with anti-CD3 and anti-CD28 induced a greater T-cell proliferation than commercial polystyrene Dynabeads (GPa range) (Lambert et al., 2017), extending the proliferative phase for both $CD4^+$ and mixed $CD4^+/CD8^+$ T-cell populations. Importantly, cells expanded using PDMS beads exhibited similar effector functionality to those expanded using Dynabeads. Similarly, electrospun fibrous meshes composed of PDMS:PCL and functionalized with anti-CD3 and anti-CD28 were more effective at stimulating T-cell proliferation than pure PCL meshes or Dynabeads, while maintaining comparable functionality to Dynabeads (Dang et al., 2018). In these meshes, microscale fibers outperformed nanoscale fibers in promoting proliferation, though both fiber types supported higher expansion than PCL-only ones. Overall, while both stiffness and geometry of the activating surface can enhance T-cell proliferation, their precise and independent contributions and their impact on functional quality remain to be fully resolved.

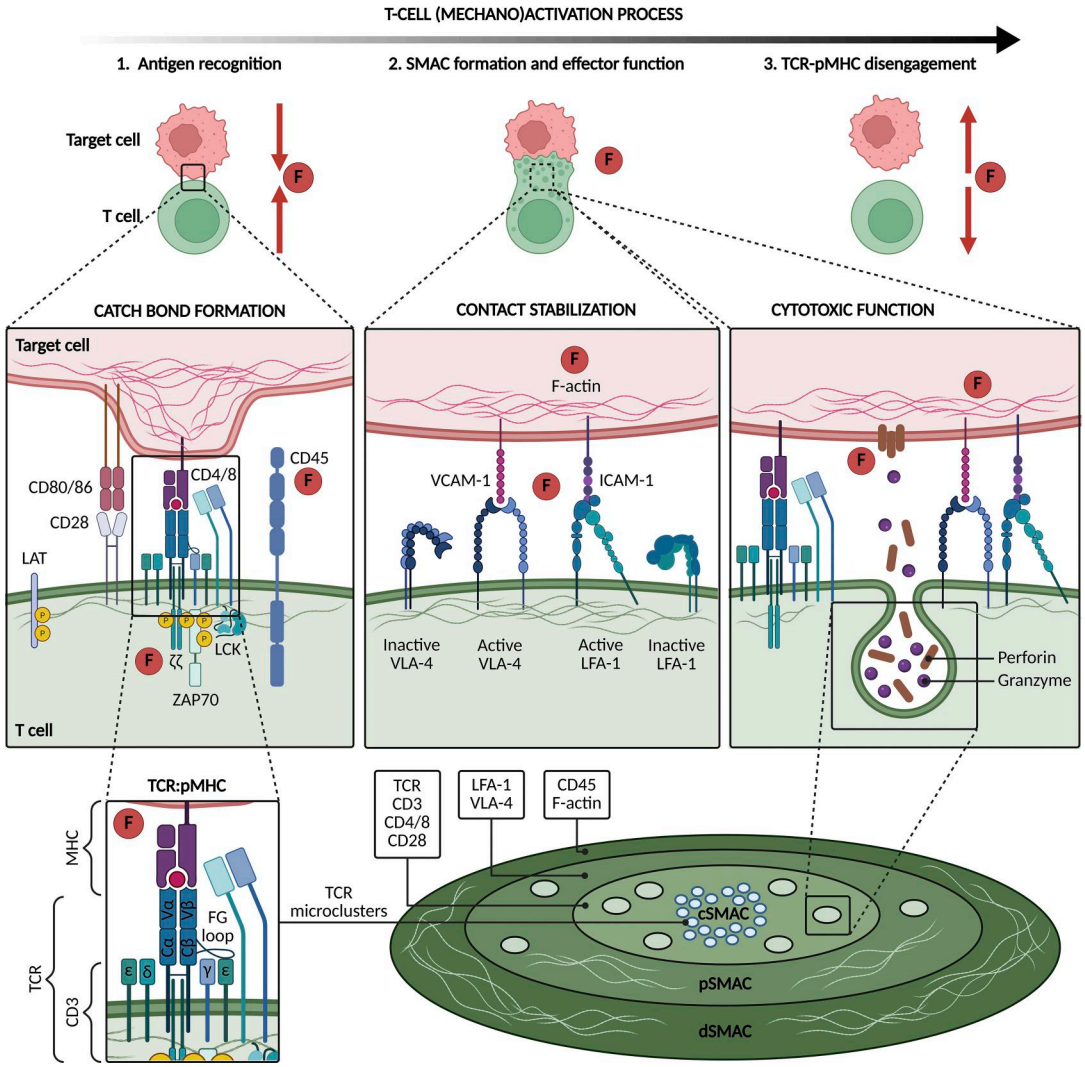

Figure 2. **Mechanobiology of T-cell activation and cytotoxic function.** T cells form transient exploratory contacts before antigen recognition. Upon engagement with cognate pMHC, the TCR experiences mechanical forces that are transmitted to CD3 subunits, initiating signaling and promoting CD45 exclusion from the contact site. Integrins such as LFA-1 and VLA-4 switch to their high-affinity conformations to stabilize the interface and couple external forces to the actin cytoskeleton. Actin polymerization and retrograde flow organize the IS and reinforce signaling. During cytotoxic responses, contractile and compressive forces, together with elevated membrane tension at the synapse, support the targeted release of perforin and granzymes. Red "F" symbols indicate regions where mechanical forces are particularly important.

Mechanics of T-cell activation and function

Selective cellular cytotoxicity is essential for accurate and proportional immune responses against pathogens or abnormal target cells (Smith-Garvin et al., 2009). In cytotoxic and helper T cells, this process is executed through the IS; a specialized cell–cell junction established at the contact site between a T cell and an APC or target cell. The IS serves as a dynamic signaling interface that integrates biochemical cues from receptor–ligand interactions with mechanical inputs arising from cytoskeletal tension and the physical properties of the environment (Chao et al., 2025).

Structurally, the IS is organized into concentric domains that together form the characteristic "bull's eye" pattern (Fig. 2) (Basu and Huse, 2017; Chao et al., 2025): (1) the central supramolecular activation cluster (cSMAC), which concentrates TCR-pMHCs and associated signaling molecules; (2) the peripheral SMAC, rich in integrins and molecules such as LFA-1 and talin; and (3) the distal SMAC (dSMAC), composed of dynamic, branched actin networks that drive receptor transport and synapse remodeling. Although this classical arrangement is not observed in all synapses, overall, these regions coordinate receptor signaling, cytoskeletal reorganization, and force generation.

The process of T-cell activation through the IS can be divided into three phases (Fig. 2). During initiation, T cells first establish nonspecifically adherent contact with potential target cells via LFA-1/ICAM-1 or ICAM-2 interactions, which stabilizes the cell–cell interface and facilitates the scanning of the target surface by extending actin-rich pseudopodia. This mechanical scanning enables the search for cognate pMHC molecules. Once the specific engagement between the TCR and the specific pMHC ligand occurs, a catch bond is formed, triggering early signaling

cascades and cytoskeletal polarization toward the contact site (Huse, 2025).

Upon ligand binding, individual TCRs rapidly aggregate into signaling microclusters (~10 receptors in each cluster) at the tips of Wiskott–Aldrich syndrome protein (WASP)–dependent (Cai et al., 2017), actin-rich protrusions similar to invadosome-like protrusions (ILPs). The microclusters are then transported toward the cSMAC, initially by retrograde F-actin flow and then by myosin II–driven actin arcs (Varma et al., 2006).

In the effector phase, sustained signaling and F-actin polymerization promote the formation of a stable synaptic structure. Coordinated actomyosin contractility generates retrograde actin flow, which drives the formation of the SMAC ring excluding inhibitory molecules like CD45 (Huse, 2017), and facilitates receptor clustering, preventing the TCRs from moving away of the pMHCs (Colin-York et al., 2019a). These interactions are mediated through TCR/CD3 complexes, integrins, and small GTPases, which recruit the Arp2/3 complex to nucleate new actin filaments. The reorganization and accumulation of F-actin also enable mechanotransduction (Box 2), triggering the secretion of cytotoxic granules (including pore-forming protein perforin and granzyme proteases), as well as cytokines that execute the effector response.

Finally, during the termination phase, signaling intensity diminishes, the actin cytoskeleton depolymerizes, and the IS progressively disassembles, allowing the T cell to detach and migrate toward new targets.

Advances in high-resolution imaging and biophysical approaches have established that T-cell activation is not merely a chemical process but a mechanically coordinated sequence of events. Each stage of IS formation and function depends on precisely regulated force generation, cytoskeletal dynamics, and sensitivity toward the surrounding environment.

Mechanics of antigen recognition at the TCR-pMHC interface

Molecular mechanotransduction

Despite the open questions regarding the mechanoimmunological mechanisms that govern cell–cell interactions at the IS, the molecular mechanosensitivity of antigen recognition is primarily attributed to the αβ TCR, which functions as an anisotropic mechanosensor (Kim et al., 2009), and is geometrically oriented to preferentially sense lateral rather than perpendicular tension. Structurally, such oblique forces are transmitted from the variable domains of the TCR (VαVβ) to the CD3 signaling subunits (CD3εγ, CD3εδ, and CD3ζζ subunit pairs, noncovalently associated with the αβ TCR) through the rigid FG loop of the TCR β constant domain, which acts as a lever coupling mechanical load to the CD3 εγ dimer situated beneath the TCR (Fig. 2). This mechanical linkage induces conformational rearrangements that expose the immunoreceptor tyrosine-based activation motifs (ITAMs) of the cytoplasmic tails of the CD3 subunits. Coreceptors CD8 (on cytotoxic T cells) or CD4 (on helper T cells) bind to the same pMHC and recruit tyrosine kinase LCK to phosphorylate ITAMs of the CD3 subunits. Phosphorylated ITAMs then serve as docking sites for ZAP70, which together with adaptor proteins like LAT propagate downstream signaling. The additional binding of costimulatory molecules such as CD28 leads antigen-bound T cells to proliferate, differentiate, or execute effector functions (Liu et al., 2021a). Thus, TCR signaling likely emerges from the integration of mechanical and biochemical inputs across multiple receptor components, rather than from a single mechanotransduction event (Wang, 2020). A key feature of TCR mechanosensitivity is the reported catch-bond behavior of TCR-pMHC interactions, whereby bond lifetime increases under applied force. Single-molecule measurements using biomembrane force probes and optical tweezers have demonstrated that tensile forces in the range of 10 pN can prolong the lifetime of TCR-pMHC bonds, thereby amplifying weak biochemical affinities into robust signaling events (Das et al., 2015; Liu et al., 2014). These observations support the idea that mechanical forces can enhance antigen discrimination by stabilizing productive interactions. However, reported force magnitudes and bond behaviors vary across experimental systems, and it remains unclear how these measurements relate to forces experienced in intact ISs.

In the last two decades, several TCR triggering models have been proposed, mainly with or without TCR/CD3 conformational changes (Chakraborty and Weiss, 2014; Liu et al., 2021a; Zhu et al., 2019). The previous description of TCR triggering aligns with the conformational change/lipid-release model, integrated within the mechanobiological framework. The latter provides a unifying framework that integrates and extends all previous models. Table 2 shows a comparative overview of different TCR triggering models and the unifying contribution of mechanobiology for each of the models.

Consistent with this complexity, the extent of T-cell activation is to be governed not only by TCR affinity, but by the kinetics and mechanics of the TCR-pMHC interaction (Faust et al., 2023). The three fundamental parameters defining the process are (1) the intrinsic affinity of the TCR for the ligand, (2) the bond lifetime under force, and (3) the magnitude of force at which the peak lifetime occurs. Although high-affinity interactions can support activation, it is the formation of catch bonds with optimal lifetimes under physiologically relevant loads that most effectively trigger signaling. This explains why low-affinity interactions can still give rise to robust responses, if their bond lifetimes are extended by force, and why coreceptor engagement (such as CD8, which forms a trimolecular TCR–pMHC–coreceptor complex) (Zhu et al., 2019) can enhance activation by increasing the bond lifetime or shifting the force at which it peaks (Jiang et al., 2011). However, it remains uncertain whether this represents a universal requirement across TCRs and ligands, or one of several possible activation modes.

Recent studies further highlight the diversity of mechanical behaviors at the TCR. Using optical tweezers to apply biologically relevant pN forces to individual TCR-pMHC bonds, Akitsu et al. (2024) challenged the current view of the TCR as a simple catch-bond receptor. By testing different TCR clones that recognize the same pMHC ligand, they identified two mechanical phenotypes. Some clones exhibited an analog behavior, consistent with the catch-bond dynamics, where increasing force gradually extends and multiple ligand engagements are required to trigger full activation. Other clones displayed a digital phenotype, entering a state of molecular resonance, characterized by rapid and

Table 2. **Comparative overview of TCR triggering models and the unifying contribution of mechanobiology**

Model	Mechanistic principle	Supporting evidence	Limitations	Mechanobiological integration	Ref.
Kinetic proofreading model	Signaling requires a minimum TCR: pMHC binding time and only persists while the TCR remains bound.	Explains antigen discrimination and how a single TCR bond with durable force can induce calcium flux.	Mechanism of how subtle differences in dwell time translate into strong signaling thresholds is unclear.	Force amplifies kinetic differences by extending bond lifetimes through catch-bond formation (~10 pN).	(McKeithan, 1995)
Kinetic segregation model	Spatial exclusion of large phosphatases (e.g., CD45) from the TCR enables LCK-mediated phosphorylation of ITAMs.	Imaging studies showing spatial segregation of phosphatases during TCR engagement.	Passive size-based segregation alone may not fully account for signal initiation dynamics.	Both passive (TCR: pMHC bond) and active (catch bond/ actin cytoskeleton) forces enhance phosphatase exclusion, promoting phosphorylation.	(Davis and van der Merwe, 2006) (James and Vale, 2012) (Chang et al., 2016)
Serial engagement model	A limited number of pMHCs serially bind to and trigger many TCRs through rapid association and dissociation cycles.	Functional assays show that cumulative temporary interactions can elicit robust calcium signaling.	Does not explain sustained signaling seen under high-force engagement.	Physiological shear forces optimize the balance between bond lifetime and turnover, allowing efficient serial triggering while maintaining sufficient signal duration.	(Valitutti, 2012) (Wofsy et al., 2001)
Allosteric/ conformational change model	pMHC binding induces conformational rearrangements within the TCR, exposing ITAMs for phosphorylation.	Supported by FRET, NMR, and biochemical studies showing conformational shifts.	Static crystal structures of TCR: pMHC show minimal structural changes upon binding.	Mechanical load provides energy for conformational changes that may be undetectable in static structural analyses.	(Lee et al., 2004) (Beddoe et al., 2009)
Conformational change/lipid-release model	Upon TCR engagement, CD3 cytoplasmic tails dissociate from the inner lipid bilayer, exposing ITAMs to LCK.	Supported by biochemical and biophysical evidence.	Mechanism of linking extracellular ligand binding to intracellular tail release is not completely defined.	Forces transmitted through the TCR via the FG loop and transmembrane helices can pull CD3 tails away from the membrane, exposing ITAMs for phosphorylation.	(Xu et al., 2008) (Shi et al., 2013) (Guo et al., 2017)

TCR, T-cell receptor; pMHC, peptide–major histocompatibility complex; LCK, lymphocyte-specific protein tyrosine kinase; ITAMs, immunoreceptor tyrosine-based activation motifs; FRET, Förster resonance energy transfer; NMR, nuclear magnetic resonance.

periodic transitions between extended and contracted conformations under load. This led to prolonged bond lifetimes, up to 10× longer than standard catch bonds, enabling full T-cell activation from a single bond. These findings suggest that TCR mechanosensitivity may not follow a single paradigm. However, whether such behaviors occur in physiological settings, and how broadly they apply across T-cell populations, remains to be determined.

Complementary approaches have shown that direct mechanical stimulation of the TCR-CD3 complex is sufficient to induce T-cell clustering, downstream signaling, and $CD4^+$ T-cell activation, even in the absence of pMHC or coreceptor engagement (Clarke et al., 2025). Activation required anti-CD3ε–coated superparamagnetic particles and external magnetic fields, an intact actin cytoskeleton, and at least 1 h of sustained force application, leading to cumulative NFAT signaling, expression of activation markers (CD69/CD25), and TCR downregulation through endocytosis. Additionally, single-molecule force sensors used to quantify TCR-pMHC interactions before and during IS formation found that most bonds within the IS experienced minimal or undetectable forces (~5–6.5 pN), far below those reported earlier for $CD4^+$ T cells (15–20 pN) (Schrangl et al., 2025). Detectable forces appeared mainly during the initial scanning phase, likely at microvillar tips probing the antigen-presenting surface, whereas when the IS was stabilized, mechanical force was reduced. These results support a model of antigen recognition with a mechanically active initial scanning phase, and a stable synapse phase that preserves bond integrity. While these results support the concept of force-dependent triggering, they rely on artificial stimulation systems and prolonged force application, and therefore may not fully recapitulate physiological activation.

Additional evidence indicates that external mechanical stimuli such as the fluid shear stress (FSS) can modulate TCR signaling. Cone-and-plate viscosimetry experiments demonstrated that FSS alone can induce NFAT translocation and partial activation, but with CD3/CD28 costimulation, it produces a synergistic enhancement of signaling that leads to sustained expression of activation markers, proliferation, and elevated cytokine production in a PIEZO1-dependent manner (Sarna et al., 2024).

As evidenced by the previous studies, reported force magnitudes at the TCR-pMHC interface vary substantially depending on the experimental approach, reflecting both biological variability and methodological differences. Single-molecule techniques such as biomembrane force probes and optical tweezers typically report forces in the range of 10–20 pN associated with

prolonged bond lifetimes and catch-bond behavior (Das et al., 2015; Liu et al., 2014). In contrast, DNA-based tension sensors and molecular force probes used in cell–cell or cell–substrate contexts often detect lower forces, frequently in the 5–10 pN range or below, particularly within mature ISs (Schrangl et al., 2025). These discrepancies arise from several factors, including differences in force application (externally imposed or cell-generated), loading rates, probe geometry, and whether measurements capture peak transient forces or time-averaged values. In addition, some works isolate individual receptor–ligand interactions, whereas others report ensemble behavior within a complex and dynamically reorganizing synapse. As a result, these studies should be viewed as complementary rather than contradictory.

Receptor cooperativity and costimulation

Beyond the TCR itself, coreceptors and other membrane molecules make essential mechanobiological contributions to T-cell activation. Traction force microscopy (TFM) has shown that both CD3 and CD28 participate in mechanosensing, with CD3 generating traction forces through the TCR complex, and CD28 amplifying these forces via PI3k signaling (Bashour et al., 2014). These forces are concentrated at the dSMAC, rich in Pyk2 and Src family kinases, forming focal adhesion–like structures that mechanically link the TCR complex to the actin cytoskeleton.

Integrin engagement further shapes the mechanical nature of the TCR complex. LFA-1 and VLA-4 transition from a bent, low-affinity state to an extended, high-affinity conformation in response to inside-out signaling triggered by TCR engagement and chemokine receptors. When LFA-1 and VLA-4 integrins bind to their ligands (ICAM-1 and VCAM-1, respectively), actin retrograde flow is slowed through talin–vinculin linkages, which together act as a molecular clutch that couples integrins to the actin cytoskeleton (Jankowska et al., 2018). This deceleration reduces the mechanical load on the TCR, acting as a negative feedback loop that fine-tunes TCR strength and duration. In cytotoxic T cells, integrins serve an additional function as mechanical checkpoints for targeted secretion. LFA-1–dependent pulling forces define the precise sites of granule exocytosis, ensuring that perforin and granzyme release occurs precisely at sites of close target engagement (Wang et al., 2022). Therefore, integrins do not only stabilize the cell–cell contact interface but dynamically regulate the force and position.

Additionally, mechanosensitive ion channels provide an additional regulatory layer. PIEZO1, activated by membrane tension, drives Ca^{2+} influx and actin remodeling necessary for TCR signaling, and its activation can effectively substitute CD3/CD28 stimulation (Liu et al., 2018).

Cytoskeletal dynamics and force generation

Cytoskeleton remodeling

All the aforementioned mechanotransduction pathways, whether transmitted through the TCR, coreceptors, or mechanosensitive ion channels, ultimately converge at the cytoskeleton, highlighting its essential role not only in generating but also in transmitting mechanical signals in T cells (Gómez-Morón et al., 2025). Upon surface engagement, T cells undergo rapid and global actin reorganization, forming a ramified cortical network that correlates with TCR redistribution and stiffens the IS, consolidating it (Blumenthal and Burkhardt, 2020; Fritzsche et al., 2017). Specifically, TCR engagement is followed by the assembly of the ring-shaped, branched F-actin network at the dSMAC, which facilitates firm adhesion and signal propagation. This process is enabled through the SI3K-DOCK2-Rac1-WAVE2-Arp2/3 signaling cascade, driving actin nucleation and polymerization, which results in the retrograde actin flow that transports TCR microclusters toward the cSMAC (Le Floc'h and Huse, 2015) (Fig. 2). Clearance of F-actin at the synapse enables the formation of secretory domains for granule release (Ritter et al., 2015).

When it comes to the contribution of other cytoskeletal proteins, early live-cell imaging studies revealed that inhibition of nonmuscle myosin IIA slows the retrograde transport of TCR microclusters and reduces ZAP70 phosphorylation, while significantly reducing sustained Ca^{2+} signaling and CasL phosphorylation (a mechanosensitive marker linked to force transmission). These findings indicate that myosin-driven mechanical forces are not required for the initiation of TCR signaling but are crucial for its maintenance and reinforcement over time (Yu et al., 2012). Building upon this, subsequent studies demonstrated that myosin II acts together with the actin nucleator WASP to generate and sustain cytoskeletal tension within the plane of the IS (Kumari et al., 2020). Continuous actin polymerization at the TCR microclusters, coupled to myosin-mediated contraction, maintains a high in-plane tension that preserves synapse symmetry and stability. After activation, WASP is degraded and tension dissipates, leading to synapse relaxation and disassembly. Additionally, actomyosin dynamics modulate microtubule growth and deformation (Rey-Suarez et al., 2021).

Such changes in the cytoskeleton are appreciated as changes in mechanical properties of the cell, showing as rapid and parallel increases in the elasticity and viscoelasticity during activation (Zak et al., 2021). At subcellular resolution, IS formation induces localized stiffening, with the lamellipodia becoming significantly stiffer than the cell body, in a Ca^{2+}-dependent manner at the periphery but independent of Ca^{2+} centrally, pointing toward different regulatory mechanisms of IS-induced stiffening (Jung et al., 2021).

Beyond T-cell cytoskeletal remodeling, actin and microtubule dynamics at the postsynaptic interface (APC or tumor cell) significantly contribute to the spatial organization and functional output of the IS (Ockfen et al., 2023).

Traction forces

Forces generated by the cytoskeleton ultimately manifest as traction forces exerted at the T-cell interface, hence the relevance of understanding how these forces are produced and regulated. TFM revealed that during activation, T cells exert substantial interfacial forces that are largely driven by actin polymerization, with myosin contractility mainly contributing to development of force in early spreading (Hui et al., 2015). Dynamic microtubules contribute to the regulation of actin retrograde flow and subsequent T-cell traction forces by suppressing RhoA activation and myosin II filament assembly (Hui and Upadhyaya, 2017). Despite these advances, the magnitude

and spatial distribution of these forces remain sensitive to experimental conditions and substrate properties, and whether the balance between different cytoskeletal elements is regulated over time is not fully understood.

Mechanobiology of cytotoxic and effector function

Cytoskeletal rearrangements and mechanical stiffening not only stabilize the IS, but also enable T cells to exert targeted forces, which is particularly important during the execution of effector functions. After TCR engagement with the pMHC, force generation is actively enhanced to improve access and discrimination of the antigen (Hu and Butte, 2016). This globally compressive synapse (de Jesus et al., 2024) leads to pN-scale forces being transmitted across the synapse (Ma et al., 2022a) to the actin cytoskeleton.

Cytotoxic T cells use mechanical force to potentiate killing efficiency, with traction stresses facilitating perforin-induced pore formation and target cell killing, with very high spatial precision (Basu et al., 2016; Tamzalit et al., 2019). In fact, cytoskeletal forces that polarize lytic granules toward the IS simultaneously deform the membrane, forming curved membrane pockets, where perforin preferentially perforates positively curved membrane regions, while granzymes are delivered to negatively curved pockets (Govendir et al., 2022). After target lysis, IS dissolution coincides with apoptotic contraction, where mechanical amplification of target cell contractility promotes T-cell detachment and supports serial killing (Sanchez et al., 2023) (Fig. 2). For a detailed description of the mechanoregulation of lymphocyte cytotoxicity, the reader is referred to the recent review by Morgan Huse (Huse, 2025).

Mechanics of T-cell migration

To further continue exerting their effector functions, T cells rely on their mechanobiological mechanisms to navigate through the complex and crowded environments by generating force, adapting to confinement, and maintaining directional motility. PIEZO1 plays a crucial role in this process, transducing local increase in membrane tension and focal adhesion formation due to chemokine receptor activation into intracellular signals that recruit integrins to the leading edge (Liu et al., 2024a). Actin bundling proteins such as L-plastin further stabilize integrin–actin linkages supporting T-cell activation and migration by reinforcing the cytoskeleton. These molecules are also required for lamellipodium formation during adhesion and migration, as well as for LFA-1 clustering in IS formation (Joshi and Morley, 2022).

Amoeboid motility, employed by T cells to move on tissues and characterized by adhesion, as well as extension and retraction phases, is characterized by F-actin and α-actinin cortical ring formation at the points of contact with the ECM, which is provided by septins (Zhovmer et al., 2024). At the rear of the cell, FML1-mediated actin polymerization provides the pushing forces necessary for the rigid T-cell nucleus to deform and pass through restrictive barriers (Thompson et al., 2020). The microtubule cytoskeleton also contributes to migration in 3D environments: its controlled instability promotes efficient migration through the Rho pathway–dependent cortical contractility (Tabdanov et al., 2021). Even during migration, T cells make use of mechanical forces to probe and recognize antigens, highlighting the continuous interplay between motility and mechanosensing (Chabaud et al., 2020).

Mechanics at the physical environment

The physical characteristics of the surrounding environment greatly influence immune cell function. Substrate stiffness and ligand mobility of antigen-presenting interfaces are critical for T-cell adhesion, spreading, and actin dynamics during the first minutes after antigen recognition (Sengupta et al., 2024). Experiments using microporous 3D scaffold matrices of tunable rigidity demonstrated that T cells can sense and respond to the stiffness of their environment, with stiffer matrices enhancing activation, proliferation, and migration speed (Majedi et al., 2020).

T cells rely on specialized membrane protrusions to explore and engage their environment (Göhring et al., 2022). Microvilli are actin projections (~70–150 nm in diameter and ~300–400 nm in length), which densely cover the T-cell surface and play a key role in overcoming the glycocalyx barrier (Pettmann et al., 2018). By exerting forces, microvillar tips can penetrate the barrier creating close membrane contact where initial TCR triggering occurs. These microvilli rapidly scan the opposing surface within seconds and stabilize only upon recognition of the cognate antigen, process that is independent of TCR signaling. As the T-cell activation progresses, some of these dynamic protrusions mature into ILPs; actin-rich, force-generating structures enriched in TCRs and signaling molecules. ILPs combine mechanical probing with biochemical signaling functions, extending deep into the target or APC membrane (Cai et al., 2017). By deforming the opposing surface and penetrating through the dense glycocalyx, they create micro- and nanoscale sites optimized for receptor engagement and signal amplification (Schaefer and Hordijk, 2015).

Simulating such interfaces in vitro, micrometer-scale topographies, such as pits of defined depth, modulate T-cell activation in a biphasic manner, with intermediate depths (~4 μm) optimizing cytokine secretion and activation, whereas excessive confinement diminishes responses (Chaudhuri et al., 2020). At the nanoscale, confinement within 200-nm pores promotes the formation of actin-rich microvilli and spatial segregation of CD45 and TCRs, generating localized signaling hotspots that sustain activation even in the absence of TCR agonists (Aramesh et al., 2021).

Mechanics in disease and dysfunction

Despite the tightly regulated cytoskeletal structure and mechanotransduction pathways, these mechanisms are often altered in pathological contexts. Cytotoxic T cell–based killing relies on a finely tuned balance between force generation and membrane mechanics. $CD8^+$ T cells efficiently eliminate stiff tumor cells, but in cancer, they fail to kill soft tumor cells, where the low membrane rigidity prevents perforin-mediated pore formation

(Liu et al., 2021b). Insufficient contractile force by nonmuscle myosin IIA or the cholesterol-enriched membranes of cancer cells could be among other factors resulting in insufficient membrane tension for perforin pore formation. Similarly, leukemic T cells also evade cytotoxic killing through cell softness (Zhou et al., 2024). In this case, downregulation of filamin A and ZAP70-mediated YAP phosphorylation and activation contribute to resistance. Interestingly, increasing target cell rigidity, either through cholesterol depletion (Lei et al., 2021) or overexpression of the actin-regulatory factor MRTF (Tello-Lafoz et al., 2021), increases susceptibility to cytotoxic T-cell lysis through increased F-actin polymerization.

The complex biophysical landscape of the TME further impairs immune cell infiltration and cytotoxic efficiency (Fig. 3). Some of the most common features of the TME are a heterogeneous ECM stiffness (Alibert et al., 2017; Golo et al., 2024; Zhang et al., 2022b) with high collagen density (Mai et al., 2024), increased solid stress (Golo et al., 2024; Zhang et al., 2022b), high interstitial fluid pressure (Zhang et al., 2022b) and shear forces (Golo et al., 2024; Zhang et al., 2022b), imbalanced ionic strength (Eil et al., 2016), acidic pH (Corbet and Feron, 2017), hypoxia (Chen et al., 2023), and dysregulated temperature (Wilander and Rathmell, 2025), which together contribute to impaired T-cell infiltration and immunotherapy resistance.

Acidic pH typical of solid tumors disrupts T-cell expansion, cytokine secretion, and cytotoxicity, primarily by impairing IL-2 responsiveness and perforin pore formation within the IS (Hodel et al., 2025; Vuillefroy de Silly et al., 2024). Paradoxically, chronic intracellular acidification has also been reported to promote metabolic adaptations that preserve T-cell stemness and mitochondrial fitness (Cheng et al., 2023). Additionally, lactic acid accumulation promotes Treg differentiation and immunosuppressive activity (Tuomela and Levings, 2023). Unlike conventional T cells, Tregs efficiently import extracellular lactate and metabolize it into pyruvate, fueling mitochondrial metabolism or gluconeogenesis (Watson et al., 2021). As a result, Tregs have a distinct survival and functional advantage in the lactate-enriched TME. Consistently, mild extracellular acidification (pH ~6.8) enhances TGFβ-driven conversion of conventional $CD4^+$ T cells to $FOXP3^+$ Tregs, revealing a novel mechanism for the increased Treg differentiation induced by lactic acid (Rao et al., 2023). Interestingly, upregulation of pH-regulatory ion channels such as Hvcn1 or suppression of acidifiers like Ae2 enhances the resistance of tumor-specific T cells to this hostile environment (Navarro et al., 2022). These findings illustrate that acidic environments can exert both inhibitory and selective effects on different T-cell subsets, complicating their overall impact on immunity.

Regarding the hypoxic conditions at the TME, it was recently shown that intratumoral hypoxia and the subsequent chronic overexpression of the activating transcription factor 4 in $CD8^+$ T cells lead to metabolic polarity, mitochondrial oxidative stress, and cell death (Alicea Pauneto et al., 2025).

Despite growing evidence that biophysical cues at the TME influence T-cell physiology, how these factors influence T-cell immunomechanics remains poorly understood. Recent work reported that exposure to H_2O_2 reactive oxygen species (ROS) increases T-cell Young's modulus independently of detectable changes in F-actin or microtubules, instead attributing stiffening to lysosomal degradation triggered by mitochondrial superoxide generated in response to H_2O_2 (Komaragiri et al., 2024). Proton leakage from compromised lysosomes may cause cytosolic acidification and protein accumulation due to impaired lysosomal proteolysis. While these findings point toward a noncytoskeletal mechanism of stiffening, they contrast with earlier studies showing that elevated ROS levels can directly remodel the cytoskeleton, for example, through actin filament severing under supraphysiological ROS levels (Wilson and González-Billault, 2015). These discrepancies may arise from differences in ROS concentration, exposure duration, or cellular context, suggesting that ROS may exert both cytoskeleton-dependent and cytoskeleton-independent effects on T-cell mechanics. Accordingly, it remains unclear which mechanisms dominate under physiological or pathological conditions. Further work is therefore needed to determine how ROS and acidic pH regulate T-cell mechanical properties.

Dysregulated mechanical features also play a key role in autoimmune diseases. Chronic inflammation remodels tissue, often stiffening the ECM through persistent fibrosis (Fig. 3), a hallmark of conditions such as inflammatory bowel disease and rheumatoid arthritis (Banerjee et al., 2022; Herrera et al., 2018). Increased ECM stiffness enhances T-cell activation, inflammatory cytokine secretion, and integrin-mediated signaling, thereby reinforcing local immune activation and perpetuating tissue damage (Santos and Lagares, 2018). Moreover, Tregs show reduced suppressive capacity on stiff substrates and experience altered FOXP3 stability when subjected to mechanical load, shifting the balance toward effector responses (Shi et al., 2023). Overall, mechanotransduction is increasingly recognized as a contributing factor in autoimmune pathology, but its precise role relative to biochemical drivers is not yet understood.

Mechanical dysregulation extends beyond pathologies. Aging has been associated with T-cell stiffening and impaired interstitial migration due to changes in nuclear mechanics (González-Bermúdez et al., 2022). Nucleus-to-cell ratio increases due to a reduced DNA methylation and lamin B1 content, leading to enlarged and stiffer nuclei. This expansion, together with decreased myosin levels, results in overall cell stiffening and impaired migratory capacity (Fig. 3).

Mechanobiology for improved immunotherapy

The promising clinical outcomes of chimeric antigen receptor (CAR) T-cell therapies in hematologic malignancies have driven efforts to extend their use to solid tumors. However, despite continuous advances in the CAR design, the mechanical and biophysical barriers of the TME continue to limit their efficacy. The TME imposes physical constraints that impair CAR T-cell trafficking and infiltration. Therefore, a thorough understanding of the mechanobiological context in which immune cells operate will be essential for the development of next-generation immunotherapies (Nguyen et al., 2022; Zhu et al., 2023).

Recent studies have started to incorporate biophysical and mechanobiological aspects to improve CAR T-cell therapies

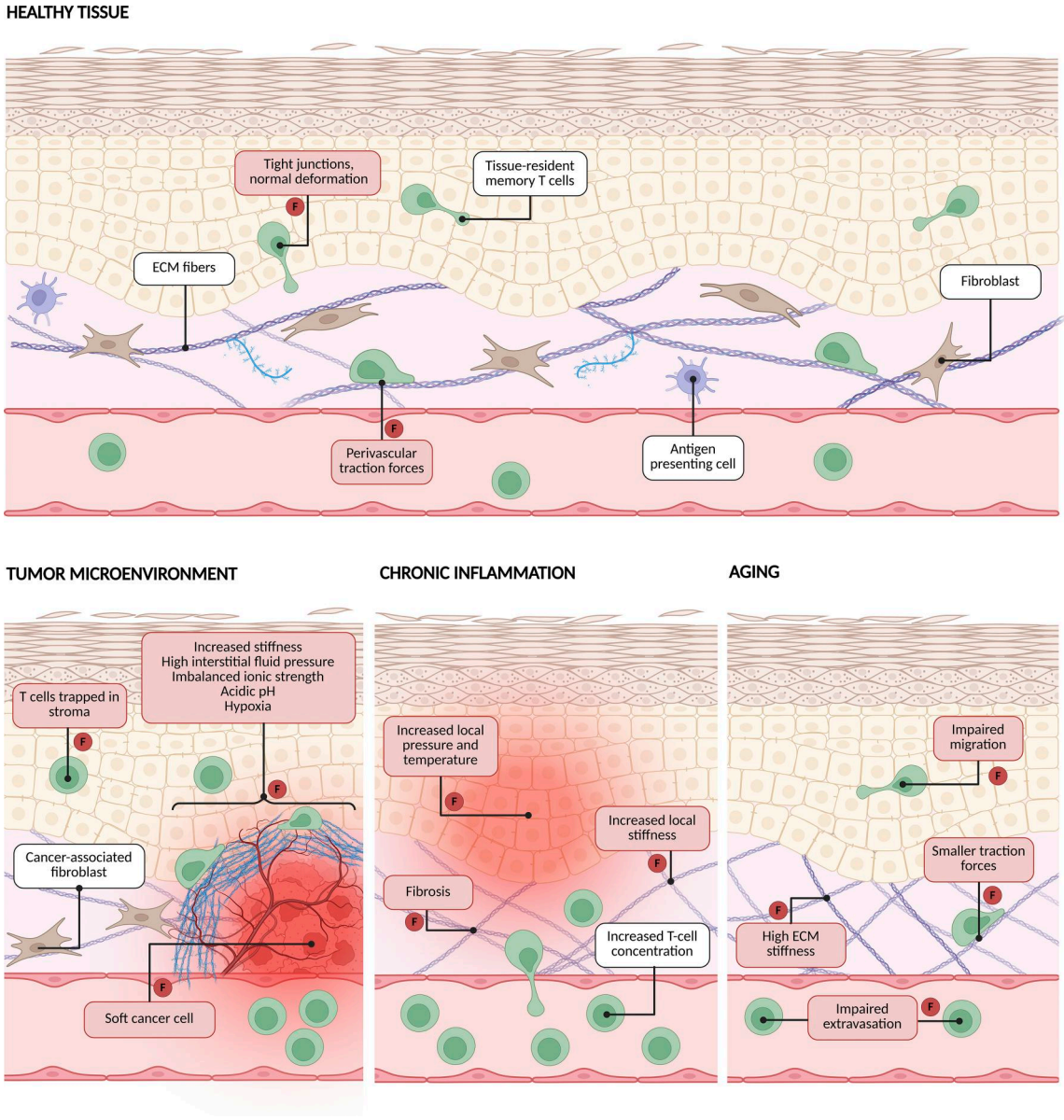

Figure 3. **Mechanobiological landscape of healthy and diseased tissues.** In homeostatic conditions, tissues contain migrating and TRM interacting with other cell types such as fibroblasts and dendritic cells. T cells traffic through blood and lymphatic vessels and crawl within the ECM by generating traction forces. In tumors, the microenvironment exhibits altered biophysical properties that impair T-cell migration and effector function. Chronic inflammation promotes fibrosis and swelling, reinforcing T-cell recruitment, but perpetuating tissue damage. Aging is characterized by increased ECM stiffness and reduced T-cell deformability, leading to impaired interstitial migration. Red F symbols indicate regions where mechanical forces are particularly important.

(Box 2) (Zhuang et al., 2023). Microfluidic platforms have demonstrated efficient ex vivo applications, including non-viral mRNA transfection by inducing transient membrane deformation (Loo et al., 2021), or allow efficient purification of CAR T-cell products (Liu et al., 2019). These systems are among the closest to clinical translation, as they integrate with existing manufacturing pipelines, although challenges remain in scaling throughput and standardizing processes.

Mechanogenetic (Box 2) advances have enabled precise and noninvasive control of CAR T-cell activation through mechanical stimuli (Zhu et al., 2020), but are currently at a preclinical stage. Focused ultrasound (FUS)–responsive CAR T cells convert ultrasound-induced thermal cues into gene expression by coupling a promoter of the heat-shock protein to CAR transcription (Wu et al., 2021). Short FUS pulses trigger transient CAR expression without immune overstimulation. Integrating this system with MRI-guided thermometry allows real-time control, where CAR expression occurs only within targeted tumor regions, thus minimizing off-tumor toxicity (Zhuang et al., 2023). Beyond directly regulating CAR expression in T cells, FUS can also be used to activate mechanogenetic circuits within the tumor itself. By inducing localized CD19 expression within a subset of cancer cells, FUS effectively converts regions of the tumor into intratumoral "training hubs" that selectively activate CD19-CAR

T cells at the disease site (Yoon et al., 2025). Once activated, these CAR T cells eliminate neighboring cancer cells, achieving robust tumor suppression while maintaining spatial specificity. The mechanosensitivity of T cells can also be exploited to enhance CAR T-cell performance, for instance, by regulating activation via PIEZO1 or FSS, and engineering T cells on biomaterials with tailored stiffness and topography ex vivo (Hyun et al., 2023). These strategies show strong in vivo proof-of-concept, but their clinical translation will depend on the safety, reproducibility, and regulatory feasibility of integrating imaging-guided activation systems.

Recently, Lv et al. expanded CAR T cells within a 3D fibrin matrix of defined stiffness, achieving both enhanced proliferation and preservation of stemness, two typically opposing goals in CAR T-cell manufacturing (Lv et al., 2025; Ren and Xu, 2025). This effect was mediated by integrin-β2–dependent mechanotransduction, where matrix stiffness led to YAP inactivation and promoted expression of stemness-related genes while maintaining MAPK-driven proliferation. Such approaches are promising for clinical translation, as they address a key bottleneck, but require scalable systems and robust standardization.

Despite these advances, manufacturing clinical-grade engineered T cells, either CAR T cells or engineered TCR (Box 2) (eTCR) therapies, remains challenged by the limited control over expansion and quality (Jeffreys et al., 2024). Variability in donor cell fitness and manufacturing conditions can give rise to dysfunctional or overactive products that trigger cytokine release syndrome or immune effector cell–associated neurotoxicity syndrome after infusion (Santomasso et al., 2019). To address these issues, recent work has eTCRs with optimized catch-bond dynamics that can maintain physiological affinities with enhanced target killing potency, but undetectable cross-reactivity (Zhao et al., 2022). However, clinical validation is still limited.

Beyond T cell–based strategies, nanomedicine provides a powerful complementary approach to overcome physical barriers that restrict T-cell penetration, activation, and cytotoxicity (Cassani et al., 2025). Many solid cancers contain excessive ECM deposition, which increases stiffness, interstitial fluid pressure, and solid stress, thereby physically excluding T cells and limiting the efficacy of adoptive cell therapies. Nanomedicine has emerged as a promising mechanobiology-based approach capable of remodeling tumor mechanics and therefore improving immune accessibility (Shen et al., 2024).

Current approaches increasingly target the mechanical and structural barriers of the ECM to improve drug delivery and T-cell infiltration (Mai et al., 2024), rather than global stromal depletion (e.g., PEGPH20), which has failed clinically (Van Cutsem et al., 2020). Photothermal or magnetic nanoparticles (NPs) such as gold nanorods (Raeesi and Chan, 2016) and iron oxide NPs (Piehler et al., 2020) disrupt collagen architecture, while collagenase-conjugated systems degrade fibrillar collagen and enhance tumor penetration (Zhou et al., 2022). Similarly, small interfering RNA–loaded NPs targeting FAK or LOX reduce ECM deposition and crosslinking, decreasing stiffness and improving immune infiltration (Zhang et al., 2022a). These strategies show promise, but translation is constrained by delivery efficiency, off-target effects, and potential toxicity associated with matrix degradation.

Other approaches exploit ECM physicochemical properties to enhance NP transport and achieve controlled release. Dense, negatively charged (Hu et al., 2025), and anisotropic (Naylor et al., 2023) tumor matrices favor specific NP geometries and surface chemistries, with rod- or disk-shaped and hydrophilic particles showing improved diffusion (Le Goas et al., 2020). Matrix-responsive systems (e.g., matrix metalloproteinase–responsive nanocarriers) enable localized release of immunomodulatory cargo, guiding T cells into tumors (Son et al., 2023; Yao et al., 2018). Currently, the clinical translation of these systems is limited by manufacturing complexity and challenges in reproducibility at a large scale. NPs can also modulate tumor physiology, for example, by reducing interstitial fluid pressure or improving perfusion via stromal targeting or vasodilation (Chen et al., 2019; Fan et al., 2013; Gao et al., 2017; Han et al., 2018). Others directly enhance T-cell recruitment, such as tumor-penetrating peptide (iRGD)–functionalized systems (Saifi et al., 2023) or gene nanomedicines inducing CXCL9/10 expression (Ma et al., 2022b).

Nanomedicine is also being leveraged to correct chemical stresses intrinsically linked to tumor mechanics, such as acidosis and hypoxia. Despite at a conceptual stage, pH-responsive NPs have been developed to release cargo upon acidic exposure (Li et al., 2016; Palanikumar et al., 2020), whereas biocatalytic nanomaterials can reverse tumor hypoxia (Zu et al., 2023), and hypoxia-activated NPs can activate the STING pathway (Song et al., 2024), ultimately boosting cytotoxicity.

Finally, emerging designs increasingly integrate mechanical and immunological design principles. NP shape, stiffness, and deformability influence circulation, tumor accumulation, and penetration, with softer particles showing improved transport in dense ECM (Deng et al., 2018; Kong et al., 2021; Tollemeto and Lammers, 2026). Shape-shifting NPs further optimize delivery by transitioning from circulation-efficient spheres to penetration-efficient geometries within the TME (Shao et al., 2022).

Together, these advances establish a shift from purely biochemical optimization toward mechanobiology-driven immunotherapies, where mechanical and physical cues are purposefully integrated to improve T-cell recruitment, overcome physical barriers, and amplify antitumor immunity where conventional therapies fail. While several strategies—particularly microfluidic devices—are approaching clinical relevance, many mechanogenetic and advanced biomaterial approaches remain at the proof-of-concept stage. Bridging this gap will require not only demonstrating robust in vivo efficacy, but also addressing scalability, safety, and regulatory constraints to enable clinical implementation.

Concluding remarks

Overall, T-cell function emerges from the integration of mechanical and biochemical cues across scales, with important implications for disease and therapy (Fig. 4). Despite increasing evidence highlighting the central role of mechanical forces in regulating T-cell behavior, the mechanobiology of T cells remains only partially understood. We still lack a comprehensive knowledge of how such forces are generated, transmitted, and

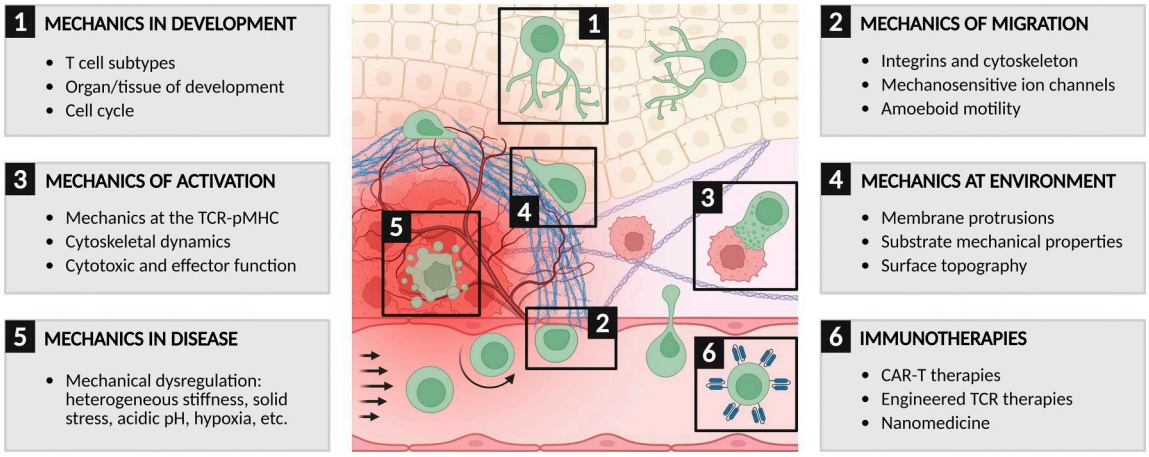

Figure 4. **Mechanobiological framework of T-cell function from development to therapy.** Schematic representation of the multiscale integration of mechanical and biochemical signals in T cells. Mechanical cues regulate T-cell development (lineage specification and proliferation), migration (amoeboid motility, integrin engagement, cytoskeletal remodeling), and activation (force-dependent TCR-pMHC interactions, signaling, and effector responses). These processes are modulated by environmental features such as substrate stiffness, viscoelasticity, and topography. In disease, mechanical dysregulation of the TME impairs T-cell infiltration and function. Emerging therapeutic strategies exploit these insights to enhance immune responses, including CAR T-cell and eTCR therapies, and nanomedicine approaches targeting biomechanical barriers.

interpreted by the cells, as well as how the mechanical properties of the T cells themselves evolve throughout their lifespan. Measuring and interpreting T-cell mechanics are inherently challenging due to their small size, spherical shape, nonadherent nature, and diverse glycocalyx that contains numerous receptors potentially involved in mechanosensing, which pose additional technical challenges to use conventional biophysical tools compared with other eukaryotic cells.

Several key unresolved questions are likely to define progress in the field over the next decade. First, what are the physiologically relevant force magnitudes, loading rates, and durations that govern TCR activation in vivo? While in vitro studies have established force-dependent signaling, there is still no consensus on the mechanical thresholds that determine functional outcomes in physiological contexts. Second, how does the TCR integrate mechanical and biochemical inputs to encode distinct cell fates? In particular, it remains unclear whether mechanical cues act as independent signals or modulate biochemical pathways. Third, how do T-cell intrinsic mechanical properties (stiffness, cytoskeletal organization, nuclear mechanics) dynamically change during activation, differentiation, and exhaustion, and how do these changes feed back into function?

At the tissue level, an additional major question is how T cells interpret and adapt to the heterogeneous and dynamic mechanical landscapes of in vivo environments, such as the TME or inflamed tissues. Understanding how parameters such as matrix stiffness, viscoelasticity, confinement, and ligand presentation collectively regulate migration and activation will be essential. Closely related is the question of how mechanical cues interact with metabolic and epigenetic programs, particularly in specialized subsets such as Tregs or exhausted T cells.

From a translational perspective, a critical challenge is to determine which mechanobiological principles can be robustly harnessed to improve immunotherapies. For example, can mechanical conditioning during ex vivo expansion enhance CAR T-cell persistence and function? Can modulation of tumor mechanics reliably improve T-cell infiltration without adverse effects?

Notably, progress in this field remains constrained by technological limitations. Techniques such as AFM or optical tweezers provide high force resolution but are largely restricted to simplified in vitro settings. Bridging these techniques with emerging fluorescent tension probes, mechanogenetic tools, or high-speed and super-resolution microscopy techniques will be critical to capture mechanical and biochemical events simultaneously and in more physiological contexts. New in vitro platforms that more closely mimic the physiological environment are also a step forward toward systematic mechanistic studies (Perucca et al., 2025).

Looking ahead, artificial intelligence has the potential to revolutionize data and image processing and predictive modeling, and for the integration of multimodal data in mechanobiology, which could enable the discovery of correlations between mechanical cues and T-cell responses (Oria et al., 2025; Tejedor and Garcia, 2025). To that end, several current caveats need to be addressed, like inherently small datasets, misinterpretation of correlation and causation in biology, and lack of standardization and limited explainability. Similarly, advances in quantum sensing and simulation may soon allow submolecular mapping of forces and energy transfer within the TCR complex, offering unprecedented resolution to decode the physics of immune signaling (Aslam et al., 2023; Lambert et al., 2013; Xu et al., 2024).

Finally, it is worth highlighting that T cells do not act in isolation. Other immune cell types, including B cells, macrophages, dendritic cells, and natural killer cells, are also mechanosensitive, and their crosstalk likely influences immune outcomes (Chen et al., 2025). Understanding these intercellular mechanical networks will be key to developing an integrated view of immune mechanobiology.

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