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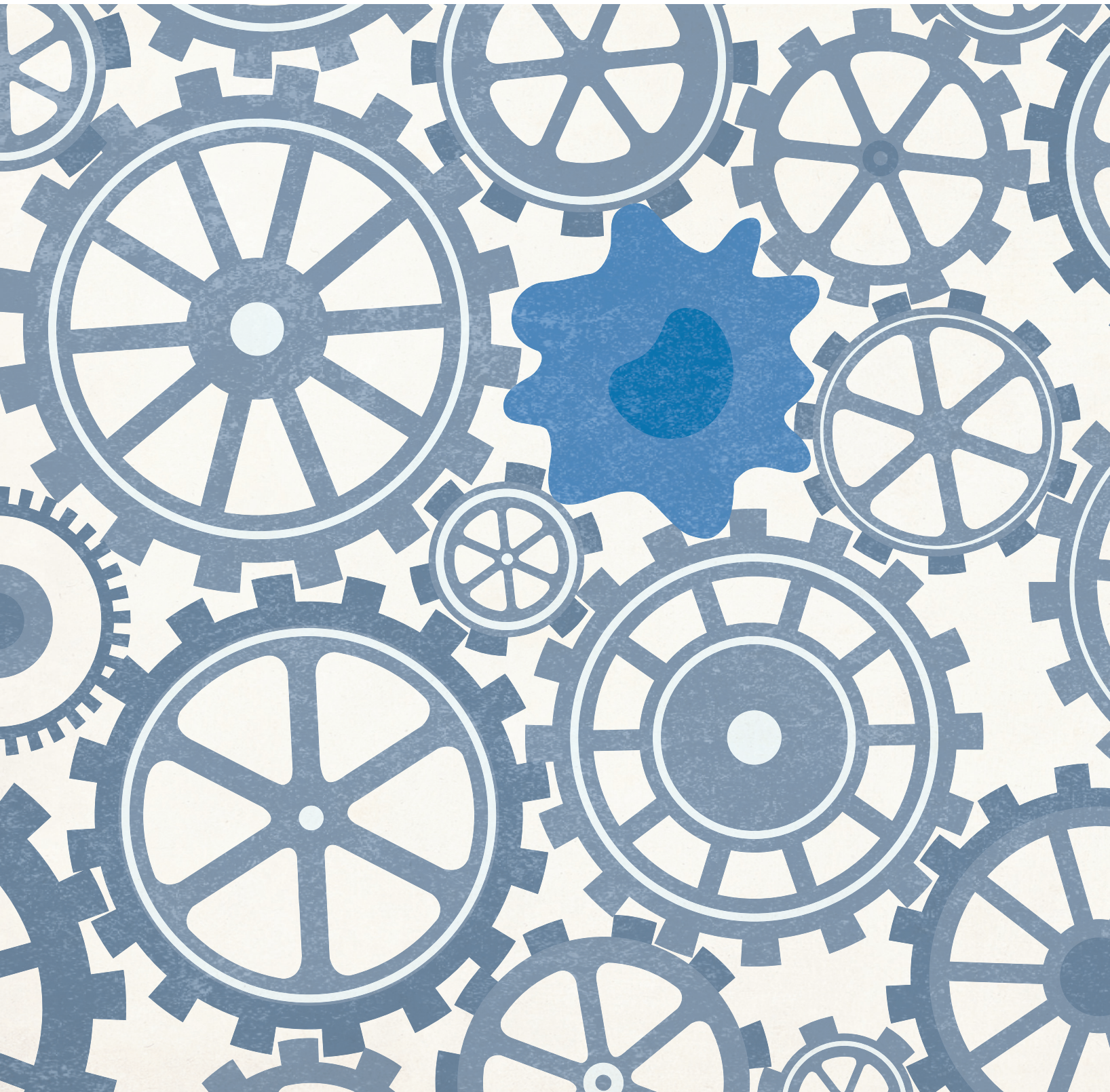

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Review article

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Mechanomedicine

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Abstract

Mechanical forces act throughout the body across multiple scales, from organs and tissues to cells and molecules, playing a vital role in maintaining tissue integrity, regulating cellular functions and supporting physiological performance. Importantly, alterations in mechanical forces and properties can be hallmarks of tissue injury and disease, and can thus serve as valuable biomarkers for disease monitoring and diagnostics and can be harnessed to modulate biological processes for therapeutic benefit. This concept, termed mechanomedicine, offers an important strategy in disease diagnosis and therapy. In this Review, we first introduce biomechanics and mechanobiology as the underlying principles of mechanomedicine and outline the properties and measurements of key mechanical signatures in health and disease. We then explore the application of mechanomedicine across scales, from organ-level and tissue-level diagnostics to cellular and molecular mechanotherapeutics, including strategies for tissue regeneration and rehabilitation. Finally, we highlight challenges and opportunities in the clinical translation of mechanomedicine approaches, in particular with regards to the innovation of materials and devices, the manufacturing of cells and organoids, the definition and standardization of mechanical biomarkers, and the integration of artificial intelligence.

Sections

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Key points

- Mechanomedicine applies principles of mechanobiology to understand, diagnose and treat diseases.
- A multiscale perspective, from organs and tissues to cells and molecules, reveals how mechanical forces and mechanical properties of materials regulate health and disease across biological hierarchies.
- Mechanical biomarkers decoded by biosensors and bioelectronics enable sensitive, real-time monitoring and early disease detection.
- Mechanically tunable biomaterials and mechano-immunoengineering can be applied for tissue regeneration and cancer therapy.

Introduction

Mechanical factors regulate key biological functions in the body and thus play an important role in disease diagnosis, monitoring and treatment. Biomechanics applies principles of engineering to investigate the structure, movement, mechanical properties and forces within organisms, whereas mechanobiology explores how mechanical cues influence biological processes, both spanning multiple scales[1–4] (Box 1). The field of mechanomedicine builds on these two concepts. Biomechanics contributes to mechanomedicine not only through diagnostic and monitoring technologies but also by facilitating the design of implants and exoskeletons, and mechanobiology primarily informs the development of targeted therapies. By integrating engineering principles with medical science, mechanomedicine, spanning scales from tissues to molecules, aims to translate mechanical insights into diagnostic tools and therapeutic strategies. Although many approaches in this field remain at the preclinical stage, a growing number of applications have demonstrated promising clinical outcomes.

Mechanomedicine can be applied to detect mechanical changes in tissues and cells for early disease detection, non-invasive and point-of-care diagnostics, and personalized, predictive health monitoring. In particular, wearable and implantable flexible electronics enable real-time monitoring of biomechanical changes in tissues such as stiffness variations in tumours[5] or alterations in blood flow[6]. Moreover, mechano-responsive materials can be integrated into biosensors to enable the sensitive detection of mechanical changes. In addition, therapeutic agents can be designed to exploit mechanical cues in a concept called mechanoceuticals. At the tissue level, mechanical stimulation techniques, such as ultrasound therapy, can be applied to promote bone, cartilage and skin healing[7]. At the cellular level, mechanically tuned microenvironments can direct cell fate and activation[8–10], which can be exploited for stem cell differentiation, cell reprogramming and immunotherapies. At the molecular level, mechanically tunable biomaterials, such as hydrogels and mechanosensitive nanomaterials[11], allow precise control of drug delivery, cell functions and regenerative tissue formation. In combination with computational tools providing quantitative insights, patient-specific responses can be predicted to optimize mechanomedicine regimens.

In this Review, we discuss key advances in biomechanics-inspired and mechanobiology-inspired strategies for disease diagnosis, monitoring and therapy, offering a holistic overview of the current landscape and future directions in mechanomedicine. We also propose a unified framework that captures the multiscale evolution of mechanomedicine, from classical biomechanics to modern therapeutic strategies.

Mechanical signatures in health and diseases

The functions of most tissues and organs are tightly linked to mechanical processes. The mechanical properties of tissues are essential for maintaining structural integrity and functional performance, and mechanical forces play a key role in blood circulation, bones and muscles as well as within cells and on cell surfaces. Importantly, mechanical forces change during growth, healing, ageing and pathological processes.

Forces, mechanical properties and their measurements

Mechanical forces and mechanical properties. Mechanical forces operate at multiple scales, affecting cellular behaviour and tissue homeostasis (Fig. 1). At the organ and tissue levels, mechanical forces, such as shear stress, compression and tension, play essential roles in morphogenesis, transport, vascular homeostasis, bone growth, wound repair and muscle function[12–14]. In addition, the mechanical properties of tissues enable physiological functions; for example, arteries require elasticity to sustain and buffer pulsatile flow, and bone demands high stiffness and toughness to support load.

At the cellular scale, cells generate traction forces through actomyosin contraction acting on focal adhesion complexes that connect the cytoskeletal networks to extracellular anchor points. This allows cells to sense mechanical properties of their environment and to reorganize and navigate through the extracellular matrix (ECM)[15]. Mechanical interactions between immune cells and target cells also play an important role in the activation of immune cells[10]. Furthermore, membrane tension and osmotic pressure contribute to cellular mechanoregulation by influencing membrane deformation, volume homeostasis and fluid balance, thereby affecting cell structure and chromatin organization[16].

At the molecular level, hydrogen bonds, ionic bonds and covalent bonds regulate molecular structure, their thermydynamic stability and affinity with binding partners. Molecular phase separation processes, such as the formation of lipid membranes, protein complexes and protein–ligand interactions, are driven by molecular shape complementarities coupled with spatially matched hydrophobic and hydrophilic interaction patches[17]. Mechanical forces acting on proteins can actively switch protein functions through mechanical unfolding, driving downstream mechanotransduction events in cells[18,19]. Similarly, the bending stiffness and torsional rigidity of DNA regulate transcription factor binding and polymerase activity.

Molecular assembly and mechanical interactions also determine the mechanical properties of the ECM, which are not only essential for maintaining structural integrity and tissue functions, but also for the regulation of cellular behaviour and tissue remodelling. For example, the mechanical properties of tissues substantially change during the development of diseases such as cancer, atherosclerosis and fibrosis[20–23]. Changes in ECM stiffness, viscoelasticity or ECM fibre tension can also influence cell contractility, motility and matrix deposition, thereby establishing a mechanobiological feedback loop that shapes tissue architecture[9,24,25].

Accordingly, alterations in the mechanical properties of tissues and cells can serve as valuable biomarkers. Importantly, accurately measuring these forces and mechanical properties and understanding how they influence tissue remodelling, cellular functions and molecular interactions are crucial in disease diagnosis and the identification of therapeutic targets.

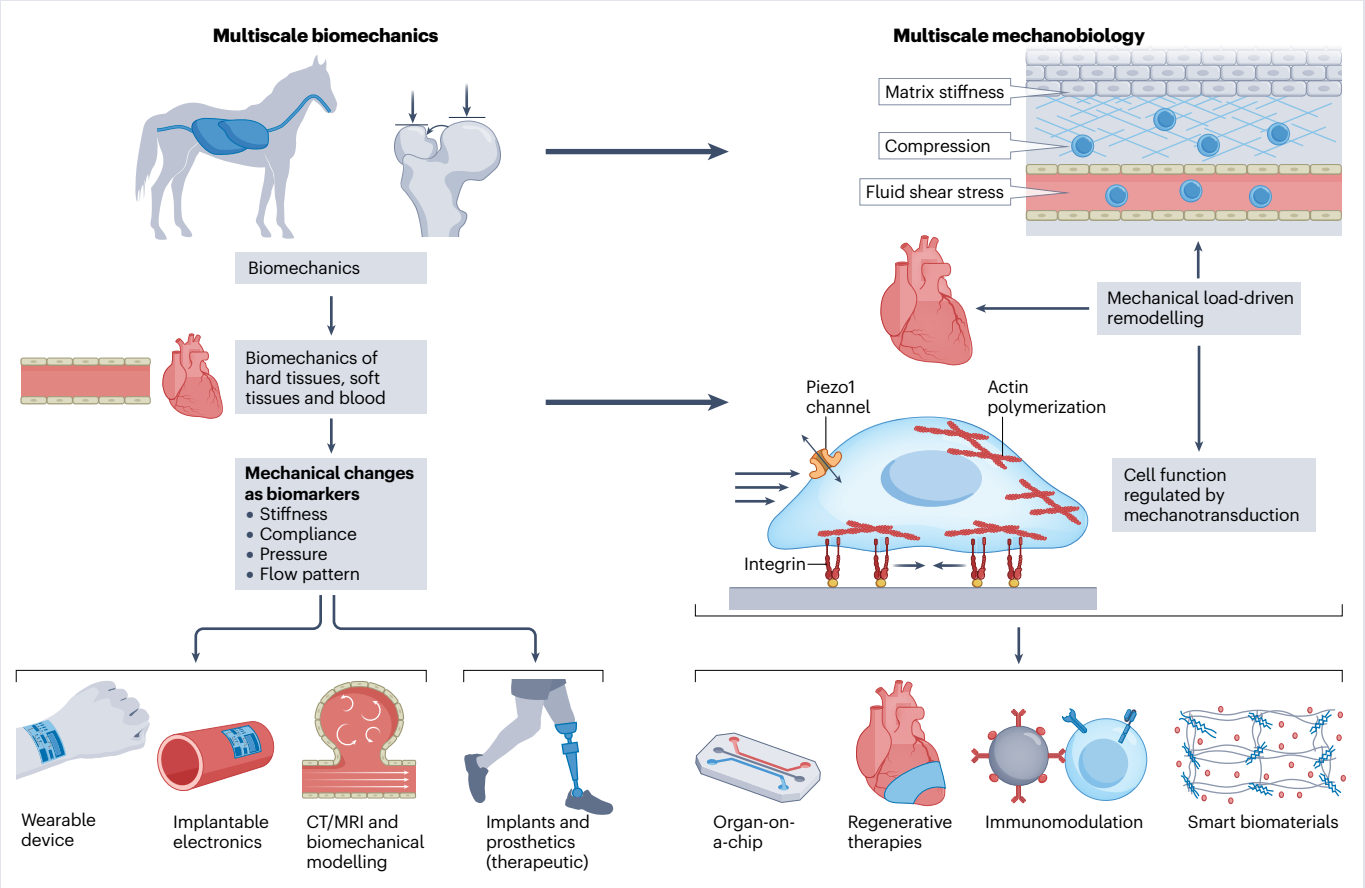
Box 1 | A short history and conceptual framework of mechanomedicine

Mechanical forces have long been studied in biological systems. In the seventeenth century, Borelli applied mechanical principles to study animal movement. In the nineteenth century, German anatomist and surgeon Wolff observed that the internal architecture of trabecular bone adapts to mechanical loading. From the 1960s, Fung and other pioneers laid the groundwork for modern biomechanics of hard tissues, soft tissues and blood[1]. Starting in the 1980s, cellular forces were measured by micropipettes[36], and forces generated by single motor proteins were probed by optical tweezers[311]. Alongside multiscale experimental approaches for measuring biological forces, computational modelling has become a powerful tool in biomechanics[151,312], including in the prediction of tissue-level forces, deformations, flow patterns and remodelling as well as alterations in protein structure–function relationships of mechanically stabilized structural intermediates[134]. Building on the foundation of biomechanics, diagnosis and monitoring tools have been developed by integrating microtechnology, flexible electronics, imaging, and computation for mechanomedicine applications and implants and prosthetics have been designed for orthopaedic therapy (figure).

Mechanobiology investigates how mechanical factors regulate biological processes across scales (figure). For example, blood flow-induced shear stress can increase prostacyclin production, activate ion channels and trigger integrin signalling in vascular endothelial cells[313–315]. In the 1980s, cells were recognized to form tensegrity structures to adjust and maintain cell shape[316], followed by the finding that cell shape regulates gene expression through mechanosensing by adhesion complexes. These studies were possible owing to the use of microfabricated adhesive islands[317] as well as microtopography and nanotopography[318].

In addition to dynamic forces, mechanical properties, such as the elasticity and viscoelasticity of the extracellular matrix, regulate cell differentiation processes[223,227] as well as the nuclear translocation of transcription factors such as YAP–TAZ[319]. In the extracellular matrix, cell-generated forces can stretch protein fibres, such as collagen and fibronectin fibres, switching their structure–function relationship[18] and thus their biochemical activity[62].

At the molecular level, fibronectin[320] and integrins were among the first proteins identified as mechano-chemical transducers that mediate outside-in and inside-out signalling through focal adhesions coupled to the cytoskeleton[15,321–323], together with other mechanotransducers such as the ion channel Piezo1 (ref. 324). Moreover, integrins exhibit catch bonds and molecular clutch behaviour at cell adhesions[325,326].



MRI, magnetic resonance imaging.

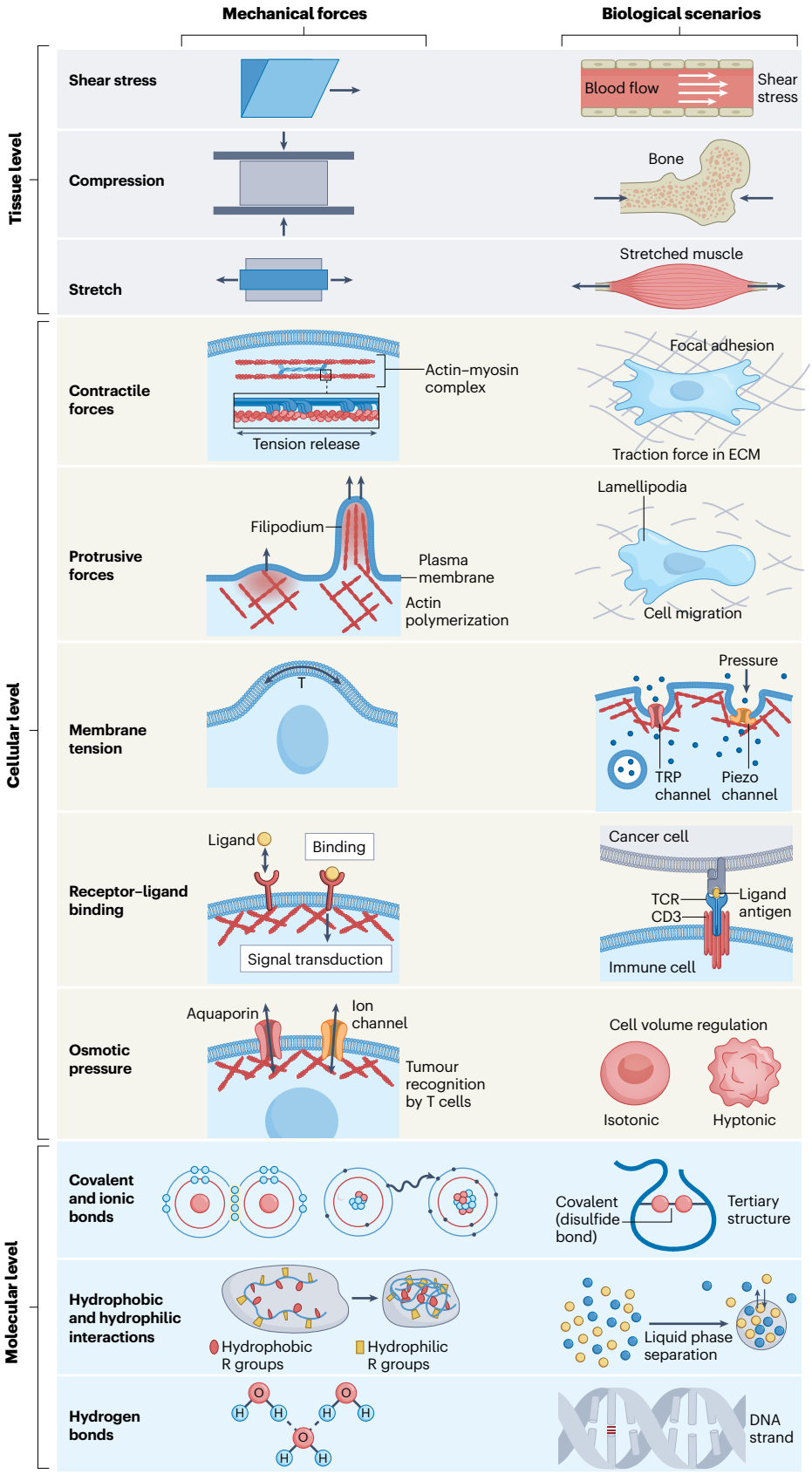


Fig. 1 | Mechanical forces across scales. At the tissue level: shear stress owing to blood flow influences vascular endothelial cells; compression plays a role in bone remodelling; muscle and tendon tissues are subject to stretching. At the cellular level: traction force occurs owing to actomyosin contraction; protrusive forces are generated through actin polymerization enabling cell migration; membrane tension regulates ion channel activity; receptor–ligand binding is crucial for immune recognition and signal transduction, exemplified by the interaction of T cell receptors (TCRs) with tumour antigens; osmotic pressure regulates cell volume in part by aquaporins. At the molecular level: covalent and ionic bonds within proteins influence protein secondary, tertiary and quaternary structures; hydrophobic and hydrophilic interactions are important in compartmentalization and phase separation; hydrogen bonds are key to the structural integrity of all biomolecules. TRP, transient receptor potential.

Measuring mechanical forces and mechanical properties. Mechanical forces and mechanical properties can be measured using a range of technologies (Fig. 2). At the tissue scale, elastography-based techniques and haemodynamic measurements, such as magnetic resonance elastography and Doppler ultrasound, can be applied to measure macroscopic parameters such as stiffness[26] and blood

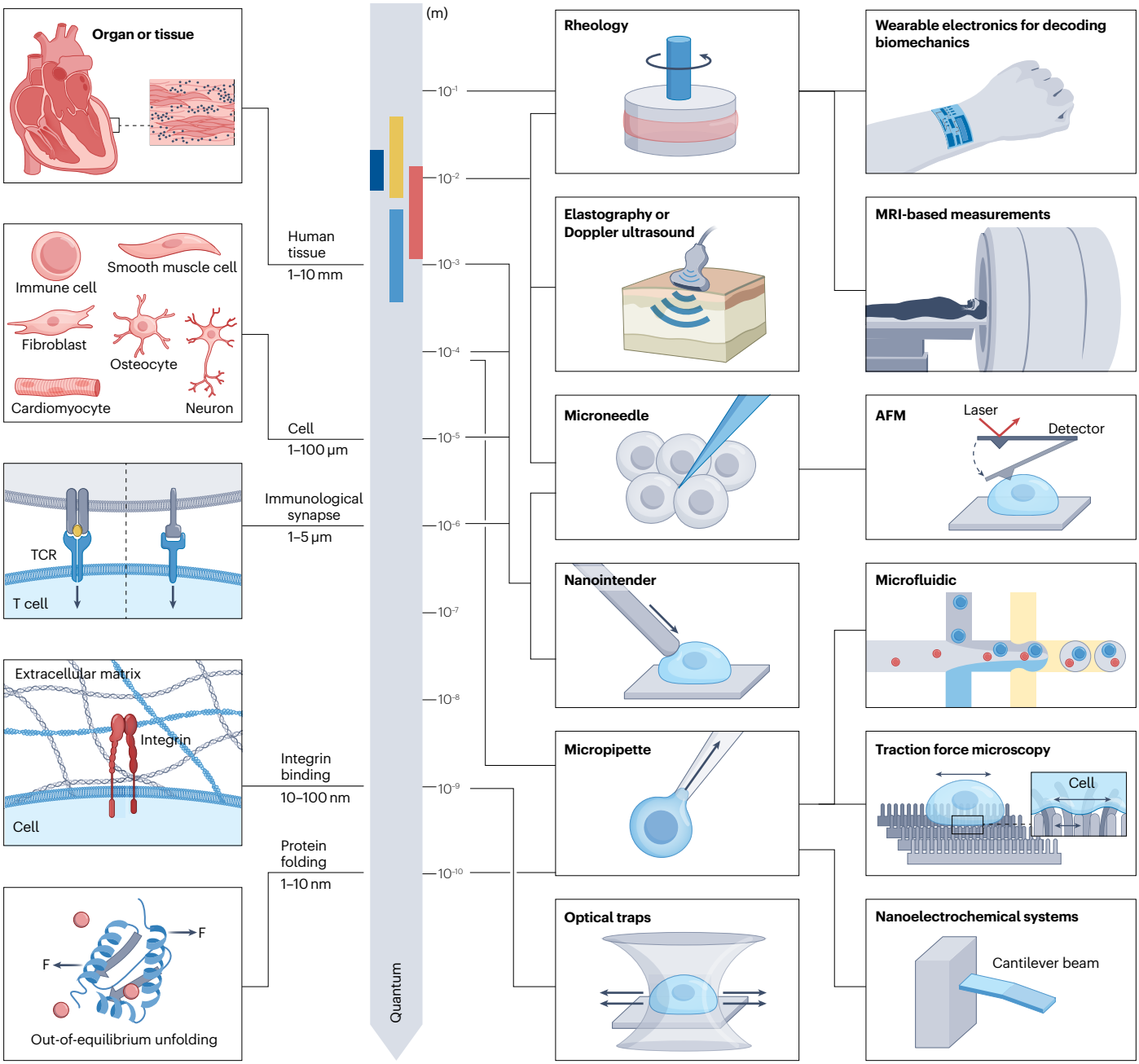


Fig. 2 | Hierarchical and multiscale measurement of mechanical properties. At the tissue scale, rheological testing and elastography methods (for example, Doppler ultrasound, magnetic resonance imaging (MRI)-based techniques) are commonly used to assess stiffness and shear modulus in vivo, with diagnostic relevance in cancer, fibrosis and cardiovascular diseases. Wearable strain sensors and flexible electronics enable real-time monitoring of muscle and joint mechanics, especially in rehabilitation and chronic disease management. Respiratory mechanics can be monitored for non-invasive assessments of airway resistance. At the cellular level, tools such as micropipettes, microfluidics, optical traps and traction force microscopy can be applied to quantify cellular deformability, traction and adhesion, which are crucial parameters in stem cell differentiation, immune activation and cancer cell invasiveness. At the molecular scale, atomic force microscopy (AFM), nanoindentation, and optical and magnetic tweezers can probe force (F)-dependent receptor activation, protein unfolding and ligand–receptor binding strength with piconewton precision. TCR, T cell receptor.

flow rate[27,28]. These parameters can serve as non-invasive biomarkers in cancer[29], fibrosis[30] and cardiovascular disease[31] monitoring. Wearable strain sensors and respiratory mechanics platforms can monitor joint function and airway resistance in real time, supporting clinical decision-making and rehabilitation feedback[32,33]. Similarly, techniques to monitor respiratory mechanics, such as forced oscillation testing, enable non-invasive assessment of airway resistance by analysing flow dynamics during breathing cycles[34]. This approach provides insights into pulmonary diseases and their underlying pathophysiology.

At the tissue and cellular levels, atomic force microscopy (AFM) and nanoindentation can be applied to map mechanical properties by applying compression forces[35]. In single-cell suspensions, micropipette aspiration can assess parameters such as cell stiffness and membrane tension[36], whereas optical stretchers and microfluidics enable high-throughput analysis of cell deformability and size[37,38], which are key indicators in cancer diagnostics, stem cell potency and immune activation. The adhesion strength of cells attached to 2D surfaces can be measured by applying fluid flow, centrifugal force or AFM, providing insights into cell–ECM interactions[35,39]. At the subcellular level, traction force microscopy can quantify forces generated at focal adhesions and map cellular traction in 2D and 3D ECM environments[40,41], offering insights into cell adhesion, migration, tumour invasion and cardiac contractility.

At the molecular level, micropipettes, AFM, and optical and magnetic traps can apply or detect piconewton forces that induce stretch-mediated protein unfolding, receptor–ligand binding or immune synapse activation, enabling mechanistic understanding of molecular mechanotransduction[35,42–44]. In addition, protein-based or nucleic acid-based molecular tension sensors allow mapping of forces with high spatiotemporal resolution at the subcellular level, allowing visualization of localized mechanical signalling[45,46]. Furthermore, nanoelectromechanical systems using frequency-addressed nanomechanical resonators enable real-time label-free single-protein mass measurements for high-resolution label-free biomolecular diagnostics and quantitative biophysical measurements[47,48].

Disease-related alterations in the mechanical environment

Progressive diseases are often characterized by alterations in the mechanical properties of the ECM or local mechanical forces, affecting tissue and organ functions. These changes can serve as mechano-markers for disease monitoring and diagnosis. For example, disturbed blood flow near the branched or curved regions of arteries can cause endothelial dysfunction, lipid and cholesterol deposition, and inflammation and atherosclerotic lesions[12,49,50]. Vascular stiffening owing to calcification can impair arterial elasticity, thereby resulting in the progression of atherosclerosis, whereas weakening of the vascular wall can result in an aneurysm[21,51,52]. Accordingly, clinical decision-making depends on the mechanical analysis of the interaction between fluid dynamics and vascular structural mechanics[52]. Similarly, following vascular surgery to restore blood flow, such as angioplasty or blood vessel replacement[53], thrombus formation, neointima formation and clogging can perturbate blood flow, which can be monitored by mechanical sensors integrated into vascular devices like the stent[6].

In the musculoskeletal system, disuse (for example, prolonged immobilization or physical inactivity), ageing or microgravity can lead to bone loss and muscle atrophy[54,55]. In degenerative diseases, such as osteoarthritis, mechanical alterations in the cartilage ECM contribute to cartilage degradation because chondrocytes experience high mechanical loading owing to cartilage-specific ECM breakdown[56–58].

In neurodegenerative diseases, such as Alzheimer's disease, high brain tissue stiffness correlates with neuronal loss and amyloid-β plaque accumulation[59]. Magnetic resonance elastography imaging has demonstrated regional brain stiffness changes in individuals with early-stage Alzheimer's disease, suggesting stiffness as a biomechanical biomarker for early diagnosis[60]. Similarly, in Parkinson's disease, substantia nigra degeneration is associated with progressive changes in brain tissue viscoelasticity, affecting neuronal connectivity and motor function[61].

The ECM also stiffens in cancer and fibrosis. Tumours often have high stiffness owing to excessive ECM deposition, altered collagen crosslinking and the contractility of surrounding stromal cells[20]. In particular, fibroblasts in the tumour microenvironment exhibit a myofibroblastic phenotype characterized by high contractility, aligning the ECM microarchitecture to promote fibrillar collagen formation[62]. This structural reorganization contributes to tissue stiffening and facilitates directional migration of tumour cells, while potentially limiting immune cell infiltration[63]. Both collagen fibre deposition and the accumulation of fibronectin fibres with reduced tension increase with tumour grade[62,64]. These mechanical alterations promote tumour cell proliferation, invasion and resistance to therapy by tuning mechanotransduction pathways and downstream cell functions in animal models[63]. For example, pancreatic ductal adenocarcinoma, one of the most mechanically stiff malignancies, exhibits high interstitial pressure and ECM densification, contributing to poor drug penetration and immune evasion, as demonstrated in preclinical models and supported by correlative findings in human cancers[65]. Similarly, fibrotic diseases, including pulmonary and hepatic fibrosis, involve pathological ECM stiffening, which perpetuates fibroblast activation and excessive ECM production in a feed-forward loop that exacerbates organ dysfunction[66]. Cells thereby not only respond to physical changes in their environment but, once turned pathogenic, might suffer from alterations in their mechanosensory system, as observed for cancer versus healthy cells[67].

Although imaging-based technologies have been clinically used to measure the changes in blood flow, artery calcification or bone density, the clinical utility of changes in mechanical properties, such as tissue stiffness and ECM viscoelasticity, as reliable biomarkers remains constrained by limited specificity and individual variations. Physiological changes, such as ageing, physical activity or muscle tension, can also alter tissue mechanics and confound disease-related interpretation, which needs to be accounted for.

Mechanomedicine for diagnosis and monitoring

Mechanical properties, including stiffness, viscoelasticity, shear modulus, adhesiveness and deformability, as well as diverse biomechanical activities, such as heartbeats, respiration, muscle contraction and cellular force generation, can be quantitatively assessed for disease detection and long-term monitoring. In addition, mechanically responsive materials enable these mechanical cues to be accurately sensed and detected.

Tissue and organ level

Mechanical properties, forces and strains can be quantitatively assessed at the tissue and organ levels[68,64]. In particular, wearable and implantable devices enable patient-centric, continuous and real-time mechanical diagnosis and monitoring at the point of care[33]. Here, bioelectronic devices serve as interfaces with tissues and organs to monitor parameters such as skin stiffness[69], epicardial strain[70], respiratory flow[71],

intraocular pressure[72] and masticatory forces[73] (Fig. 3a). These bioelectronic systems can be based on passive or active mechanical transduction mechanisms. In passive sensing modalities, changes in mechanical stimuli, such as strain or stress, alter the intrinsic properties of the sensing materials (for example, resistance, voltage, capacitance, magnetic field or optical properties), which can then be detected by bioelectronic or optical systems[33]. By contrast, active sensing modalities rely on external activation to interact with tissue and assess its mechanical properties based on its deformation. For example, ultrasound elastography can be applied to evaluate tissue stiffness; here, ultrasound waves apply mechanical perturbation to the tissue, and the resulting tissue deformation or wave motion can be detected by ultrasound imaging[74]. Similarly, in optical elastography, acoustic waves or optical forces are applied in combination with optical imaging to detect light changes in tissue[75], which can be exploited in fibrotic[76], oncological[77] and ophthalmological diagnostics[78].

Skin-interfacing devices. Bioelectronic systems are particularly suitable for interfacing with skin. The mechanical properties of skin are influenced by factors such as hydration and circulatory diseases, and can thus serve as diagnostic indicators of disease[5]. For example, reductions in elasticity owing to skin conditions and oedema can be linked to disease progression[79]. Alternative to approaches based on indentation[80] and suction[81] to assess mechanical responses, mechanical actuation can be applied to skin to elicit motion and measure vibrational frequency responses[82] (Fig. 3b). This approach enables skin diagnostics using the elastic modulus by inducing deep vibrational interactions for deep tissue monitoring. In addition, a wearable ultrasonic array can perform serial[83], non-invasive elastographic measurements of tissues up to 4 cm beneath the skin with a spatial resolution of 0.5 mm (ref. 74) (Fig. 3c). This device can map the 3D distribution of the elastic modulus ex vivo and detect microstructural muscle damage before the onset of soreness and monitor dynamic muscle recovery during physiotherapy on the human body. This technology could be applied to detect and monitor biological ageing impacting skin biomechanics as well as for in situ early screening of skin cancer, which is often associated with altered tissue stiffness. In addition, it could be used to detect skin fibrosis, which is marked by thickening and expansion of the dermis. However, physiological variations, such as ageing and body fat ratio, as well as external factors, such as device-induced compression, can also influence skin stiffness. Therefore, standardized measurements and high-resolution approaches for detecting skin depth are required to identify pathological changes[69].

Shear-wave elastography has been explored for malignant lesion and liver fibrosis diagnosis, demonstrating high sensitivity, with 95% confidence in human studies, and is being evaluated as an alternative to biopsy[84]. In addition, acoustic signals naturally emitted by the human body can be leveraged for mechano-diagnostics[85,86]. For example, a wearable acousto-mechanical sensing patch integrating a flexible circuit with soft silicone packaging can monitor respiratory airflow and intestinal motility in neonates in intensive care[85] (Fig. 3d). Body-generated acoustic waves carry vital diagnostic information in conditions such as pulmonary and cardiac disorders as well as dysphagia. By analysing sound signals in both time and frequency domains, alongside motion data, these systems can support the management of cardiorespiratory instability and disease progression in clinical and non-clinical settings.

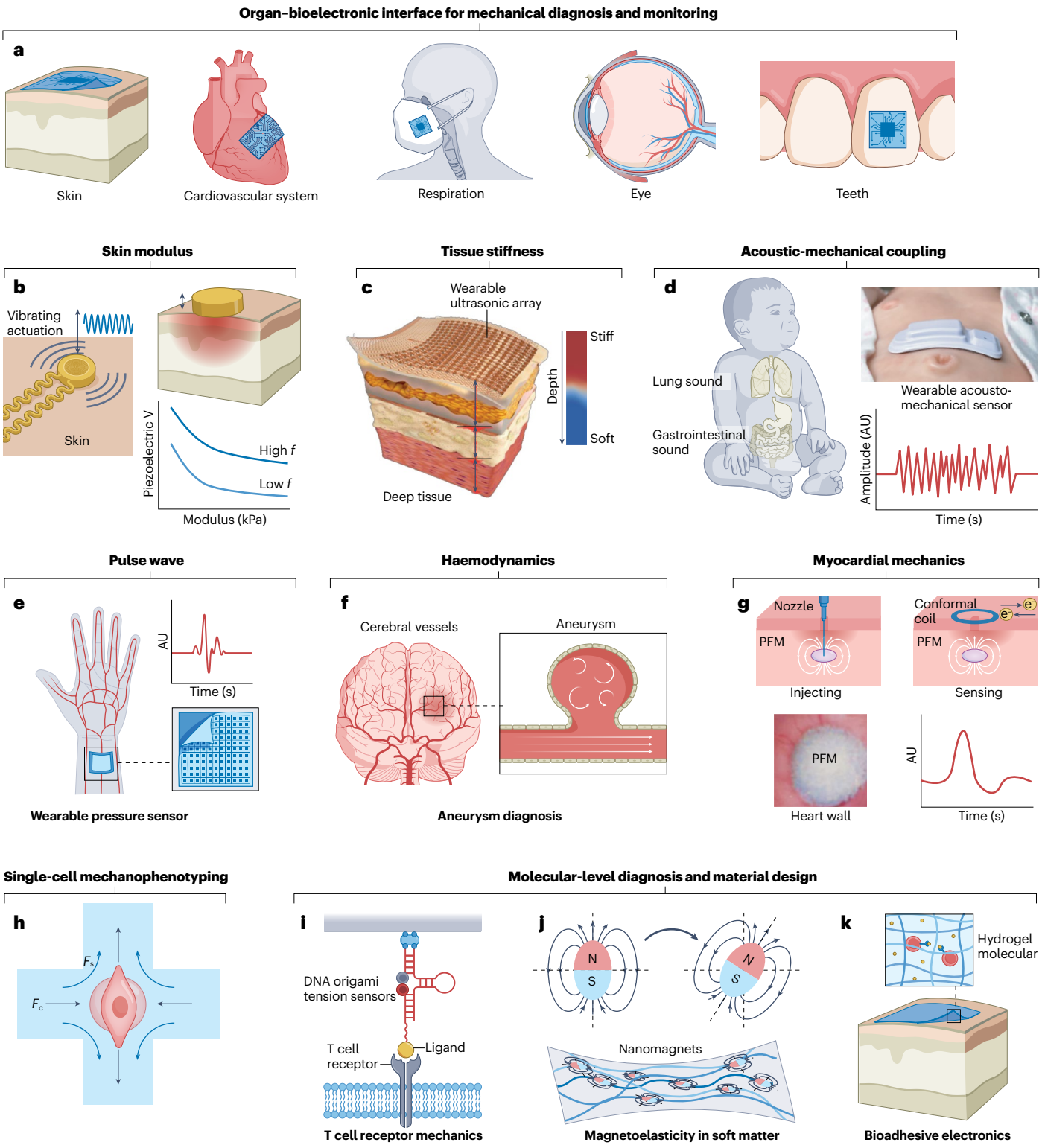
Assessing the cardiovascular system. Mechanical signals can also be measured within the cardiovascular system, including blood flow dynamics, vascular stiffness and cardiac motion, for the diagnosis of cardiovascular diseases[87,88]. For example, wearable pressure sensors enable the continuous tracking of pulse waves[89], facilitating the extraction of key mechanical signals such as blood pressure and pulse pressure (Fig. 3e). Moreover, wearable soft ultrasound sensors can directly monitor blood pressure in real time[90]. These sensors have been clinically validated and show promise as point-of-care medical technologies[27].

Vascular mechanics, such as haemodynamic analysis (Fig. 3f), can also be tracked by implantable devices[6]. For example, a battery-less wireless implant allows continuous monitoring of vascular pressure and flow rate in pig and sheep models[6]. In addition, linear stability analysis revealed that abnormal aortic dilation is linked to a transition from stable flow to unstable fluttering, defined by a dimensionless parameter that integrates blood pressure, aortic diameter, and wall mechanical properties, which can serve as a biomarker of aneurysm growth[91]. Clinical validation with 4D flow magnetic resonance imaging (MRI) data from patients and healthy volunteers confirmed this parameter as a biomarker to distinguish pathological aneurysm progression from natural growth. Moreover, genetically encoded imaging agents, such as gas vesicles for ultrasound imaging and MRI reporter genes, enable non-invasive, molecular-level visualization of biomechanical processes for mechano-diagnostics in clinical settings[92].

Other tissues. Wearable sensors are also clinically applied for the diagnosis of muscular dystrophy via motion tracking[93]. In addition, flexible ultrasonic devices enable continuous bladder volume monitoring in the urinary system[94], and piezoelectric sensors can assess gastrointestinal motility in the digestive system[95]. By capturing the changes of biomechanical signals continuously and with high precision, bioelectronics can support earlier diagnosis, personalized monitoring, and more responsive treatments. To ensure accurate signal detection and long-term device performance, key biomechanical factors, including stiffness matching, mechanical stability and sensitivity, must be carefully addressed.

Matching the stiffness of devices and tissues. Long-term monitoring by wearable and implantable bioelectronics requires a similar stiffness between the device and soft biological tissues to avoid relative motion and tissue damage and enable accurate measurements. However, materials typically employed in electronic devices, such as silicon (elastic modulus of ~140 GPa), gold (79 GPa) and poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (2.7 GPa), do not match the stiffness of soft tissues; for example, brain has an elastic modulus of ~1 kPa, the basilar membrane in the cochlea has a modulus of ~100 kPa, and skin has a modulus of ~5 kPa–140 MPa. (refs. 96,97). To reduce the stiffness of electronic components, wavy structural configurations can be implemented into electronic layouts[98] and the dimensions of electronic components can be reduced to create ultra-thin, flexible and comfortable biointerfaces[99]. Moreover, rigid substrates and backbones can be replaced with flexible polymers (for example, polyimide, parylene or polydimethylsiloxane silicone)[100,101], conductive polymers[102] and hydrogels[103].

Mechanical biostability. Implanted and wearable bioelectronics must withstand repetitive mechanical stresses throughout their operational lifespan, often enduring millions of cycles of bending, stretching or pulsation[104]. These stresses can cause mechanical fatigue, delamination of layered materials and degradation. To increase mechanical robustness, interface engineering allows strong interlayer bonding



through chemical or mechanical interlocking of materials[105]. In addition, structural strain relief can be achieved by incorporating serpentine features into flexible circuit interconnects[106] to redistribute mechanical stress and reduce localized strain, thereby supporting device longevity. Serpentines with large curvature angles and long arms relieve axial elongation strain[107]. Under complex loading conditions, such as out-of-plane deformation or sharp bending, multi-dimensional interconnections[108] or meshed geometries[109] can be integrated to

Fig. 3 | Mechanomedicine for disease diagnosis and monitoring. **a**, Bioelectronic devices can serve as interfaces with tissues and organs to monitor parameters such as skin stiffness, epicardial strain, respiratory flow, intraocular pressure and masticatory forces. **b**, The elastic modulus of skin can be quantified by applying mechanical actuation to induce motion and measure the corresponding vibrational frequency (*f*) responses. **c**, A wearable ultrasonic array can map the 3D distribution of the elastic modulus of tissue ex vivo and detect microstructural muscle damage before the onset of soreness. **d**, A wireless acousto-mechanical sensing patch can monitor respiratory airflow and intestinal motility in neonates in intensive care. **e**, Wearable pressure sensors enable the continuous tracking of pulse waves, facilitating the extraction of key mechanical signals such as blood pressure and pulse pressure. **f**, Haemodynamic analysis can predict the transition from stable to unstable blood flow to aid in the diagnosis of aneurysm growth. **g**, A permanent fluidic magnet (PFM) with intrinsically low modulus and high tissue conformability can be injected into the heart to track its beating. **h**, Mechanophenotyping relies on cellular properties, such as deformability, stiffness and viscoelasticity, as biomarkers to detect early malignancy before the appearance of morphological changes. **i**, Programmable DNA origami platforms enable force measurement between cell surface receptors (for example, T cell receptor) and ligands at the piconewton level. **j**, Nanomagnets can be incorporated into polymer wavy chains to create magnetoelastic effects in soft materials, enabling these sensors to track biomechanical signals for disease diagnosis. **k**, Bioadhesive electronics with precisely controlled adhesion forces can be designed by tuning polymer networks in hydrogels. F_s, stall force; F_c, critical force. Part **c** adapted from ref. 74, Springer Nature Limited. Part **d** adapted from ref. 86, Springer Nature Limited. Part **g** adapted from ref. 115, Springer Nature Limited. Part **h** adapted with permission from ref. 121 AAAS.

improve stability against diverse bending and torsional stresses. However, such a structural approach can demand large device sizes and may compromise electrical performance owing to long interconnection lengths. Alternatively, self-healing polymers or composites that can autonomously repair fatigue-induced microcracks before they propagate may extend device longevity[110].

Sensitivity. Achieving high sensitivity while suppressing noise by motion artefacts remains a key challenge[111]. During mechanical sensing, physiological motion and external acoustic signals can interfere with the accurate translation of mechano-electrical signals, often compounded by motion-induced contact instability[112]. To address these interferences, frequency-based filtering can be used post processing[85,113]. Moreover, signals can be temporally matched from multiple locations to eliminate external acoustic noise[86]. Alternatively, surface microstructures can be introduced to improve biomechanical sensing sensitivity and responsiveness to localized mechanical signals, while isolating sensors from ambient noise[114].

Establishing a conformal interface between bioelectronics and biological tissue can also minimize relative motion at the interface, thereby enhancing signal stability. For example, liquid-based materials can be used instead of solid-state materials to ensure conformability to dynamic tissues, such as the heart[115] (Fig. 3g), enabling stable and reliable mechanical sensing of heartbeats, even in the presence of substantial body movement. Moreover, signal processing, powered by artificial intelligence, allows filtering and decoupling of motion artefact-induced noise from mechanical sensing signals[111].

Cellular and molecular level

Assessing cellular mechanical properties. Cellular stiffness, deformability and adhesion dynamics offer biophysical markers for cell phenotyping, early disease detection and therapeutic monitoring. For example, reduced cellular stiffness, often resulting from cytoskeletal changes during phenotype transition, can be associated with increased metastatic potential in cancer cells from ovary, breast and prostate tumours[29]. Given the scale of individual cells and forces, as well as the high number of cells that need to be analysed, cellular-level mechano-diagnosis demands highly precise technologies[116] coupled with high-throughput methods[117]. For example, microfluidic systems enable mechanophenotyping[37,118,119] for diagnostics by exploiting inherent cellular properties, such as deformability, stiffness and viscoelasticity, as biomarkers for the early detection of malignancy or disease-induced changes[120,121] (Fig. 3h). Similarly, microfluidic systems allow cell sorting by shear stress or acoustic wave, for example, to isolate circulating cancer cells[122,123]. In addition, microfluidic systems can be applied to encapsulate cells in droplets for high-throughput single-cell analysis[124–126]. AFM and optical tweezers can be used to mechanically analyse cell samples from patients[127,128], albeit with limited throughput. Moreover, alterations in water and ion binding to ECM drive changes in ECM elasticity and stress relaxation, which can be exploited in the MRI detection of swelling-associated pathology[129].

Molecular mechanosensors. Mechanical force-induced deformation of biological molecules, such as proteins and nucleic acids, can be leveraged in molecular force sensors[8,130–133]. For example, a protein-based tension sensor of vinculin can assess molecular tension at focal adhesions[46], and a peptide probe can be applied to measure ECM fibre tension[134]. DNA origami-based tension sensors operate by undergoing mechanical unfolding or conformational changes in response to piconewton-scale forces. These nanostructures can be engineered to measure the binding forces involved in various intercellular interactions such as those between T cell receptors (TCRs) and antigens[135]. This capability holds potential for screening and optimizing T cell therapies for cancer treatment (Fig. 3i). Such molecular mechanosensors could complement clinical approaches in disease diagnosis and monitoring but will need to ensure reliability, scalability and interpretability.

Materials engineering. Materials can be engineered at the molecular scale to manipulate their mechanical properties, thereby enhancing their ability to sense mechanical changes. In particular, the magnetoelastic effect, that is, the change of a material's magnetic property under mechanical deformation, typically seen in rigid metals and metal alloys, can be implemented in soft materials (Fig. 3j). For example, nanomagnets can be incorporated into polymer chains to create magnetoelastic effects in soft materials[136]. Soft magnetoelastic bioelectronics based on these materials can track a range of biomechanical signals at the skin or tissue interface, such as respiration, heartbeat and pulse waves, for disease diagnosis[137].

To create a seamless and stable interface between electronic devices and biological tissues and improve sensitivity in mechanical sensing[115], permanent fluidic magnets can be used as new colloidal materials for liquid bioelectronics[115]. Furthermore, bioadhesive hydrogels, based on engineered polymer networks, enable precisely controlled adhesion forces[138] (Fig. 3k). Such hydrogels can be applied in bioelectronic devices to improve their conformability with biological systems[139]. In addition, mechanochromic materials allow

real-time visual feedback through colour change in response to mechanical deformation for biosensing[140] and the optical detection of breathing rates[141].

Therapeutic strategies in mechanomedicine

Mechanotherapeutics aim at either restoring the mechanical functions of tissues or regulating cellular behaviour through the engineering of mechanical cues. Tissue-level mechanotherapeutics rely on mechanical devices, biomechanical stimulation, or wearable and implantable bioelectronics to drive tissue regeneration and rehabilitation. Cellular-level mechanotherapeutics target the mechanical regulation of cell activation, expansion, differentiation and function, and molecular-level mechanotherapy applies mechanically tunable and mechanosensitive biomaterials for cell engineering and drug delivery.

Tissue-level mechanotherapeutics

Biomechanics and mechanical compatibility. Mechanical compatibility between devices and tissues is essential for restoring or supporting mechanical tissue functions and ensuring long-term device stability, integration and function. Mechanical compatibility can be achieved by an integrated approach encompassing material selection and biomechanical analysis as well as through the structural design and fabrication of implants or assistive devices. In addition, devices can be functionalized with proteins or peptides.

Biomechanical computational modelling, complemented by anatomical analysis of the local tissue–implant interface, can be applied in the design of implants or tissue replacements to improve mechanical compatibility[142–145]. For example, mechanical matching of skeletal replacement and fixation devices allows adequate mechanical support while minimizing adverse effects, such as stress shielding, which can lead to bone resorption and loss of the implant[146]. Similarly, stress distribution and musculoskeletal movement can be modelled for the design of prosthetics and exoskeletons[147–149] intended for rehabilitation[150–153].

The mechanical interactions of implants with surrounding tissues can influence cellular behaviour, thereby affecting implant performance and functionality. For example, mechanical mismatch of vascular grafts with native arteries at the anastomotic interface not only alters local shear stress, thereby promoting platelet activation and thrombus formation, but also locally induces abnormal strain and triggers smooth muscle cell proliferation and neointima formation[53,154]. Therefore, the mechanical properties of vascular grafts need to match those of native arteries to ensure graft patency and long-term function.

Mechanical compatibility is also key in brain–machine interfaces. Brain tissue exhibits a stiffness in the kilopascal range, whereas electrodes are typically several orders of magnitude stiffer. This mechanical mismatch can lead to local neural tissue injury, inflammation, glial scar formation and, ultimately, signal degradation or drift[32]. These issues can be addressed using ultra-thin electronics, hydrogel-based microelectronics, fibre electrodes, flexible conductive polymers or nanostructured surface coatings[155–157]. However, electrodes that maintain long-term mechanical and functional stability for both neuronal recording and stimulation have yet to be fully realized.

Bioprosthetic heart valves can substantially improve physiological haemodynamics compared with mechanical valves, reducing the need for lifelong anticoagulation. However, their intrinsic shear and bending properties, partially induced by progressive calcification, remain a challenge. Changes in tissue mechanics may increase stress concentration at suture sites, increasing the risk of leaflet tearing and structural failure over time; this challenge is currently being investigated in clinical trials[158]. For cardiac regeneration following myocardial infarction, mechanically compatible biomaterials, such as injectable materials, can support heart tissue regeneration and function[159]. In addition, native myocardium can be mechanically mimicked with a device that contains serpentine and shape-memory scaffolding; this device facilitates cardiac regeneration in a rat myocardial infarction model owing to its flexibility, dynamic adaptability and biomechanical integration with the beating heart[160,161] (Fig. 4a), without restricting cardiac motion. Furthermore, viscoelastic cardiac patches with high strength and low dynamic modulus outperform elastic patches, improve perfusion and promote myocardial repair in rat and porcine myocardial infarction models[162].

Mechanically induced tissue regeneration. Physical exercise can provide beneficial effects to bone, muscle and the cardiovascular system owing to mechanical stimulation. Mechanical forces can also promote tissue remodelling and regeneration by influencing gene expression as well as cell proliferation, differentiation and migration. These responses are mediated by mechanosensors, such as cell surface adhesion molecules (for example, integrins, cadherins) and ion channel-linked receptors, and mechanotransducers, including the cytoskeleton, intracellular signalling molecules and the nuclear lamina[8,9,163–165]. Together, these systems convert physical forces into biochemical signals, coordinating cellular functions during complex tissue remodelling processes. In addition, mechanical forces contribute to the dynamic remodelling of the ECM[62] by driving direct pulling and reorganization as well as by inducing modifications such as crosslinking or degradation through the cell secretome[15]. Moreover, mechanical loading enhances interstitial fluid flow and blood circulation[166,167], which are crucial for the efficient transport of oxygen and nutrients, as well as tissue remodelling, tumour growth and immune cell trafficking. In addition, the mechanical properties and porosity of the ECM also modulate macrophages and T cells[10,168], which can be leveraged to promote a regenerative and anti-inflammatory environment.

Ultrasound-generated mechanical waves cannot only increase skin permeability for drug delivery[169] but also aid in bone and wound repair by supplying penetrating mechanical waves that interact with tissues[170,171] (Fig. 4b). Specifically, low-intensity pulsed ultrasound accelerates bone regeneration in vitro by stimulating osteoblast differentiation and ECM remodelling, promoting mineralization and structural integrity of newly formed bone[172]. Furthermore, low-intensity pulsed ultrasound is clinically used to shorten healing time in tibial fractures, reducing the need for secondary surgical interventions[173]. In addition, wearable ultrasound arrays, in conjunction with ultrasound-responsive biomaterials, can be applied for bone healing[174]. Ultrasound therapy also promotes angiogenesis and accelerates wound healing in diabetic ulcer animal models[175]. Ultrasound-based therapies can also stimulate collagen production[176] and increase keratinocyte proliferation, making them valuable in chronic skin wound management. The intrinsic piezoelectricity of collagen further generates localized electrical potentials in response to mechanical deformation, providing bioelectric cues that modulate cell adhesion and proliferation to promote tissue regeneration[177].

Negative pressure wound therapy, in which excess exudate is removed and microdeformations are induced, accelerates the healing of chronic wounds, burns and surgical incisions, as demonstrated in randomized clinical trials[178]. Moreover, cyclic mechanical loading through active biomaterials enhances tissue regeneration by promoting cell proliferation and ECM production during wound

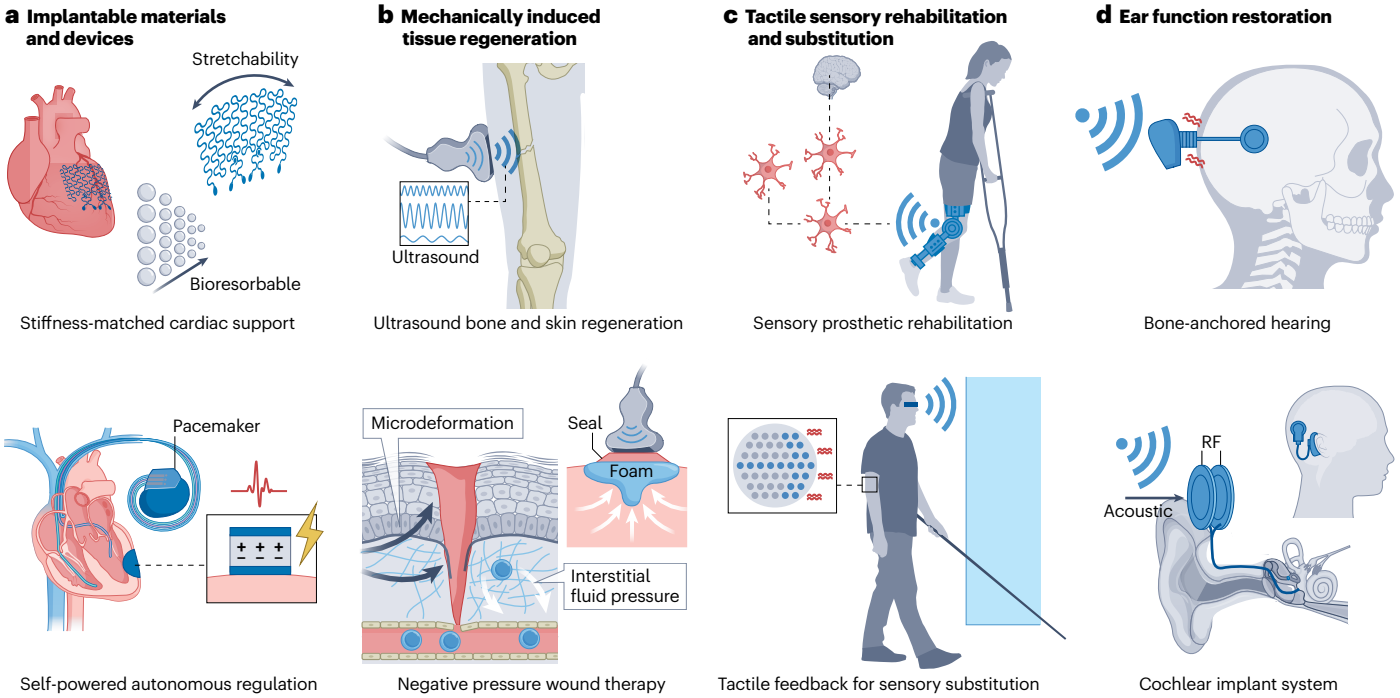


Fig. 4 | Tissue-level mechanotherapeutic applications. a, Mechanical devices can be implanted for therapeutic interventions; for example, self-powered pacemakers rely on cardiac mechanical motion to generate power through piezoelectric and triboelectric effects, enabling sustainable energy harvesting for long-term physiological monitoring. Stretchable, stiffness-matched bioresorbable materials facilitate mechanical cardiac modulation, allowing control of organ motion without restriction and eliminating the need for additional surgeries. **b**, Tissue regeneration can be mechanically induced by ultrasound, for example, for bone and skin regeneration; here, ultrasound vibration enhances osteocyte activity and promotes skin repair. Negative pressure wound therapy accelerates wound healing by optimizing interstitial fluid flow and modulating matrix stiffness. **c**, Tactile sensory rehabilitation and substitution integrate neuromuscular activation through targeted stimulation in prosthetics, enhancing nerve signalling to support adaptation and therapeutic recovery. Tactile feedback promotes multimodal perception, enabling sensory substitution to intuitively compensate for lost sensory input and improve functionality in assistive technologies. **d**, Ear function restoration systems combine wearable and implantable components to convert external mechanical acoustic signals into mechanical vibrations or electrical impulses, thereby addressing auditory sensory dysfunction. Bone-anchored hearing devices enable acoustic wave transmission through bone conduction, and cochlear systems provide electrical impulses for auditory stimulation based on a wirelessly received signal. RF, radio frequency.

healing[179]. Further, blocking mechanical tension-induced activation of Engrailed-1 can inhibit scar formation[180].

Tactile sensory rehabilitation and substitution. Tactile rehabilitation enables the restoration and enhancement of tactile sense for individuals with sensory impairments caused by injury, neurological disorder or limb loss. The precise modulation of tactile sensory input, integrated with artificial intelligence, allows both sensory augmentation and substitution, offering solutions for individuals with sensory impairments by leveraging mechanically engineered interfaces and neuroadaptive feedback systems[181] (Fig. 4c). Beyond motor control, tactile feedback systems can also create augmented reality environments that replicate real tactile experiences[182–184] for individuals with visual impairments[185,186]. Using vibratory and mechanosensitive actuators, these systems convert environmental stimuli into haptic signals, allowing users to navigate their surroundings through touch-based feedback.

Neuromuscular activation by mechanical and electrical stimulation plays a pivotal role in restoring tactile sensory and functional movement, enhancing proprioception. Mechanically responsive prosthetic limbs rely on targeted mechanical stimulation to generate sensory feedback, compensating for the lack of intrinsic sensation[187–189]. These approaches enhance motor control and rehabilitation outcomes by strengthening neuroplastic adaptation and improving proprioceptive integration. For example, neuromuscular stimulation in individuals with lower-limb prosthetics is being investigated in a clinical trial to assess whether integrated biofeedback systems improve gait control and reduce phantom limb pain[190]. Mechano-stimulating prosthetics, equipped with precise tactile stimulation[191] and integrated with multi-stimulation feedback[192], are expected to further enhance sensation, motor control and adaptive functionality.

Mechanical energy harvesting in battery-free implantable devices. Mechanical movements of tissues can be harvested to provide power for bioelectronics. For example, pacemakers, which monitor and regulate heart dynamics, play a crucial role in maintaining cardiac functionality for sustained life support. Mechano-electrical energy harvesting through triboelectric, piezoelectric and magnetoelastic approaches allows the integration of biomechanical energy sources, such as cardiac motion and blood flow, into pacemakers for long-term

monitoring[193–196]. These strategies improve implant longevity and reliability, reducing the need for surgical battery replacements. To further improve in vivo stability, liquid-based encapsulation technologies can be applied that protect bioelectronics across a range of physiological conditions, minimizing risks of material degradation and device failure[197].

Physiological regulation systems, such as deep brain stimulation and implantable neural interface systems, can also be designed with biomechanical energy harvesting and biocompatible mechanical power generation to enable battery-free therapeutics. These approaches are being explored in large animal models[198,199], paving the way for the development of autonomous therapeutic regulation.

Acoustic transduction for ear function restoration. Ears are key mechanical sensing organs, and treatment of hearing impairments relies on mechanotherapeutics provided by wearable or implantable auditory and vestibular restoration systems (Fig. 4d). For example, bone-anchored implants, typically titanium-based and surgically embedded into the skull, transmit sound vibrations through bone conduction and are particularly effective for individuals with conductive hearing loss and single-sided deafness. To improve biocompatibility and reduce complications, such as skin irritation, inflammation and infection associated with percutaneous connectors[200,201], transcutaneous sound transmission systems[202,203] can be applied. For individuals with profound sensorineural hearing loss, cochlear implants convert acoustic signals into electrical impulses transmitted electromagnetically from an external processor to an internal electrode array, which directly stimulates the auditory nerve. However, cochlear implants remain limited by low sound resolution in noisy environments[204,205]. Alternatively, vestibular implants can restore balance in individuals with bilateral vestibular dysfunction[206]. By integrating inertial sensors, such as gyroscopes and accelerometers, with targeted electrical stimulation of the semicircular canals and otolith organs, these systems aim to reestablish vestibular function.

Cellular-level mechanotherapeutics

Cells interpret extracellular mechanical cues, such as shear stress, cyclic deformation, substrate stiffness and viscoelasticity, ECM fibre strain and microtopography, to guide cell organization, lineage commitment, functional changes and tissue formation (Fig. 5a). Insights into how cells respond to these mechanical signals have inspired a range of biomedical technologies, including the engineering of functional tissues in bioreactors, disease modelling using organ-on-a-chip systems, directed stem cell differentiation in engineered environments, and cellular reprogramming and immune cell engineering for therapeutic applications.

Mechanical regulation of cells. Bioreactors offer dynamic and tunable platforms to apply controlled mechanical stimuli, such as shear stress, cyclic strain and compression, to in vitro tissue culture, mimicking physiological conditions to promote tissue remodelling and maturation. For example, perfusion bioreactors allow the mechanical conditioning of cardiac tissues, improving their functional maturation[207]. Cyclic mechanical strain applied within bioreactors promotes collagen deposition and supports the in vitro development of functional, implantable blood vessels[208]. Shear stress-conditioned endothelial cells promote engraftment of engineered vascular grafts, reducing thrombosis and graft failure rates[209,210]. In cartilage tissue engineering, dynamic mechanical stimulation within bioreactor systems enhances chondrogenic ECM production and functional maturation of engineered cartilage constructs[211–213].

Bioreactor systems can also be extended to organ-on-a-chip technologies. For example, lung-on-a-chip models can be applied to study how mechanical stress alters alveolar permeability and barrier function in lung infections[214,215]. Furthermore, bioreactors can be used to engineer patient-specific tissue grafts as physiologically relevant disease models[216]. For example, bioreactor-guided cardiac tissue engineering enables modelling of heart failure through the generation of mature human myocardium with patient-specific contractile dysfunction[217].

Mechanical cues also have a key role in the differentiation and reprogramming of cells[218–220]. For example, dynamic mechanical strain promotes the differentiation of mesenchymal stem cells (MSCs) into smooth muscle cells[221], whereas compressive forces in 3D hydrogels induce MSC differentiation into chondrocytes[222]. Mechanical properties of ECM such as elasticity can direct MSC differentiation into neural, muscle or bone cells in a stiffness-dependent manner[223]; neural stem cells differentiate into mature neurons on soft substrates[224], whereas transforming growth factor-β (TGFβ) signalling drives MSC differentiation into smooth muscle cells or chondrocytes, depending on whether the substrate is stiff or soft, respectively[225]. Furthermore, substrate viscoelasticity plays a crucial role in stem cell differentiation. For example, high creep hydrogels promote smooth muscle cell differentiation, whereas rapidly relaxing gels enhance osteogenic differentiation of MSCs[24,226,227]. Moreover, nanoporous surfaces or micropillars can promote MSC differentiation toward the osteogenic lineage[228,229]. In addition, mechanically tuned hydrogels can influence embryonic development[230] and guide the morphogenesis of complex tissues such as the intestine[231].

Cell reprogramming, that is, the conversion of differentiated cells into induced pluripotent stem cells or other cell types, such as neurons or cardiomyocytes, offers the potential to generate virtually any cell type in the body for tissue regeneration and disease modelling[232,233]. This process involves a fundamental switch in cell identity, driven by changes in the epigenetic landscape, including the conversion of closed heterochromatin into open euchromatin and vice versa[234]. In addition to transcription factors and biomolecules, mechanical cues also play a role in regulating the epigenetic state[163,235]. The nuclear lamina not only provides structural support for the nucleus and its genetic material but also acts as a scaffold for chromatin organization and a physical link between the cytoskeleton and intranuclear components[164,165,236]. Changes in cell and nuclear morphology can influence the cytoskeleton, nuclear lamina, activity of histone-modifying enzymes and histone modifications, thereby modulating the reprogramming process[237–241]. In particular, transient mechanical squeezing of cells can partially disrupt the nuclear lamina and heterochromatin, thereby increasing cellular plasticity for reprogramming[239,242]. This phenomenon not only offers opportunities for cell engineering in vitro but also has implications in cell phenotype changes in vivo during cell trafficking in microcirculation and 3D tissues. Interestingly, fibroblasts cultured in spheroids or submitted to compressive force exhibit chromatin remodelling and a rejuvenated phenotype[243], and tension anisotropy drives phenotypic changes of fibroblasts[244]. ECM stiffness also considerably impacts chromatin structure, displaying a biphasic effect on chromatin accessibility and reprogramming efficiency; notably, fibroblast-to-neuron conversion is most efficient at an intermediate stiffness of approximately 20 kPa (ref. 245). Furthermore, viscoelastic substrates reduce lamin A/C expression, decrease chromatin condensation, enhance

chromatin dynamics, and promote the reprogramming of fibroblasts into neurons or induced pluripotent stem cells[246].

Mechano-immunoengineering. Mechanical cues play an important role in the activation, migration and function of immune cells such as neutrophils, macrophages and T cells[10,168,247]. For example, TCR signalling at the immune synapse involves mechanosensitive mechanisms. TCRs exert mechanical forces on antigen-presenting cells (APCs) to enhance antigen recognition and activation, a process that has become a foundation for mechanotransduction-based immunotherapeutic design[248–250]. Given the mechanosensitive nature of TCRs, APC-mimicking platforms can be engineered to optimize TCR engagement and immune synapse formation[251,252] (Fig. 5b). Notably, regulatory T cell induction is sensitive to the stiffness of the substrate[253], and viscoelastic gels or synthetic APCs can regulate the formation of T memory stem cells crucial for the durability of immunotherapy[254,255]. Concurrently, several biomimetic APC platforms have been designed for T cell expansion, although their mechanical properties have not yet been well characterized[256–260].

Other immune cells also rely on mechanosensing for their activation and function. For example, B cells use mechanical forces to promote antigen internalization[261]; natural killer cells depend on CD16-mediated mechanotransduction for efficient antibody recognition[262]; and macrophage polarization is tuned by spatial confinement[263,264] and matrix stiffness[265]. Similarly, in haematopoietic stem cell differentiation, delta-like ligand 4 (DLL4) activation plays a crucial role in lineage commitment[266,267]. Accordingly, mechanotransduction-optimized DLL4-presenting beads might provide a tool for haematopoietic stem cell differentiation by mimicking the native mechanical microenvironment[268].

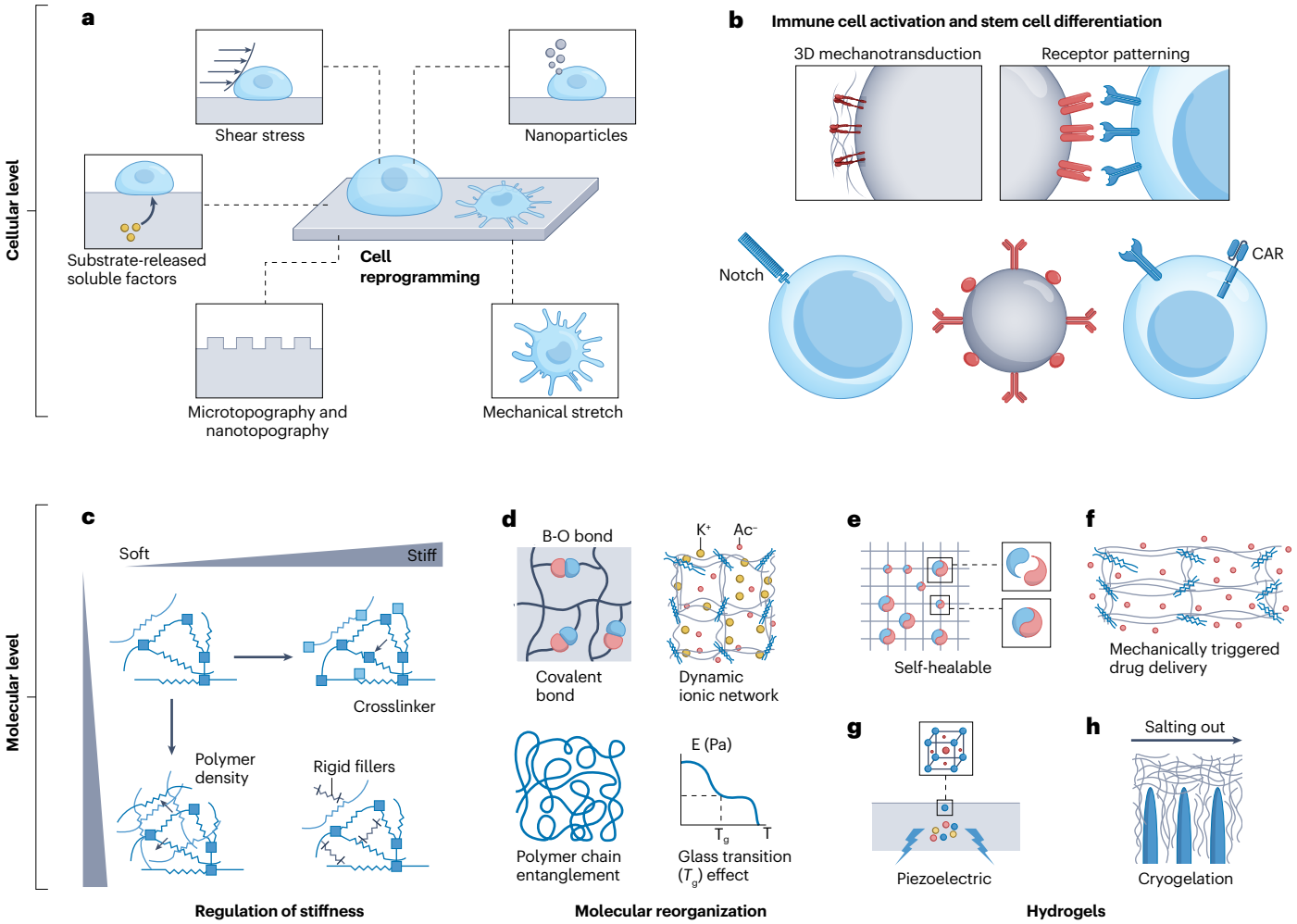


Fig. 5 | Cellular and molecular mechanisms underlying mechanotherapeutics. **a**–**h**, At the cellular level, cell reprogramming can be facilitated by mechanical stimuli, such as shear stress, nanoparticle interactions, substrate-released factors and mechanical stretch, creating environments that induce intracellular changes (**a**). Synthetic cells can be designed to regulate immune responses or stem cell differentiation through mechanotransduction and receptor patterning (for example, T cell receptor and chimeric antigen receptor (CAR) engagement) (**b**). At the molecular level, dynamic materials can respond to external forces; molecular reorganization occurs through covalent bonding, ionic networks and polymer chain entanglement (**c**); stiffness in hydrogels can be modulated through crosslinking and polymer density (**d**); self-healing hydrogels autonomously repair damage (**e**); mechanically triggered drug delivery enables force-responsive release of therapeutic agents (**f**); piezoelectric hydrogels generate electric signals (**g**); and cryogels with porous structures can be created through cryogelation to increase mechanical robustness (**h**). T_g, glass transition temperature.

The mechanical properties of the tumour microenvironment also profoundly influence immune cell infiltration, activation and therapeutic response. Although integrin-based adhesions are crucial for cell migration, cancer cells and immune cells in 3D confined space may adopt an amoeboid mode of migration with low integrin dependence or use polarized water permeation to drive migration[269,270]. High ECM stiffness in tumours promotes glycolysis for cancer cell migration and proliferation, but acts as a physical and biochemical barrier, limiting immune cell access and dampening anti-tumour responses[271–275]. For example, stiff ECM causes the exhaustion of $CD8^+$ T cells through Piezo1 signalling[276]. Therefore, tumour stiffness can be modulated to enhance immune cell therapy. On the other hand, tumour cell softness suppresses cytotoxic T cell killing owing to the inhibition of membrane pore formation by perforin[277] or cholesterol enrichment in the plasma membrane[278], suggesting a heterogeneous response of tumor cells to immune cell therapy.

It is worth noting that recent advances in synthetic biology for mechanotherapeutic applications have shown promising results. To increase tumour killing potency, mutants of the TCR can be engineered to enhance catch bond formation[279]. In addition, mechano-actuation of immune cells with temporal and spatial control allows targeted treatment with minimal off-target effects using a sonogenetics approach, which leverages mechanically sensitive genetic circuits responsive to ultrasound stimulation; this enables the in vivo induction of chimeric antigen receptor (CAR) expression in engineered immune cells[280] and the local activation of therapeutic bacteria[281] to release apoptotic agents or immune-checkpoint inhibitors, demonstrating potent tumour suppression and immune activation in multiple mouse models.

Molecular engineering of materials as mechanotherapeutics

Biomaterials can be engineered with precisely controlled mechanical properties to direct cell behaviour, promote tissue regeneration or improve drug delivery. For example, hydrogel properties, such as viscoelasticity and ligand density, can be independently and precisely modulated to influence cellular processes[282,283] (Fig. 5c). In particular, dynamic hydrogels can be designed that respond to mechanical cues in real time, incorporating reversible crosslinks, stress-responsive networks and self-healing properties by exploiting covalent and ionic bonds, polymer chain entanglement, and phase transitions such as glass transition dynamics (Fig. 5d). For example, photodegradable hydrogels allow the dynamic tuning of mechanical and chemical properties[284]. Reversible covalent bonds, such as boronic ester and disulfide bonds, provide tunable crosslinking that enables stress relaxation and material remodelling under physiological conditions[285,286]. Polymer chain entanglement further contributes to viscoelastic properties, allowing materials to exhibit both solid-like and fluid-like behaviours, depending on mechanical loading[287]. Additionally, the glass transition temperature of polymeric networks can be tuned to control drug release kinetics in biodegradable delivery systems because glass transition temperature influences polymer chain mobility, degradation rate and molecular diffusion[288]. Such mechanically and chemically tunable dynamic hydrogels can be applied in regenerative medicine, immunoengineering and disease therapy[289,290].

Functional and responsive hydrogels can also be engineered to actively interact with biological systems. For example, self-healing hydrogels that incorporate reversible crosslinking mechanisms can recover their structure after mechanical damage[291] (Fig. 5e). These materials are particularly valuable in wound healing applications[292], soft robotics[293] and implantable biomaterials[294] that require mechanical resilience and longevity. Mechanically triggered drug delivery can be achieved by engineering the chemical composition or architecture of materials. For example, drugs can be loaded into mechanically responsive materials through cyclic compressive loading[11], physical encapsulation[295], covalent tethering[296] or affinity binding[297]. The drug can then be released in response to mechanical stimuli, such as ultrasound or compressive, tensile, shear or magnetic forces, through mechanisms such as carrier deformation, bond breakage or mechano-responsive structural transitions[11,298,299] (Fig. 5f). Piezoelectric hydrogels generate electrical signals in response to mechanical deformation, creating mechanically activated bioelectronic interfaces that can stimulate nerve regeneration[300], enable osteoarthritis treatment[301] and promote stem cell differentiation[302], making them promising for electrostimulation-assisted therapies (Fig. 5g). Cryogelation hydrogels, produced by a freeze–thaw process, form macroporous structures that enhance cell infiltration, nutrient diffusion and mechanosensitivity, making them promising for applications in tissue scaffolding[303], tumour immunotherapy[304] and injectable biomaterials[305] (Fig. 5h).

Outlook

Mechanomedicine leverages biomechanics and mechanobiology principles for diagnostics, therapy and regeneration. However, the clinical translation of mechanomedicine faces challenges related to technological development and clinical integration. For example, mechanical diagnostic devices, in particular implantable bioelectronic devices, must demonstrate long-term biosafety and biostability within complex in vivo environments. This will require encapsulation strategies and material designs capable of withstanding prolonged exposure to biofluids and mechanical stress. Biomaterials or living materials can be incorporated to reduce inflammation, fibrosis and adverse immune responses[306]. Devices must also be sufficiently small and lightweight to be worn or implanted comfortably without compromising their sensing, processing or actuation capabilities[307]. Implantable devices also require reliable, scalable power solutions. Batteries are typically bulky and have a limited lifespan. Alternatively, wireless energy transfer and harvesting of biomechanical energy can be explored to create self-sustaining, closed-loop systems[308]. Importantly, motion artefacts owing to biomechanical motions of the body can introduce noise in diagnostic data. Conformal device-tissue interfaces, adaptive filtering and artificial intelligence-assisted real-time data processing can enhance signal fidelity and diagnostic accuracy. Mechanomedicine devices must also be cost-effective and scalable and, in some cases, stretchable and bendable. Therefore, manufacturing processes are required to produce these devices at scale and reasonable costs.

In diagnostics, deep learning algorithms can aid in the analysis of imaging-based elastography to extract mechanical properties of tissues for the assessment of fibrosis and tumours[309]. Artificial intelligence models could also assist in surgical decision-making for conditions, such as aneurysms, by evaluating parameters, for example, aneurysm size, wall thickness, vascular mechanical properties, shear stress and blood pressure. Furthermore, bioelectronic technologies allow continuous, multimodal acquisition of biomechanical signals, including respiratory airflow, muscle deformation and cardiovascular dynamics[33]. These signals could be interpreted by artificial intelligence models to support early disease detection, risk stratification, postoperative monitoring and pathological assessment. Such individual health data, synthesized with biomechanical insights, could promote

adaptive, real-time diagnostics and clinical decision-making. Artificial intelligence can also aid in the optimization and personalization of implants, prosthetics and device placement by incorporating local anatomical geometry and mechanical stress distribution.

At the molecular level, a major challenge in mechano-diagnosis lies in the identification and validation of mechanical biomarkers that reflect changes in tissue biomechanics and that can be integrated with biochemical and immunological indicators of injury, inflammation and disease. Artificial intelligence-powered discovery platforms are likely to accelerate this process by correlating mechanical biomarkers with specific disease types and stages. Artificial intelligence might also aid in the discovery of new drugs and targets related to mechanosensitive signalling pathways by integrating multi-omics data with patient-specific profiles. Importantly, mechanomedicine should be considered at all scales, from the cellular to tissue and whole-organ scale. For example, biomechanical simulations based on patient-specific imaging and mechanical data could be integrated to improve diagnostic accuracy and inform therapeutic decision-making. Ultimately, linking mechano-diagnostic insights directly to therapeutic decision-making will be essential to achieving the full potential of mechanomedicine.

A promising future direction lies in integrating mechanosensing with mechanical stimulation, function and therapy. For example, the performance of intelligent prosthetics and robotic surgical systems could be enhanced by combining mechanosensing with precise movement control. In addition, mechanically tunable and responsive materials might enable new sensing and therapeutic applications. For example, micro-fabrication and nano-fabrication, chemical synthesis, and synthetic biology allow the rational design of materials with controlled mechanical properties and responsiveness to external stimuli. The development of these materials will be further accelerated by generative models and data-driven discovery, which can predict mechanical behaviour, optimize material composition and guide the creation of structures with tailored functionalities. Moreover, mechanically triggered processes, such as drug delivery or material degradation, can be programmed to respond to local tissue mechanics or non-invasive actuation signals, such as ultrasound, opening new opportunities for precision therapies[310].

The integration of precisely tailored mechanical cues, delivered through materials or dynamic forces, with biochemical signals will be essential for advancing cell fate engineering and large-scale cell manufacturing in vitro. A deeper understanding of how mechanical stimuli regulate the epigenetic state of cells will improve the efficiency of directed differentiation and reprogramming. In vivo biomaterial-based 'training centres' could be designed for immune cells, and temporal control over material mechanics and degradation can be coordinated with tissue regeneration. Mechanical cues will also play a pivotal role in organ-on-a-chip systems, where they can be harnessed to simulate microcirculation and immune cell trafficking, thereby reducing reliance on animal testing and accelerating therapeutic discovery.

Importantly, the definition, measurement and clinical interpretation of mechanical biomarkers should be standardized. For example, mechanical parameters, such as stiffness, stress relaxation and frequency-dependent stiffness, are commonly measured using techniques such as AFM, micropipette aspiration, rheology analysis and elastography; however, the resulting outputs often lack standardized definitions and are not comparable across laboratories. Community-driven definitions and benchmarks are thus required to allow clinical translation of mechanical biomarkers. Finally, ethical considerations with regards to mechanomedicine must be addressed, including the management and privacy of large-scale biomechanical data (Box 2).

The future of mechanomedicine lies in the integrative exploitation of biomechanics, bioelectronics, mechanobiology, cell engineering, materials engineering, artificial intelligence and computational modelling. By targeting or exploiting mechanical features in health and disease, mechanomedicine holds promise for reshaping diagnosis and monitoring, enhancing regenerative therapies and improving outcomes across diverse clinical areas.

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Box 2 | Ethical and translational considerations in mechanomedicine

Mechanomedicine presents a range of ethical challenges, particularly in diagnostic and therapeutic applications involving invasive, autonomous or long-term interventions. One major concern is the use and interpretation of sensitive health data. Wearable and implantable bioelectronics used for continuous biomechanical monitoring generate large volumes of personal data, raising concerns about privacy, informed consent and data ownership, particularly when artificial intelligence is used to analyse and process these mechanical signals. Transparent data governance, user education and regulatory oversight will be essential for public trust. In addition, algorithmic bias in mechano-diagnostic platforms may reduce their accuracy for underrepresented populations, potentially reinforcing healthcare disparities.

Mechanical biomarkers also require rigorous clinical validation to avoid false positives, in particular if non-specific changes in stiffness or compliance are interpreted as indicators of disease. Bridging the interpretability gap between mechano-diagnostic outputs and clinical decision-making will be key to clinical integration.

Importantly, implanted devices must demonstrate long-term mechanical compatibility and stability to avoid effects such as stress shielding; for example, stiff orthopaedic implants might reduce natural bone loading, leading to bone resorption, or micromotion may cause implant loosening and chronic pain[146]. In brain–machine interfaces, mechanical mismatch between electrodes and neural tissue can lead to fibrotic encapsulation, compromising signal quality and stimulation effectiveness[327]. Long-term clinical data, mechanically compatible biomaterials and personalized implant design are thus required and must be made equitably accessible.

Finally, mechanical interventions may unpredictably affect cellular behaviour. For example, stem cell differentiation is influenced by both chemical and mechanical cues in the microenvironment, and mechanical forces may activate multiple signalling pathways. Therefore, mechanical interventions must be carefully evaluated in both physiological and pathological conditions to ensure specificity and safety.

As mechanomedicine moves toward clinical translation, comprehensive ethical frameworks must be established that address data handling, long-term safety, biological specificity and equitable access.

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Author contributions

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Competing interests

The authors declare no competing interests.

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