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Tuning immunity through tissue mechanotransduction

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Abstract | Immune responses are governed by signals from the tissue microenvironment, and in addition to biochemical signals, mechanical cues and forces arising from the tissue, its extracellular matrix and its constituent cells shape immune cell function. Indeed, changes in biophysical properties of tissue alter the mechanical signals experienced by cells in many disease conditions, in inflammatory states and in the context of ageing. These mechanical cues are converted into biochemical signals through the process of mechanotransduction, and multiple pathways of mechanotransduction have been identified in immune cells. Such pathways impact important cellular functions including cell activation, cytokine production, metabolism, proliferation and trafficking. Changes in tissue mechanics may also represent a new form of ‘danger signal’ that alerts the innate and adaptive immune systems to the possibility of injury or infection. Tissue mechanics can change temporally during an infection or inflammatory response, offering a novel layer of dynamic immune regulation. Here, we review the emerging field of mechanobiology, focusing on how mechanical cues at the scale of the tissue environment regulate immune cell behaviours to initiate, propagate and resolve the immune response.

Mechanotransduction is the process by which cells convert mechanical cues to biochemical signals, activating cellular pathways and influencing their function. Although fundamental roles for mechanical stimuli have long been recognized in developmental biology and in organ systems that receive significant mechanical stress, such as the cardiovascular and skeletal systems, these stimuli are now emerging as important orchestrators of inflammation and immune responses^{1–5}. In pathophysiological environments where tissue mechanics are altered, profound changes in mechanotransduction components occur at the cellular level, such as in adhesion molecules, ion channels and cytoskeletal proteins, and in their associated signalling pathways. Dysregulated tissue mechanics are seen in many diseases. In atherosclerosis, lung fibrosis and the peri-tumoural environment^{6–9} there is enhanced tissue rigidity. By contrast, other diseased tissues, such as abscesses and the necrotic core of tumours^{10,11}, are associated with mechanically softer tissue than in the healthy state. Understanding how these tissue-scale biophysical cues impact immune cell activation, metabolic reprogramming and downstream effector functions may provide new insights to treat these disorders.

Even under homeostatic conditions, immune cells face numerous forces as they circulate the body and encounter various tissue types. Cells that become resident in tissues experience stretching and shearing forces

over time, as they are mechanically influenced by the extracellular matrix (ECM), interstitial fluids and neighbouring cells. These tissue-level forces tune subsequent immune responses. Previous reviews have focused on the role of mechanical forces in immune cell trafficking¹² and molecular-level forces in triggering immune cell receptor activation^{13,14}. In this Review, we discuss the tissue-level mechanical cues and forces that intersect with immune cell activation and effector functions, including danger sensing and cytokine production. We detail how such signals tune immune cell responses and provide an integrated picture of immunity through the lens of mechanobiology to better highlight the emerging field of mechanobiology.

Mechanosensing pathways

We begin by examining how immune cells sense exogenous forces. Cells within tissues experience multiple types of mechanical force, including tension, compression, shear stress, interstitial flow and hydrostatic pressure (BOX 1 and reviewed in REFS.^{15–17}). In addition, the physical properties of the tissue surrounding the cells, including matrix rigidity, topography or architecture, also provide isometric mechanical cues that impact cellular function (BOX 1 and reviewed elsewhere^{18–20}). As we detail in the sections below, evolutionarily conserved pathways sense changes in these physical aspects of the

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ECM and can trigger mechanosensors in immune cells. It is important to note that immune cells do not just passively experience these exogenous cues but can also contribute to them, generating either reciprocal or additive forces upon the matrix and upon neighbouring cells.

Immune cells share with other cells conserved pathways by which they can sense and respond to these mechanical cues (FIG. 1). Major mechanosensors include adhesion molecules (such as integrins), ion channels (including transient receptor potential vanilloid type 4 (TRPV4) and the PIEZO family of mechanically activated cation ion channels) and cytoskeletal components^{21–23}. These mechanosensors transduce cues leading to Ca²⁺ fluxes, cytoskeletal reorganization and transcriptional regulation. In addition to cell-surface mechanosensors, the cytoskeletal network of filaments and tubules further allows cells to sense, withstand and respond to mechanical signals by transducing extracellular cues to the nucleus for dynamic rearrangement of chromatin following mechanical stimulation^{24,25}. Actin filaments also form scaffolding at focal adhesions to support multiprotein signalling hubs while executing morphological changes of cells through polymerization-driven expansion, depolymerization or contraction with myosins^{26,27}. External stress on cells results in reorientation of actin–myosin fibres (into ‘stress’ fibres) in parallel orientation to the force²⁸. Cytoskeletal mechanotransduction is further propagated to the nuclear envelope through direct connections with the nuclear lamina via the linker of nucleoskeleton and cytoskeleton (LINC) complex, which comprises transmembrane proteins from the nesprin and SUN families^{29,30}. These components mediate nuclear morphology and cytoskeletal force transmission with subsequent chromatin organization and gene regulation^{31–33}.

Actin dynamics are largely regulated by a family of Rho GTPases, which themselves are controlled by many proteins and a diverse range of post-translational

modifications that regulate subcellular localization and GTP exchange^{34–39}. Molecules further downstream that influence actin dynamics promote the bundling of filaments⁴⁰, the severing of filaments^{41,42}, capping of actin⁴³, branching of filaments^{44,45} and more. Important secondary mediators of force transduction include serum response factor (SRF), its coactivator myocardin-related transcription factor A (MRTFA) and yes-associated protein (YAP) or its homologue, transcriptional co-activator with PDZ-binding motif (TAZ). The role of these factors in the context of immune cells will be reviewed in the following sections.

Mechanotransduction in immune cells

A central question in immunology is how cells discern danger in the tissue environment. Traditionally, research has focused on components derived from invading pathogens (for example, lipopolysaccharide (LPS)) or damaged cells as the initiating danger signals that induce immune responses. However, emerging evidence suggests that biophysical cues may also regulate immune cell function and effector responses. For thousands of years, it has been known that ‘tumour’ (rigidity) is an early, cardinal sign of tissue inflammation (in addition to ‘calor’ (warmth), ‘rubor’ (redness), and ‘dolor’ (pain)). We now understand that the earliest changes in tissue mechanics are prompted before the activation of immune responses, by epithelial and stromal cells themselves in response to Toll-like receptor (TLR) ligands such as LPS. These signals prompt dramatic increases in the production of high molecular weight hyaluronic acid, which traps water and swells tissue (that is, causes oedema) over the course of minutes to hours. Endothelial cells respond to TLR signals by increasing the permeability of the endothelium, leading to fluid and protein leakage into the tissue. Immune cells experience these mechanical changes as they traverse these tissue environments, and these mechanical cues play an active role in the early recognition of danger and in the initiation of immune responses.

Many innate immune cells are adherent and contact-dependent, making them exquisitely sensitive to mechanical stimuli such as changes in ECM stiffness. Immune cells are frequently studied using engineered systems for their responses to mechanical cues (BOX 2), and such studies have illuminated roles for mechanotransduction in immune cells. Mechanosensing of substrate rigidity by macrophages has been shown to influence phagocytosis^{46,47}, the mode of migration⁴⁶, cellular reactive oxygen species (ROS) production⁴⁸, healing ability⁴⁹, cell morphology⁵⁰ and secretion of both anti-inflammatory and pro-inflammatory cytokines^{47,49,51,52}. As a general trend, compared with macrophages grown on softer materials, macrophages cultured on a stiffer substrate show enhanced effector functions and produce more pro-inflammatory cytokines when exposed to TLR ligands. For instance, macrophages cultured on rigid polystyrene make more tumour necrosis factor (TNF) and interleukin-6 (IL-6), but less IL-10, in response to LPS stimulation when compared with the same cells cultured on soft fibrin hydrogels⁵¹. For TNF, this trend held across a range

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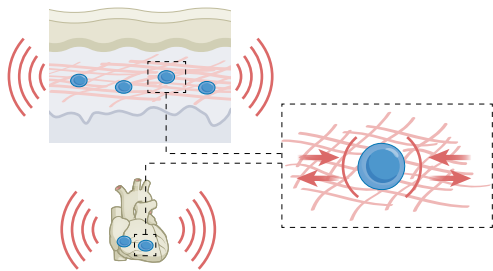
¹⁵These authors jointly supervised this work: Wendy F. Liu, Daniel A. Winer, Manish J. Butte.

Box 1 | Mechanical cues experienced by immune cells

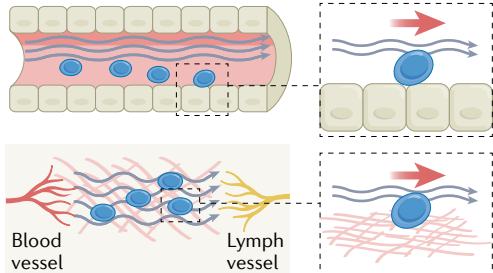
Immune cells experience diverse mechanical cues (see the figure). Active forces (left side of the figure) include tension and compression, the pulling and pushing forces that lengthen or shorten cells, causing cytoskeletal reorganization and generating contractile forces that elicit reciprocal tension on extracellular components^{18,160}; shear stress, a force acting parallel or tangential to the surface of an object — experienced by cells interfacing with fluids, such as flowing blood or interstitial fluid¹⁶¹; interstitial flow, the flow through the spaces of the extracellular matrix (ECM) — arises from plasma leaving the capillary, passing through tissues and draining into lymphatics¹⁶², and tensile and compressive forces also

stimulate interstitial flow^{163–165}; and hydrostatic pressure, exerted by a non-moving fluid and present in the bone marrow¹⁶⁶ and vasculature¹⁶⁷ and during pressure changes in the lungs⁵⁹. The biophysical properties of tissues (right side of the figure) that determine how forces impact immune cells are shaped by the ECM¹⁶⁸. The stiffness (rigidity) of the tissue is measured as the elastic modulus (*E*), which relates how resistant a tissue is to deformation under the application of forces applied to an area of tissue. The stiffness of most soft tissues is typically less than 10 kPa, whereas in diseased states, such as fibrosis, stiffness exceeds 20 kPa^{59,65,167,169–184}.

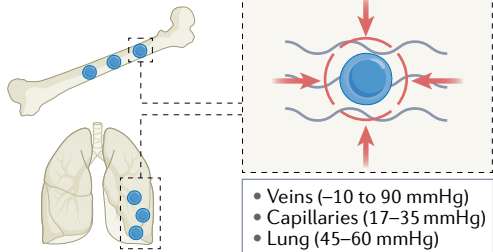
Tension and compression



Shear stress and interstitial flow

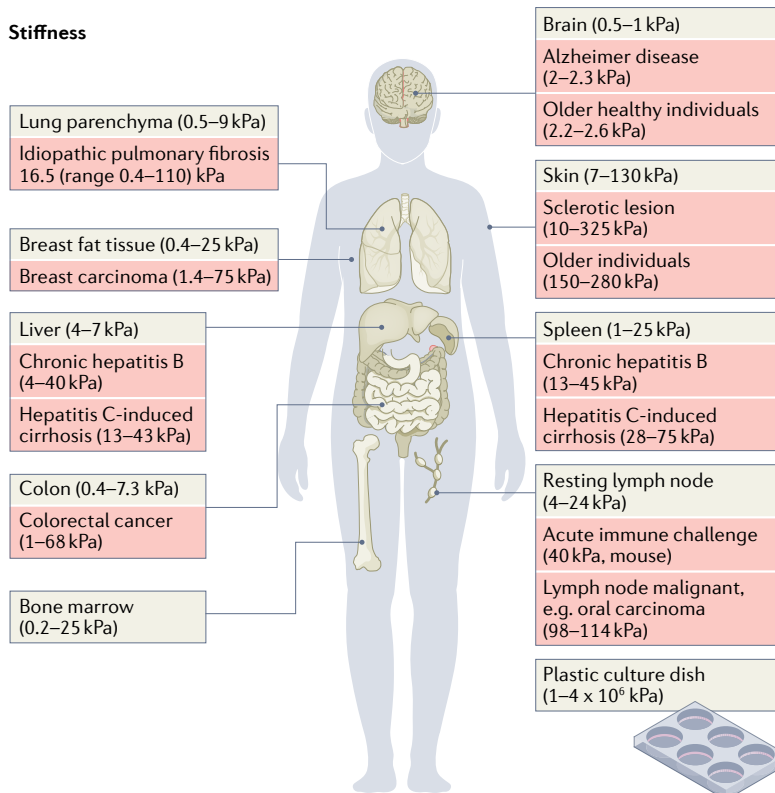


Hydrostatic pressure



- Veins (–10 to 90 mmHg)
- Capillaries (17–35 mmHg)
- Lung (45–60 mmHg)

Stiffness



of LPS doses and with different TLR agonists, including Pam3CSK4 (a TLR1/TLR2 agonist) and FSL1 (a TLR2/TLR6 agonist)^{47,49,51}. Consistent with these findings in macrophages, bone marrow-derived dendritic cells grown on a stiff substrate (50 kPa, mimicking fibro-inflammatory disease) produce increased levels of pro-inflammatory cytokines — including IL-1 α , IL-1 β , IL-6, IL-12 and TNF — following LPS stimulation and show increased activation and proliferation compared with dendritic cells cultured on soft hydrogel (2 kPa, mimicking the physiological stiffness of most soft tissues)⁵³. Therefore, the mechanical signal transduced by a stiff ECM into innate immune cells tunes the inflammatory phenotype as they respond to pattern recognition receptor (PRR) ligands. Mast cells are also sensitive to

mechanical stretching, which enhances their degranulation and secretion of histamine, and their release of active transforming growth factor- β 1 (TGF β 1)^{54,55}.

Mechanosensing in innate immune cells is not limited to sensing changes in tissue stiffness or tension. Circulating monocytes are also affected by fluid shear stress, where high shear stress promotes adhesion, phagocytosis and pro-inflammatory cytokine secretion⁵⁶. Similarly, neutrophils that endure shear force show enhanced phagocytosis, greater platelet–neutrophil aggregation and amplified cytosolic Ca²⁺ levels leading to increased cell activation^{57,58}. Macrophages also become pro-inflammatory when exposed to cyclical hydrostatic pressure⁵⁹. These data suggest that a multitude of mechanical stimuli can influence

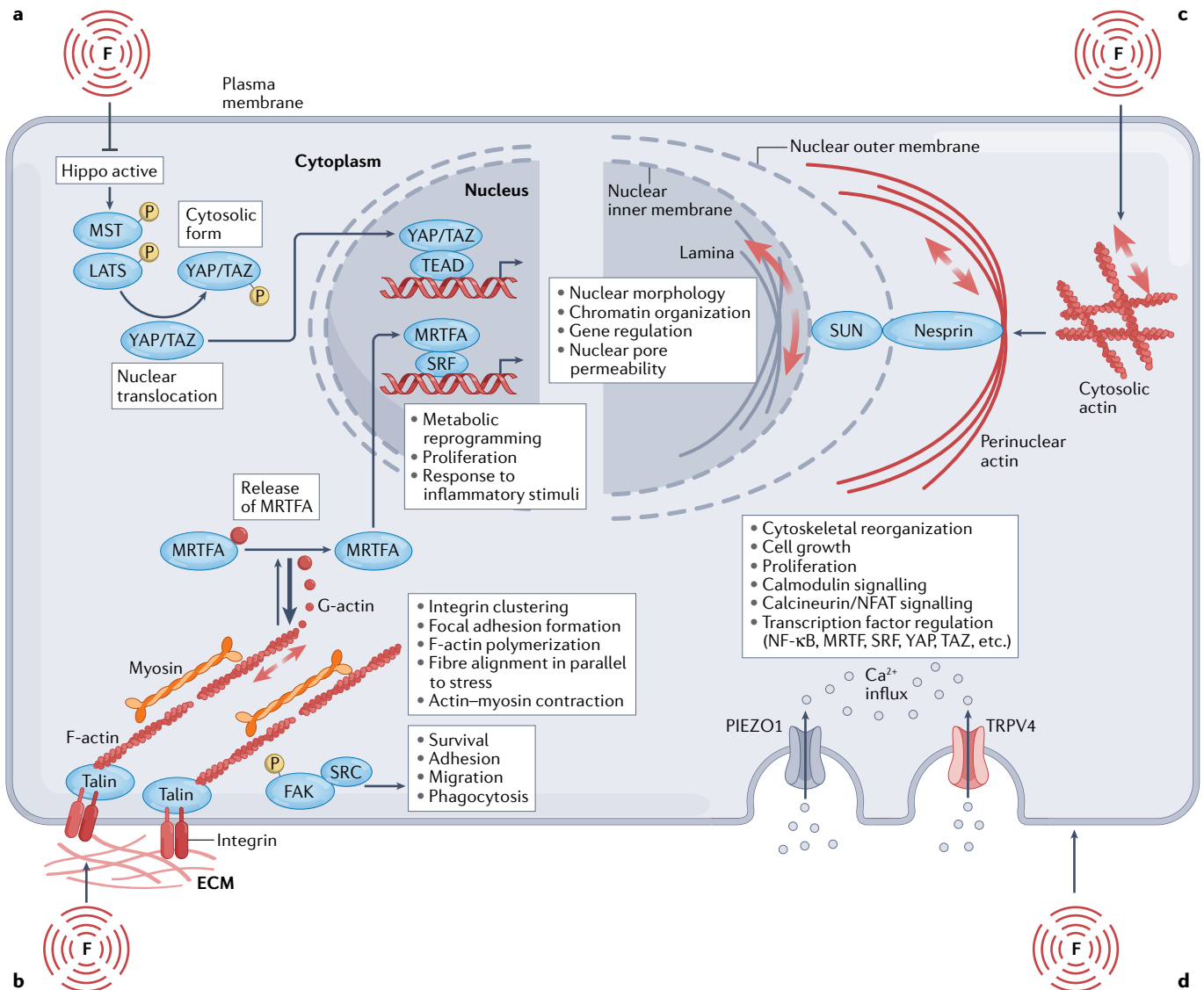


Fig. 1 | An overview of mechanotransduction pathways in cells. **a** | Classical Hippo pathway activation induces phosphorylation of kinases MST1 and/or MST2, as well as LATS1 and/or LATS2, which in turn phosphorylate yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). Phosphorylated YAP and TAZ are sequestered in the cytoplasm. Upon Hippo pathway inhibition, such as in response to mechanical force (denoted by F), YAP and TAZ translocate to the nucleus and drive gene expression that is key to immune function, including genes involved in cellular metabolic reprogramming, proliferation and responsiveness to inflammatory stimuli, through the TEA domain (TEAD) transcription factor family. **b** | Integrins anchor cells to the extracellular matrix (ECM), cluster and form focal adhesions, which act as multiprotein signalling hubs. Focal adhesion kinase (FAK) and SRC are key downstream effectors of focal adhesions, orchestrating various immune cell functions. Focal adhesions execute cell morphological changes either by actin polymerization-driven expansion or depolymerization and contraction with myosin.

Polymerization of actin filaments (F-actin) subsequently reduces availability of G-actin (depicted by heavy arrow), decreasing its association with myocardin-related transcription factor A (MRTFA), which causes nuclear translocation of MRTFA, association with serum response factor (SRF) and gene transcription responsible for metabolic reprogramming, proliferation and cell responses to inflammatory stimuli. **c** | Mechanotransduction is also propagated directly from the cytoskeleton to the nuclear envelope via the linker of nucleoskeleton and cytoskeleton (LINC) complex, which includes the transmembrane proteins SUN and nesprin. LINC mediates nuclear morphology, chromatin organization, gene regulation and nuclear pore permeability, which also facilitates the nuclear translocation of YAP and TAZ and MRTFA. **d** | Transient receptor potential vanilloid type 4 (TRPV4) and PIEZO1 cation channels are activated by mechanical stimuli inflicted on the plasma membrane. Their activation promotes Ca²⁺ influx, impacting the regulation of many transcription factors, inflammatory signalling pathways and cytoskeletal reorganization.

effector functions in innate immune cells, tuning their inflammatory response.

Adaptive immune cells also respond to mechanical cues. T cells and B cells recognize cognate antigens either as peptides bound to the MHC molecules on the surface of antigen-presenting cells (APCs) or as immobilized whole proteins, respectively. Forces generated

from this contact modulates their behaviour¹⁴, making the physical properties of antigen-presenting surfaces influential to adaptive immune cell responses. For example, T cells that are stimulated by ‘stiff’ dendritic cells require a lower antigen concentration for activation than do T cells stimulated by ‘soft’ dendritic cells⁶⁰. In fact, dendritic cells actively elevate cortical stiffness

'M1-like' inflammatory macrophage

'M1' and 'M2' are classifications historically used to define macrophages activated in vitro as pro-inflammatory (when 'classically' activated with IFN γ and lipopolysaccharide (LPS)) or anti-inflammatory (when 'alternatively' activated with interleukin-4 (IL-4) or IL-10), respectively. However, in vivo macrophages are highly specialized, transcriptomically dynamic and extremely heterogeneous with regards to their phenotypes and functions, which are continuously shaped by their tissue microenvironment. Therefore, the M1 or M2 classification is too simplistic to explain the true nature of in vivo macrophages, although these terms are still often used to indicate whether the macrophages in question are more pro-inflammatory or anti-inflammatory.

during maturation, suggesting that increased cytoskeletal stiffness is a biophysical mechanism central to proper priming of T cells⁶⁰. Substrate stiffness is also a modulator of adaptive immune cell behaviour, and has been shown to regulate T cell spreading^{61,62}, migration, gene expression, cytokine secretion⁶², proliferation⁶³ and cytotoxic function⁶⁴. When tissue stiffness was specifically increased from 4 kPa (similar to what is encountered in a resting lymph node) to 40 kPa (resembling a swollen lymph node), it promoted T cell proliferation, activation and metabolism, while lowering the antigen dose needed to elicit effector responses⁶⁵. T cells crawling through an artificial, mechanically tuned environment will alter their threshold for activation in a manner that depends more on the substrate stiffness than the stiffness of the APCs offering antigenic stimulation⁶⁶. Thus, T cells can separately sense both environmental cues as well as the mechanics of the APCs with which they interact. For B cells, the rigidity of antigen-presenting substrates regulates B cell receptor (BCR) accumulation⁶⁷, antigen uptake⁶⁸, proliferation, class switching and antibody production⁶⁹. B cells appear to sense the mechanics of follicular dendritic cells in the lymph node germinal centre and the forces required to extract antigens from the surface of follicular dendritic cells as a way of promoting the preferential uptake of high-affinity antigens over low-affinity antigens from the environment⁶⁸. A recent publication also reported that different biomaterial implants with essentially distinct mechanical properties affect the B cell response to muscle injury⁷⁰. For instance, synthetic polyester implants induced certain B cell pathways including strengthening their presentation of antigens and expressing inflammation-related genes.

Given that biophysical cues and forces in the environment are emerging as important modulators of immunity, it is important to understand the mechanisms and signalling processes by which mechanical cues influence immune cell activation and effector function. Below, we outline key studies linking mechanosensing pathways to immune cell effector outputs (see Supplementary Table 1 for a summary). In particular, we focus on two mechanosensing pathways — mechano-gated ion

channels and Hippo signalling — that have been linked to inflammation.

Ion channels: PIEZO1 and TRPV4. Exposure of physical stimuli to the plasma membrane can trigger ion influx through channels and transporters⁷¹. Two of these mechano-gated ion channels have been well characterized in immune cells: PIEZO1, a member of the Piezo family of mechanically activated cation channels⁷², and TRPV4, a member of the TRP superfamily of non-selective cation channels⁷³. Mechanical deformations of the plasma membrane directly open the channels of PIEZO1 and TRPV4. TRPV4 can also open in response to osmotic stress and temperature changes, and indirectly through inflammatory mediators such as arachidonic acid or histamine^{74,75}. Both PIEZO1 and TRPV4 facilitate influx of extracellular Ca²⁺, leading to activation of Ca²⁺-regulated signalling pathways that influence cellular metabolism and effector functions. One example of signalling modulated by Ca²⁺ in immune cells is the calcineurin–NFAT transcription factor pathway, which is essential for T cell activation^{76,77}. Elevation of intracellular Ca²⁺ triggers calcineurin, a protein phosphatase, to dephosphorylate NFAT and allows it to translocate into the nucleus⁷⁸. Studies have shown that PIEZO1-mediated Ca²⁺ influx can activate NFAT in cells such as osteoblasts⁷⁹, but this has yet to be verified in immune cells. PIEZO1 expression is particularly abundant in mechano-active tissues such as the lungs, bladder and skin⁸⁰, and PIEZO1 is transcriptionally expressed across a wide range of immune cell subsets, whereas TRPV4 expression appears more limited to a few myeloid subsets⁸¹.

During macrophage activation, PIEZO1 co-localizes and coordinates with TLR4 to enhance ROS production via a calmodulin-dependent protein kinase II (CAMKII)–MST1/MST2–Rac axis, increasing pathogen ingestion and killing⁴⁸. Stiff substrates were shown to activate PIEZO1, triggering Ca²⁺ influx that enhanced NF- κ B activation and F-actin formation in bone marrow-derived macrophages stimulated with LPS and IFN γ , leading to a more prominent 'M1-like' inflammatory macrophage phenotype⁴⁹. Intriguingly, although bone marrow-derived macrophages cultured on a stiff substrate also have Arginase 1 (ARG1) expression in response to IL-4 and IL-13, PIEZO1 activity independent of a stiff substrate suppresses the IL-4/IL-13-induced expression of ARG1, demonstrating that mechanotransductive signals can override one another⁴⁹. Moreover, ECM stiffness was shown to govern population expansion and pathogenic cytokine release by myeloid-derived suppressor cells in a PIEZO1-dependent manner through the silencing of the tumour suppressor protein retinoblastoma 1 (RB1) by histone deacetylation⁸².

In response to cyclical hydrostatic pressure, PIEZO1 activation in macrophages leads to the production of endothelin 1 (EDN1), which stabilizes hypoxia-inducible factor 1 α (HIF1 α) to optimize antibacterial defence against *Pseudomonas aeruginosa*⁵⁹. Of note, HIF1 α is a major inducer of glycolysis, bridging PIEZO1 activity with glycolysis-driven inflammatory responses, highlighting mechanical regulation of immune cell

Box 2 | Engineered systems for mechanobiology

Engineered systems are often used to simplify the study of the effects of mechanical cues and matrix physical properties on cell function. These systems are now being applied to study tissue-level forces on immune cells^{66,185}. Engineered biomaterials often include a combination of synthetic polymers and extracellular matrix (ECM) proteins to control mechanical properties and biochemical ligands separately and precisely. Polyethylene glycol, polydimethylsiloxane and polyacrylamide (PA) are good examples, and mechanical properties are controlled by cross-linking. The materials are further conjugated with ECM proteins that offer natural adhesive ligands to cells, such as collagen, fibronectin or arginylglycylaspartic acid peptides. Most biomaterials employed in studies, such as PA, demonstrate only linear elasticity, whereas natural tissues demonstrate both time-dependent (viscoelastic) and time-independent responses. To control topology or adhesive geometry, materials with microscale features can be fabricated by using photolithography or electrospinning techniques¹⁸⁶. Moreover, cells can be placed on flexible membranes, in flow chambers or in bioreactors that are connected to pumps or motors to apply mechanical forces including stretch, shear stress and hydrostatic pressure. Further advances in such tools and technologies will enable the creation of biomaterials that better mimic physiological conditions, allowing for more sophisticated studies linking mechanical cues and cell function.

Immunological synapse

The site of discrete contact formed between an antigen-presenting cell (APC) and a T cell. Similar synapses have been described in other immune cells such as natural killer cells or cytotoxic T cells, where the contact is formed with a target cell. It is important in establishing adhesion with the partner cell and polarization of the signalling and cytotoxic machinery. This structure is heavily influenced by the cytoskeleton and transduces controlled secretory signals, thereby allowing the directed release of cytokines or lytic granules towards the APC or target cell.

metabolism⁸³. Consistent with this concept, the addition of the PIEZO1 agonist, YODA1, to mouse dendritic cells *in vitro* induced expression of the major glycolytic genes *MYC* and hexokinase 2 (*HK2*), as well as *SLC2A1* (which encodes the glucose transporter GLUT1), and also boosted TNF production⁵³. Furthermore, PIEZO1 plays an important role in shear stress-induced inflammation, where it contributes to adhesion of circulating monocytes, activation of CD11b integrin (also known as Mac1), increased phagocytosis and release of pro-inflammatory cytokines⁵⁶. These findings indicate that various mechanical signals can mediate innate inflammatory responses. It will be interesting to assess how PIEZO1 impacts immune cell function across different tissue types and disease states.

Studies have only recently begun to shed light on a role for PIEZO1 in regulating adaptive immunity. *In culture*, (partial) small interfering RNA-mediated knock-down of PIEZO1 in human CD4⁺ T cells reduced T cell receptor (TCR) activation and proliferation by weakening calpain-dependent immunological synapse stabilization⁸⁴. Notably, unlike in osteoblasts, the Ca²⁺-calcineurin-NFAT pathway was not activated by agonist-induced opening of PIEZO1 in that system. By contrast, another study showed that CD4⁺ T cell-specific deletion of *Piezo1* in mice did not impair T cell proliferation or TCR-evoked Ca²⁺ signalling⁸⁵. Genetic deletion of *Piezo1* instead enhanced expansion of regulatory T (T_{reg}) cell populations by promoting TGFβ signalling. The conflicting requirement for PIEZO1 in T cell activation in these two systems might be the consequence of the experimental approaches used. Furthermore, PIEZO1 is responsible for maintaining a peri-arteriolar niche of lymphoid progenitors in the bone marrow; depletion of PIEZO1 from the niche caused a decline of lymphoid cells and a compromised immune state⁸⁶. These initial studies support the hypothesis that PIEZO1 tunes effector functions of adaptive immune cells. However, more work is needed to better elucidate the role of PIEZO1 in adaptive immunity, especially in showing its mechanical role.

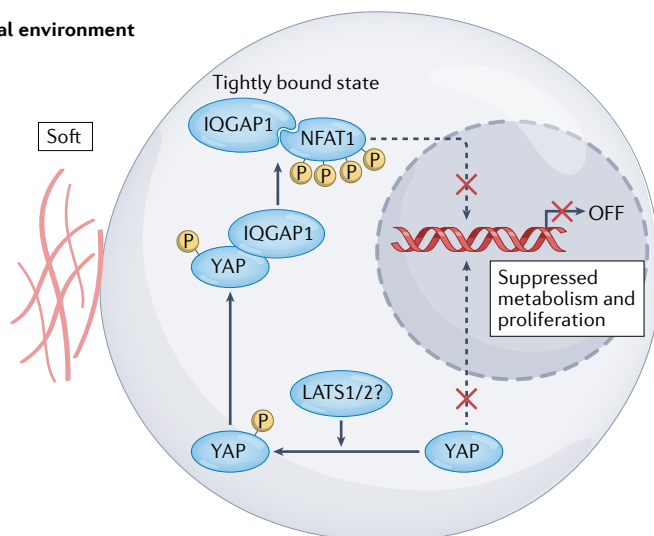
Similarly to PIEZO1, the role of TRPV4 has been largely studied in innate and tissue-resident immune cells, especially macrophages. TRPV4 facilitates skin-resident macrophage acquisition of a pro-inflammatory phenotype in conditions of high stiffness (50 kPa)⁴⁷. Stiff matrices had a synergistic effect on IFNγ and LPS-induced polarization during macrophage activation, and the effect was reliant on functional TRPV4. TRPV4-deficient mice also had a reduced ability to clear bacteria during *Mycobacterium tuberculosis* infection owing to delayed phagosome acidification and reduced generation of reactive nitrogen species⁸⁷. Similarly, during infection with *P. aeruginosa*, the presence of TRPV4 enhanced pathogen clearance by macrophages⁸⁸. Specifically, TRPV4-mediated TLR activation of p38 via dual-specificity phosphatase 1 (DUSP1) increased macrophage phagocytosis on stiff matrices⁸⁸. Interestingly, p38 activity was shown to attenuate inflammatory cytokine production through inhibition of JNK, which reduced infection-associated tissue damage. Resident cardiac macrophages also stimulate myocardial tissue remodelling and coronary angiogenesis through TRPV4-mediated

sensing of mechanical stress associated with heart failure, suggesting a role for TRPV4 in promoting tissue regeneration⁸⁹. By contrast, another study demonstrated that TRPV4 enhanced the release of cytokines such as IL-1α, IL-1β, IL-6, IL-8 and CC-chemokine ligand 2 (CCL2) in response to equi-biaxial stretch, a form of tension exerted by mechanical ventilators⁹⁰. Conflicting results show there is still much to learn about TRPV4 in immune cells. Contradictory findings may arise from differences in cell sources, differentiation protocols, agonist dosing and adherent substrates. Still, TRPV4 has emerged as an important link between mechanosensing and pathogen clearance.

YAP and TAZ of the Hippo signalling pathway. Recent studies directly link mechanotransduction via the Hippo signalling pathway to immune cell responses. Classically, this pathway is modulated by cell contact and density⁹¹. These mechanical cues activate the kinases MST1/MST2 and LATS1/LATS2, which in turn phosphorylate the two homologous effector proteins YAP and TAZ⁹². Phosphorylated YAP and TAZ are sequestered in the cytoplasm, and depending on the kinase and phosphorylation site, become a substrate for degradation in the proteasome⁹³. Upon inhibition of the Hippo pathway kinases, YAP and TAZ move into the nucleus to drive gene expression through their binding with transcription factors, particularly members of the TEA domain (TEAD) family⁹⁴. YAP and TAZ can also translocate in response to ECM stiffness and cell patterning⁹⁵. In immune cells, this tunes effector fates through transcription of genes integral to metabolic reprogramming, proliferation and activation-related functions. For example, nuclear YAP and TAZ direct LPS and IFNγ-triggered M1-like macrophage activation and IL-6 production, while inhibiting macrophage polarization towards an IL-4 and IL-13-induced M2-like anti-inflammatory phenotype⁹⁶. Similarly, stiff substrates drove nuclear localization of YAP in macrophages and potentiated an inflammatory response after stimulation with LPS, as determined by elevated levels of NF-κB phosphorylation and pro-inflammatory cytokine production⁵¹. YAP and TAZ can also be immunomodulatory when sequestered in the cytosol (as in softer environments), where they can inhibit antiviral defence by impairing type I interferon production through interaction with the protein kinase TBK1 and interferon regulatory factor 3 (IRF3)^{97,98}. This cytoplasmic interaction blocks IRF3 translocation to the nucleus, limiting the transcription of interferon-related genes.

Indeed, stiffness-mediated nuclear localization of YAP and TAZ has profound effects on innate immune cell signalling and metabolism. YAP-TEAD and TAZ-TEAD complexes govern the expression of genes involved in glycolysis, in glutamine metabolism and in glucose and amino acid uptake via both directly induced transcription or indirect induction. The importance of YAP and TAZ in regulating metabolism has been reviewed elsewhere⁹⁹. Notably, altered metabolic reprogramming is a fundamental step in immune cell activation, effector function and maintenance¹⁰⁰. Linking mechanotransduction-mediated Hippo signalling to

Soft mechanical environment



Stiff mechanical environment

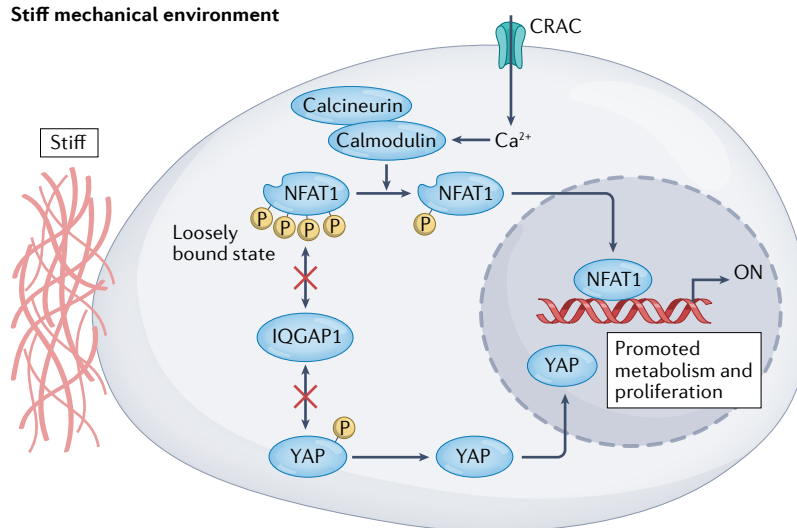


Fig. 2 | Mechanical regulation of T cell activity through YAP. When T cells are in tissues with a soft extracellular matrix (ECM) microenvironment, yes-associated protein (YAP) is phosphorylated (likely by LATS1 or LATS2) and localized in the cytoplasm, where it interacts with IQGAP1. Owing to YAP and IQGAP1 interaction, NFAT1 is preferentially sequestered in the cytoplasm, and this results in attenuated cellular metabolism and proliferation. Conversely, when T cells encounter a stiff ECM microenvironment, YAP is dephosphorylated and migrates to the nucleus. Additionally, NFAT1 is no longer sequestered in the cytoplasm through IQGAP1–YAP interaction. Thus, with the help of calcium release-activated channels (CRAC), calcineurin and calmodulin, NFAT1 can be dephosphorylated and is free to translocate to the nucleus to induce T cell activation-related gene expression.

metabolism in immune cells, upon contact with stiff substrates, TAZ translocates to the nucleus in bone marrow-derived dendritic cells and splenic dendritic cells and induces the transcription of genes that shape metabolic processes in these cells in response to PRR signals⁵³. Such genes include the master regulator of glycolysis *MYC*, the glycolysis gene *HK2*, the glucose transporter *SLC2A1* and the pentose phosphate pathway gene *PGLS*. Because of activated TAZ, dendritic cells cultured on stiff ECM have amplified activity in glycolysis, the tricarboxylic acid cycle (TCA) and the pentose phosphate pathway, which facilitates dendritic cell activation and

pro-inflammatory function. Tension-mediated priming of dendritic cell metabolism occurred even without PRR input, although to a lesser extent, raising the possibility that tension acutely primes immune cell metabolism prior to activation, potentially to ready the cell in a stiff environment for optimal effector response.

In adaptive immune cells, there is similar stiffness-mediated subcellular localization of YAP and TAZ (FIG. 2). In T cells, phosphorylated YAP modulates activation by regulating the binding affinity between NFAT1, a transcription factor regulating T cell activation and metabolism, and its scaffolding protein IQGAP1, based on matrix stiffness⁶⁵. YAP stabilizes NFAT1–IQGAP1 interactions in the cytoplasm in response to soft ECM contact, attenuating metabolic reprogramming and T cell activation. However, when T cells sense a stiff microenvironment YAP translocates to the nucleus, freeing NFAT1 from the NFAT1–IQGAP1 binding complex and enabling induction of downstream metabolic genes. Thus, as the mechanical environment goes from inflamed (stiff) to basal (soft), YAP mediates downregulation of T cell responses. This softness-driven inhibition also protects bystander tissues from T cell-mediated autoimmunity, as evidenced by accelerated development of type 1 diabetes in mice models when T cells lack YAP⁶⁵. YAP-suppressed metabolic pathways include glycolysis, mitochondrial respiration and amino acid uptake. Consistent with these findings, a recent study reported that YAP knockout boosts CD8⁺ T cell production of cytotoxic cytokines and degranulation factors¹⁰¹, which may be related to the loss of the cytosolic functions of YAP. Knockout of YAP also perturbs T_{reg} cell function, resulting in reduced TGFβ–SMAD signalling¹⁰². Some functions of YAP and TAZ may also occur independently of mechanical signals. For example, when interacting with the transcription factor RORγt instead of TEAD1, TAZ decreases acetylation of *FOXP3*, leading to attenuation of T_{reg} cell differentiation¹⁰³. Nonetheless, YAP and TAZ remain key intermediates of mechanical signal tuning of innate and adaptive immunity.

Integrins. Many cells are physically anchored to their extracellular environment through integrins. This family of transmembrane heterodimeric receptors is composed of α-subunits and β-subunits that bind to ECM proteins¹⁰⁴. Upon binding to the matrix, integrins cluster to form focal adhesions, or multiprotein hubs that are connected to the cytoskeleton. Physical deformation of cells leads to cytoskeletal rearrangements, including actin bundling and stress fibre formation, which directly activates intracellular signalling pathways¹⁰⁵. Focal adhesion kinase (FAK) and Src, two non-receptor tyrosine kinases, are important downstream effectors of focal adhesions. Under mechanical engagement, this complex directs a network of factors, such as RhoA, Rac1 and Cdc42, that modulate morphological changes, cell motility, adhesion, development, proliferation, survival and inflammation^{106,107}.

The role of integrins is well studied in leukocyte migration; however, integrins are also mechanosensitive and actively regulate immune cell effector functions. For example, LFA1 (also known as α_L integrin and

CD11a–CD18) undergoes a conformational change in response to high substrate rigidity that increases its affinity for immobilized intercellular adhesion molecule 1 (ICAM1)¹⁰⁸. This process occurs during dendritic cell maturation¹⁰⁹. Higher affinity binding between LFA1 and ICAM1 also promotes the activation of immune cells, including T cells and natural killer cells^{110–112}. Stiff matrices have been shown to enhance integrin CD11b-mediated phagocytosis in macrophages¹¹³ and LFA1-mediated actin cytoskeletal polymerization in T cells³¹, which promotes MRTFA translocation and consequent gene expression^{114,115}. In addition, strong FAK activation downstream of integrins elicited by high substrate stiffness facilitates B cell spreading and adhesion, enhancing B cell activation response⁶⁷. Despite these important functions of integrins in the immune system, some immune cells do not require integrins to fulfil certain effector functions in the presence of mechanical cues that occur during cell migration, or in response to infection or autoimmunity. For instance, studies have reported that integrins may be dispensable for some aspects of dendritic cell migration from tissue to lymph node, natural killer cell migration for protection against viral infection, T_{reg} cell migration to the central nervous system during experimental autoimmune encephalomyelitis as well as T cell priming by dendritic cells during *Trichuris muris* infection^{116–119}. Nonetheless, integrins still have important roles in transducing mechanical cues into effector responses in many contexts.

The MRTFA–SRF pathway. SRF and its coactivator MRTFA also link mechanotransduction, cytoskeleton dynamics and cell function. Cytoplasmic MRTFA is predominantly bound to G-actin. Mechanical stimuli induce polymerization of actin filaments, thereby reducing G-actin and causing the release of MRTFA. This allows MRTFA to translocate to the nucleus, where together with SRF it induces gene transcription^{115,120,121}. In myeloid cells, this transcriptional activity affects migration, phagocytosis and cytoskeletal gene expression¹²². In dendritic cells, MRTFA–SRF also modulates cell cycle progression, adhesion and lipid metabolism¹¹⁴. RNA sequencing of *Mrtfa*^{-/-} dendritic cells showed a reduction in cholesterol metabolism when compared with wild-type cells¹¹⁴, possibly connecting mechanotransduction and cholesterol metabolism. Lipid and cholesterol metabolism are critical for dendritic cell function¹²³. Thus, attenuated cholesterol metabolism in *Mrtfa*^{-/-} cells will most likely impair their immune functions, although this has yet to be shown. In macrophages, MRTFA and SRF integrate signals of spatial confinement into immunomodulating pathways¹²⁴. This is especially relevant for tissue-resident macrophages, which can be tightly packed in tissues and increase in size upon activation, causing spatial confinement. The spatial confinement of macrophages suppresses the expression of late LPS-activated genes — such as those encoding IL-6, CXCL9 and inducible nitric oxide synthase (iNOS) — by downregulating histone deacetylase 3 (HDAC3), inhibiting the removal of dimethylated histone H3 K36 (H3K36me2) marks, and reducing inflammatory tone¹²⁵. The transcription of such late-responsive genes is further

modulated by MRTFA and SRF, which are generally induced by LPS, but reduced by spatial confinement, thus providing another link between mechanical cues and cytokine production.

Another member of the myocardin-related transcription factor family, MRTFB, has been shown to have some redundant functions to MRTFA in certain contexts, such as neuronal migration, cardiac function and haematopoietic progenitor cell chemotaxis^{126–128}. Both proteins also play important roles in cancer cell immunosurveillance, and their overexpression elevates tumour cell rigidity resulting in increased killing by cytotoxic T lymphocytes and natural killer cells¹²⁹. However, whether MRTFB directly responds to force induction to modulate downstream expression in immune cells themselves still requires further investigation.

LINC complex and nuclear lamins. The LINC complex and nuclear lamins are major modulators of mechanotransduction in the nucleus. Their expression influences many immune effector functions including chemotaxis, inflammation, proliferation and activation^{130,131}. A-type lamins and the LINC complex were found to mediate T cell immunological synapse formation by promoting actin skeleton polymerization and downstream gene expression related to T cell activation, as well as ERK1 and ERK2 phosphorylation¹³². Indeed, T cells that lack lamins or have disconnected LINC–lamin complexes have impaired activation and proliferation. Similar to many mechanosensitive proteins in immune cells, A-type lamins together with the LINC complex have the ability to bridge actin remodelling and transcription in the nucleus, therefore hinting to their indispensable role in immune mechanotransduction. As research on the LINC complex and nuclear lamins has mainly been performed in T cells, more work is needed to better elucidate their roles across other cell types, and their link with other mechanotransduction pathways.

Model linking mechanotransduction and immune cell function. Innate immune cells probe the tissue environment for danger signals to alert them for activation. Tissue-level mechanical stresses that occur in disease states, such as acute oedema during infection or increased stiffness with fibrosis, can activate mechanosensors in immune cells, allowing their signalling pathways to synergize with inputs from PRRs to boost immune effector functions (FIG. 3). When tension forces are reduced, homeostasis is restored and the inactivity of mechanosensors raises the threshold for danger signalling, and immune activation is subsequently reduced. Thus, we favour an integrated model by which tissue-level mechanotransduction directly tunes innate signalling pathways involved in danger sensing.

This ability to tune responses to danger signals in distinct physical environments probably evolved as an additional layer of regulation atop biochemical cues. The integrated signals promote immune activity during early immune responses, which is often dynamically associated with transient increases in tissue rigidity (for example, those seen in oedematous inflamed tissues, inside proliferating lymph nodes or following cell trafficking from

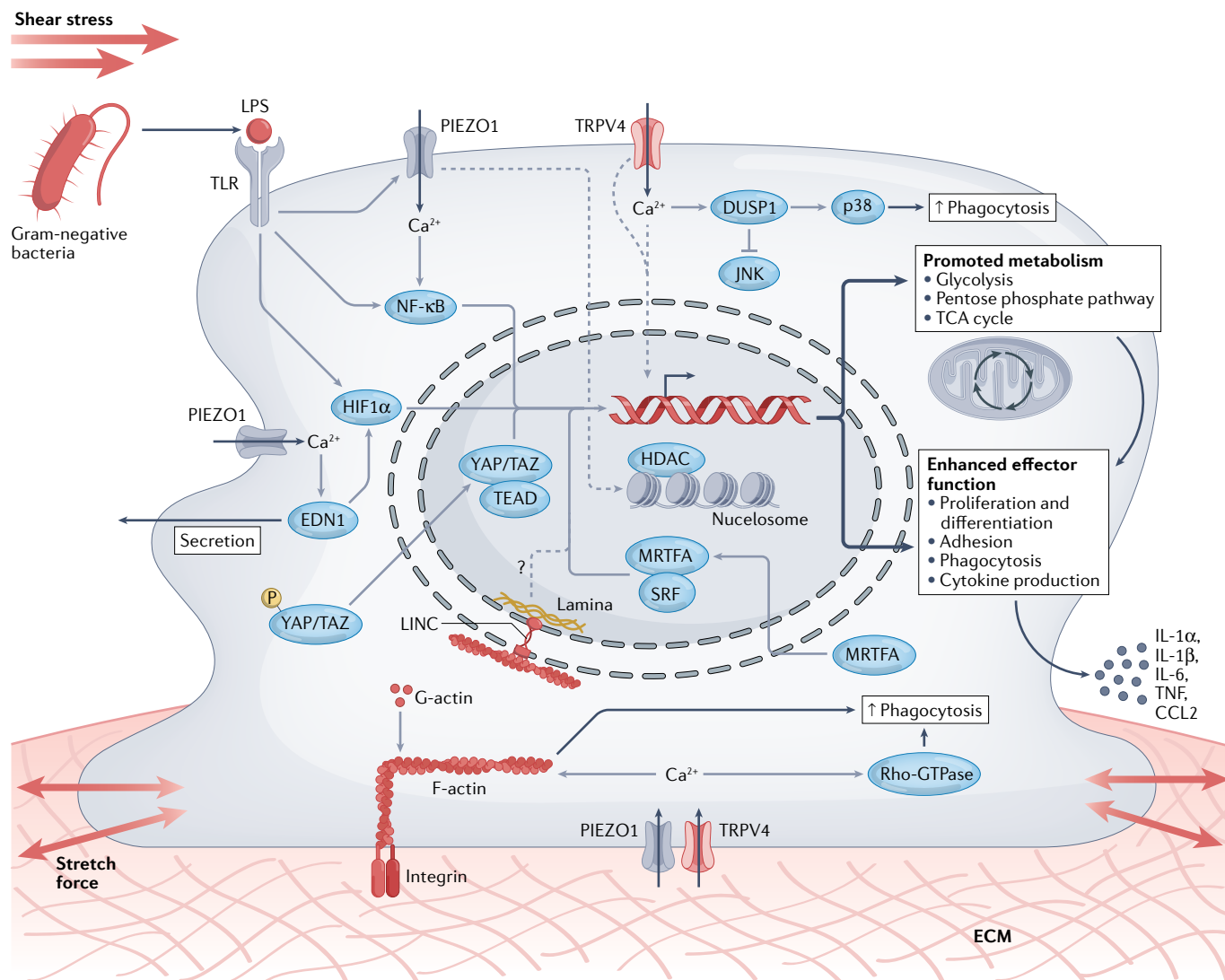
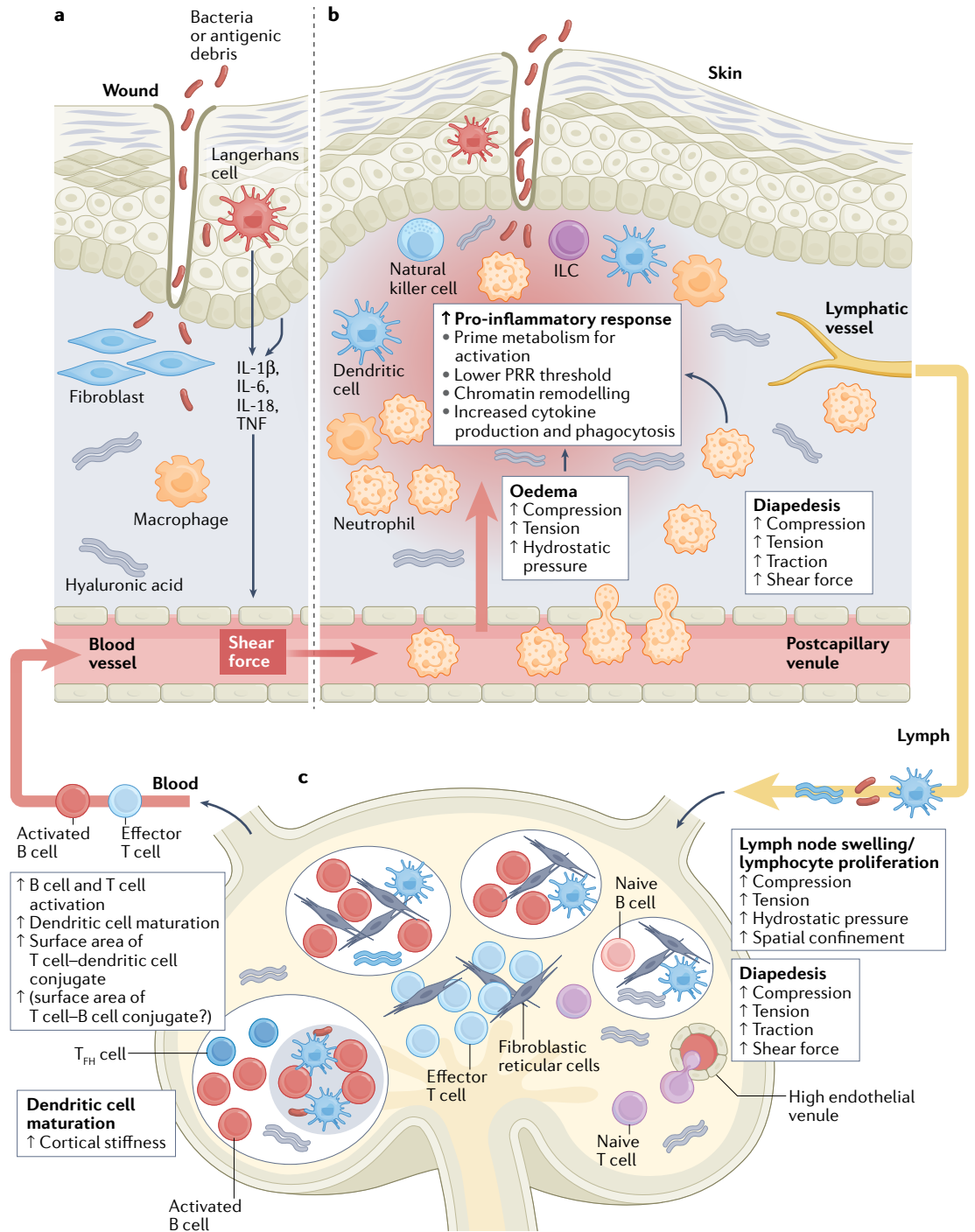


Fig. 3 | Integration of mechanotransduction pathways and innate immune cell activation. Pattern recognition receptor (PRR) stimulation accompanied by mechanical force causes PIEZO1 co-localization with some Toll-like receptors (TLRs). Force-triggered opening of transient receptor potential vanilloid type 4 (TRPV4) and PIEZO1 leads to Ca^{2+} influx. Elevated cytosolic Ca^{2+} levels induce actin polymerization and activate Rho GTPase, boosting phagocytosis. Concurrently, F-actin formation depletes G-actin availability, and without G-actin to bind to, myocardin-related transcription factor A (MRTFA) is shuttled into the nucleus where it forms a complex with serum response factor (SRF). MRTFA–SRF enables transcription of immune effector genes, such as those encoding interleukin-6 (IL-6) and CXC-chemokine ligand 9 (CXCL9), generally skewing the cell towards an enhanced inflammatory phenotype. Ca^{2+} also enforces TLR signalling by promoting the expression and activation of endothelin 1 (EDN1) and NF- κ B. EDN1 stabilizes hypoxia-inducible factor 1 α (HIF1 α), promoting TLR-induced HIF1 α accumulation. Active NF- κ B and HIF1 α translocate to the nucleus and drive metabolic and inflammatory gene expression. Additionally, TRPV4-dependent Ca^{2+} influx prompts

dual-specificity phosphatase 1 (DUSP1) to activate p38 and inhibit JNK activity, further enhancing phagocytosis. The mechanosensitive molecules yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) also translocate to the nucleus upon activation, bind TEA domains (TEADs) and induce transcription of genes that boost glycolysis, the pentose phosphate pathway and the tricarboxylic acid (TCA) cycle. This immunometabolic regulation through multiple mechanosensitive inputs mediates robust cell proliferation and increases the production of inflammatory cytokines, such as IL-1 α , IL-1 β , IL-6 and CC-chemokine ligand 2 (CCL2). PIEZO1 also activates histone deacetylases (HDACs) to further induce inflammatory cytokine output. Dashed lines represent pathways where there are still major gaps in understanding the transduction mechanisms, and solid lines depict more well-described pathways. Linker of nucleoskeleton and cytoskeleton (LINC) complex modulation of immune activation has been shown in adaptive cells only, but we hypothesize it also plays a role in innate immune cell regulation. ECM, extracellular matrix; LPS, lipopolysaccharide; TNF, tumour necrosis factor.

the blood into crowded or stiffer tissue spaces). These signals also reinforce resolution of immune responses and quiescence when stiffness is reduced by homeostatic mechanisms such as degradation of accumulated glycosaminoglycans (GAGs) and apoptosis of crowded cellular environments⁶⁵. According to this model, the threshold for immune cell activation would be high

when cells encounter danger signals within a mechanically soft environment. Such a mechanism might serve to reduce autoimmunity and inadvertent immunopathology in precious, irreplaceable tissues such as the brain. Likewise, according to this model, fibrotic and ageing tissues that become mechanically stiffer over time may be more likely to promote inflammation and



autoimmunity. Supporting this viewpoint, older patients and patients with interstitial lung diseases or restrictive lung physiology have worse outcomes after respiratory viral infections including influenza and COVID-19 (REFS. 133–135). However, whether a threshold ultimately exists during chronic disease or ageing when immune cells become unresponsive, exhausted or potentially show resolving phenotypes by long-standing continuous exposure to biophysical cues and/or environmental forces remains to be seen. Similarly, it will also be important to better understand potential inflammatory implications of insufficient mechanotransduction in immune cells.

Although we have focused on direct mechanotransduction in immune cells, it is important to note that mechanosensing pathways can impact immunity indirectly through mesenchymal cells, such as fibroblasts, stromal cells and endothelial cells. These cells express a similar constellation of mechanosensing pathways, often to a greater extent than in immune cells. Indeed, stromal cells such as fibroblasts sense ECM mechanics and, consequently, recruit immune cells such as macrophages^{136,137}. In both mouse and human endothelial cells, the activity of YAP and TAZ is suppressed by unidirectional blood flow with low shear stress⁹. YAP and TAZ inhibition dampens pro-inflammatory gene

◀ Fig. 4 | **Mechanical forces modulate acute immune responses.** **a** | Danger signals in the skin (such as those arising from bacteria or tissue damage) activate Langerhans cells and stromal cells to produce inflammatory cytokines and/or hyaluronic acid to promote oedema and attract immune cells to the infection site. **b** | Within minutes to hours, diapedesis of cells from the vasculature into inflamed tissues occurs. This requires force-sensing at the molecular level (shear force-dependent catch bonds) and at the cellular level (cells squeezing through endothelium and extracellular matrix (ECM)). Forces exerted by diapedesis prime circulating immune cells to acquire an enhanced pro-inflammatory phenotype. Simultaneously, local oedema occurs. Mechanosensation of oedema further drives a pro-inflammatory phenotype in tissue-resident cells that encounter pathogens. **c** | Eventually, antigenic debris, hyaluronic acids and activated dendritic cells traffic to the lymph node. There, fibroblastic reticular cells sense activated dendritic cells and change their shape to allow for imminent increases in lymph node size. Migrating T cells and B cells encounter mechanical forces as they squeeze through high endothelial venules and into interfollicular and follicular spaces. After activation, T cells and B cells proliferate in the lymph node, causing lymph node swelling and stiffening, which propagates mechanical forces onto cells. T cells crawling through a stiff lymph node increase the contact area for T cell–antigen-presenting cell (APC) conjugates, which may also impact T follicular helper (T_{FH}) cell interactions with germinal centre B cells. Activated T cells and B cells eventually migrate to the infection site via the blood, continuing to experience multiple mechanical stimuli at the inflamed tissue. Resolution of the infection leads to breakdown of hyaluronic acid, decreasing oedema and leading to the refractoriness of immune cells to danger signals. The resulting diminishment of inflammatory cytokines reduces immune cell trafficking and promotes their apoptosis through cytokine withdrawal-induced cell death and other mechanisms. Under the influence of ageing and other factors, tissue may not return to a ‘healthy’ baseline and might, instead, adopt remodelling changes including collagen deposition (scarring) and elastin degradation, leaving a lasting mechanical imprint at the inflammatory response site. ILC, innate lymphoid cell; IL, interleukin; PRR, pattern recognition receptor; TNF, tumour necrosis factor.

expression, and decreases the local infiltration of monocytes. Similarly, TRPV4 governs stretching-induced inflammation and expression of pro-inflammatory factors, including IL-6, IL-8, cyclooxygenase 2 (COX2), matrix metalloproteinase 1 (MMP1) and MMP3, which contributes to tissue degradation in human annulus fibrosus cells¹³⁸. Given the critical crosstalk that occurs between the stroma and the immune system, a better understanding of how mechanical inputs link these two cellular compartments represents an important avenue for future research. This topic will be especially important in understanding acute and chronic integrated disease processes, such as responses to tissue injury, bacterial infections, inflammatory diseases and fibrosis.

Mechanoimmunology in health and disease

The acute and chronic rigidification of tissue following inflammatory stimuli has long been recognized¹³⁹, but the physiological or pathophysiological roles of tissue mechanics in regulating immune responses have not been appreciated until recently. Here, we discuss how mechanical signals associated with altered tissue mechanics shape immunity within physiological and pathophysiological tissue environments. Unfortunately, we lack many comprehensive, in vivo studies of the impacts of mechanosensing by immune cells in pathophysiological states. Although in vitro studies have yielded important, reductionistic insights into the responses of immune cells to biophysical cues, these studies often fail to fully recapitulate integrative cell–cell responses, as well as true three-dimensional viscoelastic properties of tissues. Therefore, we offer here a perspective synthesizing the best available in vitro and in vivo studies to date.

Acute pathogen challenge. During an acute infection, early activation of PRRs induces stromal cells to produce copious amounts of hyaluronic acid, and the resulting oedema and inflammation drive extensive changes in tissue mechanics¹⁴⁰. Surveillance of affected tissues is increased by neutrophils, which are recruited from the blood to the site of oedema. In the blood, circulating neutrophils must endure shear stresses to create and maintain a catch bond with the endothelium. The tethering catch bond is mediated by selectin and glycosylated ligand interactions, initially P-selectin and P-selectin glycoprotein ligand 1 (PSGL1)¹⁴¹. Only with adequate shear stresses from blood flow do high-affinity catch bonds form and neutrophils extravasate. Upon successful diapedesis, the neutrophil continues to experience forces, including compression, traction and tension, as its plasma membrane deforms to allow for extravasation into the tissue. Migration of neutrophils through dense tissue drives mechanical changes upon the nucleus, and the resulting chromatin changes promote inflammatory transcripts¹⁴². These rapidly recruited innate immune cells migrate into dense tissues, probing the tissue ahead of them by means of a nuclear-mechanical gauge¹⁴³. They produce cytokines, inflammatory lipids and exosomes to increase blood flow, induce capillary leakage and augment pain sensation.

At the site of infection, tissue swelling applies mechanical forces, such as tensile stress and hydrostatic pressure, onto resident innate immune cells. Data from in vitro studies suggest that such forces are important in priming innate immune cell metabolism to ready these cells for the bioenergetic demands of activation, as well as in providing the cells with a mechano-dependent co-stimulatory signal that can reduce the signalling threshold necessary for optimal TLR stimulation^{48,51,53,144}. Thus, pathogen-mediated triggering of PRRs elicits an acute effector response with a level of magnitude that is tuned by signals from the physical environment. Many minor, local bacterial infections are cleared by the resulting deluge of innate effectors.

Over hours, antigenic debris and hyaluronic acids are trafficked to the draining lymph node where they coat APCs¹⁴⁰, which increases their ability to interact with T cells¹⁴⁵. As circulating T cells and B cells enter a lymph node through high endothelial venules, they also experience shear forces upon catch-bond formation, and extravasation induces forces onto these lymphocytes similar to those encountered by neutrophils entering sites of infection. T cells within a secondary lymphoid organ can be subsequently activated by an APC, such as a dendritic cell, a process that is also influenced by mechanical forces. During migration to the secondary lymphoid organ, activated dendritic cells go through a maturation process that improves their ability to stimulate T cells. Stromal cells in the lymph node, especially fibroblastic reticular cells, undergo mechanical changes upon interacting with activated dendritic cells, further driving changes in lymph node mechanics during acute infections¹⁴⁶.

Activation of T cells and B cells within encapsulated spaces, that is, lymph nodes, leads to robust proliferation and crowding, driving further deviation from ‘normal’ tissue mechanics. Lymph node tissue mechanics

Annulus fibrosus

A ring of fibrous tissue, such as that surrounding an intervertebral disc or heart valve.

affects T cell activation. In particular, *in vivo* mouse models have shown that at the height of an infection with lymphocytic choriomeningitis virus the lymph node reaches 40 kPa, and decreases to 4 kPa when the infection resolves⁶⁵. When T cells crawl through matrices of 40 kPa stiffness, they show increased activation regardless of the stiffness of the APC owing to increased contact area of the T cell–APC conjugate⁶⁶. This mechanosensing by T cells involves YAP. T cells also bind to hyaluronic acids through CD44, a mechanosensitive receptor that is important for T cell extravasation, although future studies are needed to determine whether this interaction promotes T cell suppression or activation in the context of mechanics. Late remodelling of the lymph node architecture may occur in the days to weeks following acute inflammation¹⁴⁶, which can have profound effects on tissue stiffness, such as in fibrosis or scarring, due to enhanced deposition of collagen and remodelling of the ECM. The integrative processing of mechanical signals into immune responses to infection is shown in FIG. 4.

Wound healing and fibrosis. Immune cells play an important role in wound healing, and recent studies suggest mechanosensing may drive immune cell-dependent responses involved in aberrant healing, such as scarring and fibrosis¹⁴⁷. There are four stages in wound healing: haemostasis, inflammation, proliferation and remodelling. During haemostasis in the skin, tissue-resident cells such as fibroblasts, myofibroblasts and macrophages endure tensile forces, which are generated by the skin's resistance to breaking. If an injury breaks the skin, the haemostatic phase transitions into the inflammatory phase, and fibroblasts, macrophages and neutrophils will travel to the site of the wound where they recognize tissue damage and create a pro-inflammatory environment. There is a subsequent generation of vascularized ECM, known as granulation tissue, through which epithelial cells migrate to close the wound. Fibroblasts then differentiate into myofibroblasts, which synthesize collagen and ECM components including hyaluronic acid to generate a scar¹⁴⁸. Higher mechanical tension in the healing wound can clinically worsen the healing response and lead to hyperplastic scars¹⁴⁹. There is speculation that some of this mechanism is mediated through tension-induced FAK activity in fibroblasts¹⁵⁰. These tension-primed fibroblasts release high levels of CCL2 to recruit immune cells (that is, CCR2⁺ inflammatory macrophages), which ultimately help orchestrate inflammation and potentiate scar formation¹⁴⁹. Using a high-tension scar model, global CCL2-knockout mice showed a 70% reduction in scar formation at 10 days post injury. This study demonstrates a direct link between mechanotransduction, recruitment of macrophages and aberrant wound responses¹⁴⁹. Moreover, another study using a similar high-tension model of scarring showed that treatment of skin wounds with verteporfin, an inhibitor of YAP and TAZ, prevented an engrailed 1-expressing subset of fibroblasts from generating a fibrotic response¹⁵¹. Further insight into the roles of mechanosensing in scar formation is needed, particularly to assess the direct impacts of different

mechanosensing pathways in immune cells during wound healing.

Cancer. One of the hallmarks of the solid tumour microenvironment is that it is often stiffer than healthy tissue, which typically results from abnormal physical properties of the ECM. Numerous works have demonstrated the co-progression of tumorigenesis and mechanical stiffness^{152,153}. The stiffness of the ECM can forestall immune responses by acting as a physical barrier that blocks motility. The collagen-rich ECM around tumours includes features such as alignment of fibres in the perivascular regions and around nests of tumour epithelial cells. This ECM has been shown to alter the migration of T cells and restrict them away from tumour cell nests¹⁵⁴. Furthermore, breast cancer tissue samples that show a high collagen density in the ECM surrounding the tumour have fewer infiltrating T cells¹⁵⁵. Beyond this stiff barrier of solid tumours, the tumour cells themselves are often mechanically softer and more heterogeneous than neighbouring healthy cells¹⁰. As tumours hit a mechanical barrier owing to the constraint offered by nearby tissues, they undergo a change from a proliferative phenotype to a metastatic phenotype. The resulting metastatic cells are alternatively said to be mechanically stiff because they crawl on basement membranes¹²⁹ or mechanically soft because they have to crawl through small pores created by their own ECM 'fence'¹⁵⁶. How tumour-infiltrating immune cells respond to the heterogeneous mechanical environment of tumours has barely been studied. However, tumour killing by cytotoxic T cells was shown to be potentiated when the tumour cells are mechanically rigid because stretched tumour membranes are more susceptible to T cell-delivered perforin¹⁵⁷. The impact of this differential capability to kill tumour cells may promote the survival of tumour cells that are able to repopulate the tumour⁶⁴. Much more work is needed to study whether therapeutic alterations of the ECM could impact tumour stiffness and the associated immune response to improve clinical outcomes. For example, collagenases, lysyl-oxidase inhibitors (which block the cross-linking of collagen) or hyaluronidases could be employed to modify the tumour ECM.

Conclusions and outlook

Mechanical changes in tissues occur with the natural process of ageing and in disease states such as infection, tissue injury and cancer. These mechanical changes influence immune cells, tuning their effector functions, with the potential to promote both adaptive and maladaptive responses. The alterations in ECM that underlie tissue changes and the mechanotransducing pathways that sense tissue mechanics offer therapeutic targets for diseases such as fibrosis and cancer. Regardless of the advances presented in this Review, the field of mechanoimmunology is still in its infancy; improved means to measure tissue mechanics *in vivo* are needed. Consistently, we lack *in vivo* models that specifically test the impact of mechanical forces on immune cells in various pathophysiological states. Thus, many findings inferred from *in vitro* testing may need to be revised as the field matures. Furthermore,

measurements of tissue mechanics, as well as constructive interpretation of the findings, have hardly made their way into clinical practice, and thus offer ripe potential for exploiting MRI, ultrasound and other modalities to probe mechanics and guide therapeutic algorithms^{158,159}. Further study into the regulation of immune responses by

tissue mechanics will no doubt provide new insights with direct applications into boosting or resolving inflammation, treating autoimmunity and promoting regenerative healing after tissue injury or infection.

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Author contributions

All authors contributed to the design and writing of the manuscript and the generation of the figures.

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