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Review article

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Mechanical state transitions in the regulation of tissue form and function

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Abstract

From embryonic development, postnatal growth and adult homeostasis to reparative and disease states, cells and tissues undergo constant changes in genome activity, cell fate, proliferation, movement, metabolism and growth. Importantly, these biological state transitions are coupled to changes in the mechanical and material properties of cells and tissues, termed mechanical state transitions. These mechanical states share features with physical states of matter, liquids and solids. Tissues can switch between mechanical states by changing behavioural dynamics or connectivity between cells. Conversely, these changes in tissue mechanical properties are known to control cell and tissue function, most importantly the ability of cells to move or tissues to deform. Thus, tissue mechanical state transitions are implicated in transmitting information across biological length and time scales, especially during processes of early development, wound healing and diseases such as cancer. This Review will focus on the biological basis of tissue-scale mechanical state transitions, how they emerge from molecular and cellular interactions, and their roles in organismal development, homeostasis, regeneration and disease.

Sections

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Introduction

Biological materials, such as cells and tissues, are active physical materials, that is, entities that sense and respond to their environment and that can use energy to generate forces that lead to the deformation of cells and tissue[1]. This activity interplays with the passive mechanical properties of cells and tissues, that is, how they respond to applied force and deformation, often referred to as tissue rheological properties. From the rheological perspective, tissues can behave as elastic, 'solid-like' materials in which they deform in response to extrinsic force and retract back to their original shape upon removal of the load (Supplementary Table 1 and Fig. 1). At the other end of the spectrum, tissues can exhibit 'fluid-like' behaviour, in which they deform but retain that deformation upon removal of the force. Changing between solid-like and fluid-like states can be referred to as a 'mechanical state transition' or a 'jamming–unjamming' transition.

The ability of a tissue to deform and flow when subjected to an applied force is defined as tissue fluidity[2,3] (Fig. 1). From a biological perspective, tissue fluidity is defined as the ability of cells to move within a tissue by changing shape and by rearranging extracellular junctions[3,4]. Cells in a fluid-like tissue can easily move by exchanging neighbours and remodelling adhesive contacts. In a solid-like tissue, the movement of cells is limited. Importantly, these tissue-scale changes also impact the local transmission of mechanical signals (Box 1), thereby linking tissue-scale changes to the behaviour of single cells. For example, cell proliferation within a confluent cell layer can lead to an increase in local pressure, which may induce long-range tissue flow if the tissue is in a fluid-like state but triggers local deformation and mechanosignalling in a solid-like state[5–8].

Tissues can also display viscoelastic or viscoplastic properties (Supplementary Table 1 and Fig. 1), which enable them to respond differently to different durations of mechanical stresses (defined as force applied to an area at a given time) while preserving tissue integrity. Viscoelasticity describes materials that present both viscous and elastic properties. Viscous materials resist deformation upon application of a force, whereas elastic materials strain proportionally to the force and then immediately return to their original state once the mechanical stress is removed[9,10]. Most biological materials are considered viscoelastic to varying degrees. By contrast, viscoplastic materials undergo unrecoverable deformations after a load level is reached. For example, a tissue can display solid-like viscoelastic behaviour in response to an ectopic force[11] but, if the force is applied for an extended period of time, the same tissue can adopt more fluid-like, viscoplastic properties and undergo permanent deformation[12,13] (Fig. 1). Viscoplastic behaviour allows forces to drive irreversible morphogenesis during development whereas viscoelastic properties facilitate reversible deformations to buffer short-term mechanical fluctuations (stochastic dynamics in a non-equilibrium state; also described as 'noise') during tissue homeostasis such as the rhythmic beating of the heart[14–16].

Dynamic changes in tissue-scale mechanical properties occur throughout development and facilitate (patho)physiological processes such as adult tissue regeneration or the onset or progression of disease. A tissue can switch between two states in a process termed a jamming–unjamming transition. Such transition behaviour has been modelled using computer simulations[17,18] and observed during development, tissue homeostasis and repair, where high tissue fluidity (unjammed state) promotes cell migration and morphogenesis, whereas jamming to a more solid-state stabilizes and strengthens the tissue structure[18–24], a property essential for homeostasis. Thus, understanding the fundamental mechanisms of tissue behaviour entails understanding the mechanisms and functional roles of tissue mechanical transitions. Accordingly, various biophysical tools have been developed to quantify and characterize tissue-scale and cell-scale mechanics (Table 1). Importantly, mechanical properties may often not be directly measurable due to technical limitations and are instead inferred from cell dynamics or relative shape changes.

How mechanical state transitions occur depends on how forces are transmitted, dissipated or insulated between cells and across tissues. In this Review, we first briefly introduce the cellular machineries that endow cells and tissues with active physical material properties. We then describe how tissue mechanical transitions facilitate various pathophysiological processes, from development through adult homeostasis to disease and ageing. We highlight the roles of force transmission, force dissipation and force insulation during such transitions by using biological examples from different model organisms and physiological states, and conclude with an outlook on mechanical noise, its ubiquitous nature, and how it is buffered to enable robust tissue transitions throughout life.

Dynamic regulation of molecular machinery drives mechanical state transitions

The physical states of tissues, be it solid, fluid or somewhere in between, are emergent properties of the complex interactions of cells with each other and with their environment[1,3,25] (Fig. 1). Cell-intrinsic material properties are predominantly determined by the cytoskeleton, consisting of actin, intermediate filaments and microtubule networks, and in part through properties of the nucleus and plasma membrane[26,27]. For tissues, cell–cell adhesions, cell–matrix adhesions, cell shape and tissue architecture are also key factors in determining the physical states of a tissue and how they may transition upon intrinsic or extrinsic stimuli. We will discuss these cell-intrinsic and cell-extrinsic determinants of tissue mechanics in the following sections.

Cell-intrinsic determinants of tissue mechanics

The cytoskeleton is a 3D, interconnected meshwork of biopolymers contained within the cytoplasm of cells. It is composed of a complex network of actin filaments, intermediate filaments and microtubules (Fig. 2). These cytoskeletal networks allow cells to sense external stimuli and enable them to move and change shape[26]. Each cytoskeletal component differs in its mechanical stiffness, assembly dynamics, polarity and the associated molecular motors, defining the architecture and function of the networks they form.

Filamentous actin and myosin II are assembled just below the plasma membrane in a structure called the actomyosin cortex. Both also assemble into contractile filaments termed stress fibres when cells encounter mechanical stress, for example, a rigid substrate (Fig. 2). These stress fibre structures resist and generate force through actomyosin contractility, allowing cells to maintain or change their shape (for details, see refs. 26,28,29). For example, upon wounding, fibroblasts develop prominent stress fibres that allow generation of tension and extracellular matrix (ECM) remodelling to facilitate migration and wound closure[30]. Changes in actomyosin contractility are transmitted to neighbouring cells and the ECM through adhesion molecules such as cadherins and integrins, respectively. These adhesion molecules can link to and regulate actomyosin cytoskeleton organization, as will be discussed in more detail in the following section. At the tissue scale, contractility in epithelia determines tissue fluidity and reducing contractility promotes fluidity[24]. Fluidity has been further proposed to be modulated by stochastic fluctuations on myosin II activity at

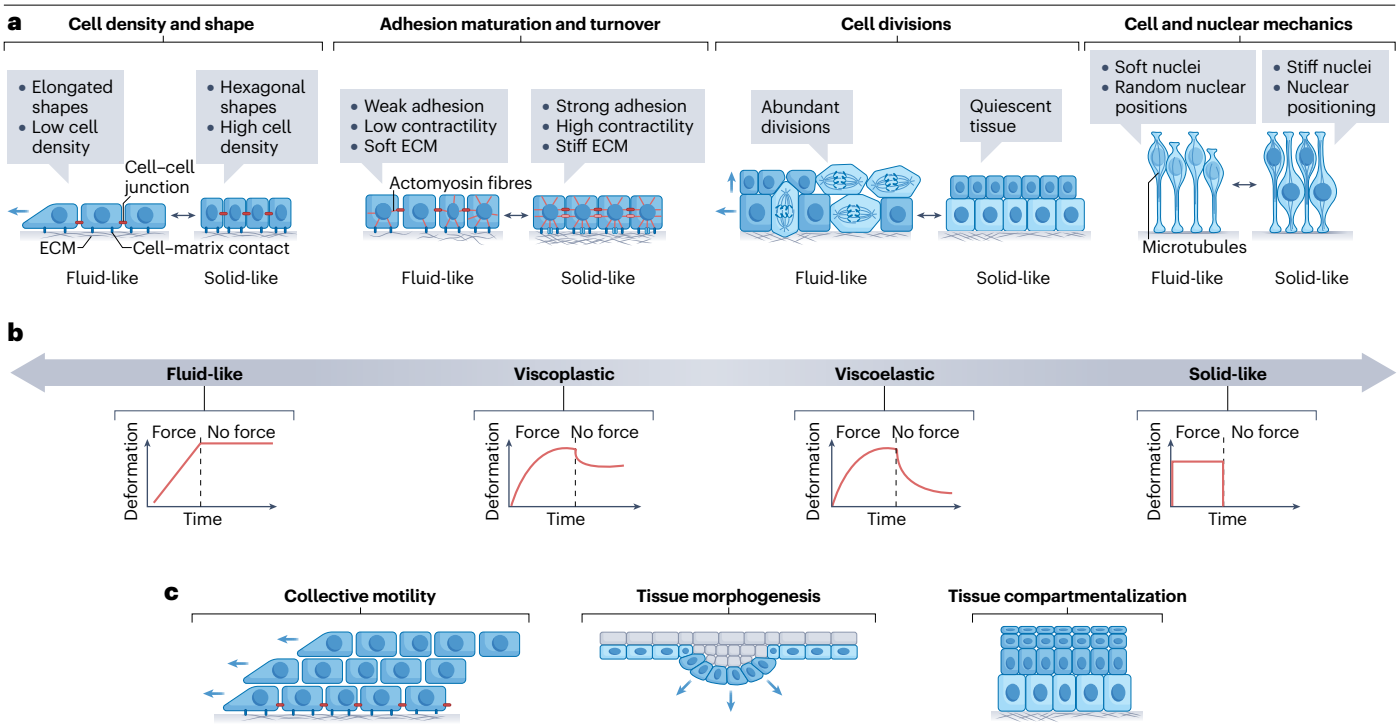

Fig. 1 | Definition and biological basis of tissue mechanical properties and state transitions. Tissues have biological properties that range from fluid-like to solid-like and in between viscoplastic and viscoelastic states. **a**, Tissue mechanical states are determined by molecular and cellular processes that regulate cell shape, density, adhesion and dynamics. Elongated cell shapes, low cell density, and low levels of cell–cell and cell–matrix adhesion promote fluidification whereas hexagonal cell shapes, high cell density and high levels of adhesion (or low fluctuations) promote jamming. Additionally, cell divisions and interkinetic nuclear movements associated with cell division in some cell types, such as neurons, promote fluctuations and thus tissue fluidification. **b**, In a fluid-like state, the tissue responds to force by gradual deformation that persists even when force is removed. A solid-like (elastic) tissue responds immediately to force by deformation and returns to the initial shape once the force is removed. In viscoplastic and viscoelastic states, the tissue deforms in response to a force in a time-dependent manner, where the response is elastic on short time scales followed by viscous flow on long time scales. The stronger the elastic component, the more the tissue will return to its original shape after removal of the force. The stronger the plastic component, the less the tissue will return to its original shape after removal of the force. **c**, Fluid-like behaviour is seen during development, for example, during collective migration. Viscoplastic and viscoelastic properties are required to generate tissue shapes during morphogenesis. Solid-like behaviour is seen in mature tissues that resist deformation in homeostatic conditions. ECM, extracellular matrix.

junctions, which leads to dynamic shortening and lengthening of cellular junctions, driving neighbour exchange[1,31,32].

Whereas the actomyosin cytoskeleton is a well-established force generator for cell motility and shape changes, the role of microtubules in force generation is less evident. Microtubule-associated molecular motors, such as kinesins, can generate forces to push or pull microtubules[33]. Indeed, the microtubule network has been proposed to be the main force generator in epithelial sheet folding during *Drosophila melanogaster* gastrulation[34]. However, exerting productive forces generally requires mechanical coupling to the cell boundary and, although microtubules grow persistently in the cytoplasm, they commonly transition from growth to shrinkage once reaching the cortex, thus limiting their ability to deform cells[33]. Disruption of the microtubule network increases actomyosin contractility, indicating that dynamic reorganization of the microtubule network can indirectly influence cellular force generation[35–38]. In addition, studies in plants show that microtubules can have dual roles in cell geometry sensing and force generation[39,40].

Microtubules can resist compressive forces and buckle in response to cytoskeletal forces due to their mechanical interactions with the surrounding elastic cytoskeleton[41]. However, microtubule plus-ends are also sensitive to compression-induced catastrophes (that is, a sudden switch from growing to shortening of the microtubule), which limits the load-bearing capacity required for direct mechanical function[42] (Fig. 2). It is thus likely that the load-bearing properties of microtubules are determined by the localization of assembly-promoting factors at sites of mechanical stress[43]. Indeed, studies on *D. melanogaster* cellularization revealed a rapid softening of the blastoderm and an increase of external friction driven by microtubule rearrangements, where a highly connected microtubule meshwork during early cellularization rearranges into a network of only weakly interacting microtubule asters[44], providing an example of how the dynamic properties of microtubules enable dynamic regulation of tissue mechanics.

Intermediate filaments are the least stiff of the three cytoskeleton polymers and can resist tensile forces and shear stress[26]. Owing to their non-polar nature, intermediate filaments are not involved in active force generation but have been shown to help maintain nuclear integrity and regulate cell stiffness[45,46]. Thus, although intermediate filaments have not been directly implicated in tissue mechanical state

transitions, they are likely to have a role, at least indirectly, due to their impact on cell stiffness and deformability (Fig. 2).

Owing to its fluid bilayer of lipids, the plasma membrane is commonly thought of as a passive element in cell mechanics. However, the plasma membrane is increasingly recognized as an integrator of mechanical and chemical signals and is linked to the cytoskeleton to affect cell shape, motility and, therefore, tissue mechanics[47,48]. Studies in the early mouse embryo indicate membrane fluctuations caused by dynamic variability in effective membrane tension (defined both by in-plane tension of the lipid bilayer and membrane attachments to the underlying cortex) in driving cell and tissue fluidity and thereby in the sorting of cell lineages in the blastocyst[49]. Another potentially highly relevant but, to date, still poorly understood aspect is the rheology of the cytoplasm, which can also undergo dynamic rheological changes in response to force and regulate cell stiffness by impacting microtubule dynamics[50–52] (Fig. 2).

The nucleus, as the largest and stiffest organelle in the cell, is also well positioned to determine cell and tissue rheology (Fig. 2). Correlative analyses have revealed that a more elongated nuclear shape coincides with increased fluidity[53]. A recent non-peer-reviewed preprint showed that, in the zebrafish (*Danio rerio*) retina, where the nuclei are large in proportion to overall cell size, an increase in nuclear volume is sufficient to trigger tissue jamming[54]. Interestingly, in this nucleus-triggered jammed state, high nucleus stiffness translated into a stiffer tissue, implicating nuclear stiffness in determining tissue mechanical properties[54]. The nucleus can also generate active stresses in the tissue, especially in the form of interkinetic movement where the nucleus moves apicobasally during the cell cycle[55]. These interkinetic movements have been shown to maintain the high tissue fluidity of the mouse neuroepithelium by promoting fluctuations of the apical cell area[20].

Cell junctions as determinants of tissue mechanics

In a multicellular tissue context, single cells couple cell-intrinsic mechanical properties to other cells or to their extracellular environment in order to transmit mechanical forces across cells. Thus, the mechanical properties of multicellular tissues emerge from the collective physical interactions between their cells. Cells connect to other cells through cell–cell junctions, such as adherens junctions, tight junctions and desmosomes, each tethering to different cytoskeleton structures to couple mechanical forces across cells. Adherens junctions consist of clusters of classical cadherins (E-cadherin, P-cadherin, N-cadherin and VE-cadherin) that are calcium-dependent adhesion molecules with homophilic binding activity. Adherens junctions form cell–cell contacts that connect to the actomyosin cytoskeleton (Fig. 2). Desmosomes mediate cell–cell adhesion through desmosomal cadherins (desmogleins and desmocollins) and anchor the intermediate filament network to the plasma membrane. Tight junctions seal epithelial and endothelial tissues and mediate paracellular permeability and cell polarity[25,56–58]. The role of cadherins in cytoskeletal organization is particularly well studied for E-cadherin. E-cadherin-mediated adhesion results in local remodelling of the actomyosin cytoskeleton at cell–cell contacts, which reduces interfacial tension to stabilize adhesion[59]. Actomyosin contraction-generated cortical tension and cell–cell adhesion represent two fundamental and evolutionarily highly conserved force-generating and force-transmitting cell properties, and the balance between both controls tissue mechanical states and morphogenesis[7,60–63]. In addition, desmosomes have essential roles in tissue mechanics, particularly in organs where mechanical stability is of importance such as the heart and skin[64]. For more details on cell-scale and signalling processes controlled by adhesion, we recommend recent reviews[65,66].

Cells connect to the extracellular environment predominantly through integrins that link the actomyosin network to the ECM[67,68]. Integrins are heterodimeric cell surface receptors expressed on all adherent cells[69] (Fig. 2). Integrins bind to a large variety of ECM proteins, including collagens, fibronectin and laminins[67,70]. The ECM is a fibrous meshwork of connective tissue that serves diverse roles, including providing mechanical resistance to tissue, separating tissue compartments from each other (such as epithelia from mesenchyme), acting as a substrate for cell migration, regulating cell proliferation and survival, controlling stem cell differentiation, and contributing to

Box 1

Mechanosignalling and mechanochemical feedback loops

The coupling of extrinsic forces to cellular force-sensing machineries and the subsequent activation of biochemical signalling molecules and signal propagation is collectively termed mechanosignalling or mechanotransduction[248]. The outcomes of mechanotransduction encompass virtually all biologically relevant aspects of cell behaviour, including cell proliferation, survival, metabolism, cell fate determination, and alteration of cell morphology and migratory properties[248]. Several cellular compartments are involved in mechanotransduction, including the plasma membrane, the cytoskeleton, the nucleus and other organelles. The plasma membrane is a central site for mechanotransduction, where integrin-based cell–matrix adhesions and cadherin-based cell–cell adhesions assemble multiprotein complexes[249]. These adhesion complexes can convert mechanical forces into biochemical signals, including signalling cascades involving phosphorylation, ion fluxes and other second messenger activation[175,249,250]. These cascades are initiated by mechanosensitive molecules, for example, through mechanical unfolding of individual proteins or protein complexes[249]. Additional mechanosensitive pathways include stretch-induced activation of mechanosensitive ion channels such as Piezo1 and Piezo2 (ref. 251).

A mechanochemical feedback loop is essentially a reciprocal interaction between mechanical and biochemical signals[252]. At the molecular scale, this involves the conversion of chemical energy in the form of ATP into mechanical work (such as myosin motor movement) and vice versa (such as stretch-induced ion channel opening). On the scale of tissues, an example of mechanochemical feedback are extracellular regulated kinase (ERK) waves, whose propagation depends on local stresses and tissue rheology but which also trigger corresponding changes in contractility and downstream biochemical signalling cascades that propagate into neighbouring cells[253–255].

Table 1 | Biophysical tools used to measure tissue mechanics

Biophysical tools/ techniques	Description	Properties measured	Current main applications	Advantages	Main limitations
Atomic force microscopy[239]	Indentation probing technique where deflection of a cantilever is used to extract mechanical properties of the biological material indented by the cantilever	Stiffness, adhesion, elasticity, viscosity, tension, compression and shear force	Extracellular matrix stiffness, cell cortex and nucleus stiffness, and cell membrane tension measurements	Can be coupled to mechanical testing or high-resolution imaging; nanoscale spatial resolution	Requires direct contact with the measured material; imposes mechanical stress on sample
Brillouin microscopy[240]	Imaging technique based on light scattering caused by density-induced fluctuations from the material	Elasticity, acoustic velocity and longitudinal modulus	Extracellular matrix stiffness, cell mechanics, including cytoplasm and cytoskeleton rheology	Non-invasive method to measure intact tissues	Complex data analysis and interpretation
Explant or oil droplet shape analysis[241]	Image-based technique that measures the deformation of an explant or oil droplet in response to mechanical stresses such as compression or stretching	Stiffness, elasticity and viscosity	Tissue-scale mechanical properties; developmental biology	Real-time dynamic measurements of tissue mechanical properties	Probes need to be incorporated into the measured structure, which is difficult to achieve for thin tissues such as epithelia; photosensitivity of living tissues
Ferrofluid droplets[242]	Magnetic technique that involves measuring tissue deformations caused by application of a magnetic field following ferrofluid injection	Stiffness, viscosity and elasticity	Tissue-scale mechanical properties; developmental biology	Real-time dynamic measurements of tissue mechanical properties; can be coupled to mechanical testing	Probes need to be incorporated into the measured structure, which is difficult to achieve for thin tissues such as epithelia; photosensitivity of living tissues
Magnetic bead traction force microscopy[243]	Magnetic technique that involves attaching magnetic beads to cells or tissues and measuring the resulting deformation when a magnetic force is applied to it	Stiffness, contractility and viscoelasticity	Cell contractility and adhesion forces	Can be coupled to mechanical testing	Requires measured material to have uniform and well-defined mechanical properties and cells to be able to attach to substrates whose deformation is measured
Micropipette aspiration[244]	Mechanical technique that involves suction of the cell or tissue using a small glass micropipette	Stiffness, adhesion and viscoelasticity	Cell cortex and nucleus stiffness and cell membrane tension measurements	Real-time measurements of living cells; direct access to cell membranes	Requires direct contact with the measured material; imposes mechanical stress on sample; lack of subcellular resolution
Parallel plate compression[245]	Mechanical technique used to measure deformation caused by compressive loading between two parallel plates	Yield strength and compressive and elastic modulus	Cell cortex stiffness	Real-time measurements of living cells	Lack of subcellular resolution; considers measured material to be purely elastic
Laser ablation[246]	Optomechanical technique where high-powered lasers are used to cut cells or tissues and their subsequent 'recoil' response reflects tension across the ablated structure	Relative changes in junctional tension, tissue tension, elasticity and viscosity	Junctional tension in epithelia	Real-time measurements of living tissue	Interpretation is limited by model applied
Optical tweezers[247]	Optomechanical technique where a focused laser beam is used to trap and manipulate microscopic objects such as beads attached to a cell surface or injected inside cells	Stiffness, elasticity and viscoelasticity	Cell cortex and nucleus stiffness; cytoplasmic rheology	Real-time measurements of organelle-scale rheology	Limited trapping range (micrometre scale), constraining its use in larger cells or tissue

tissue deformation[69,71]. In addition to the fibrous connective tissue ECM network, integrins bind components of a specialized ECM known as the basement membrane — a thin, sheet-like ECM primarily composed of laminin and collagen IV that surrounds most tissue compartments and functions to separate them from each other[70,72]. The linkage of integrins to the contractile actomyosin cytoskeleton facilitates force transmission from the ECM into the cell[73]. Importantly, this force transmission is bi-directional, and cell-generated force is also required for

efficient ECM remodelling, altering its material properties[68]. Collectively, adhesion has a central role in tissue mechanical state transitions. However, it has not yet been conclusively demonstrated that changes in adhesion alone are sufficient to facilitate changes in tissue dynamics.

Cellular interactions enable tissue-scale force coupling

Integration of cell-scale forces into patterns of tissue-scale forces is required to generate changes in tissue shape and mechanics. In principle, active mechanical stress in a tissue propagates, causing deformation at a distance; however, the speed and distance of force transmission are influenced not only by friction generated by cell–substrate adhesion but also by the physical state of the tissue. A good example of polarized active cellular forces is the formation of the zebrafish myotome, where local anisotropic stresses, generated by differentiating, slowly elongating muscle cells, co-operate with the plastic-like rheological properties of the tissue to generate the specific v-shaped morphology of the tissue[74]. In many cases, mechanical force propagates in waves that travel over distances that are orders of magnitude larger than the cell size in confined epithelia[75]. These waves require active cellular behaviours, such as contractility, indicating that cells actively respond to external forces to maintain the strength of the mechanical signal as it propagates through the tissue[76–79]. In other scenarios, force generation across cell length scales is more direct, utilizing supracellular actin cables that facilitate the coordinated application of tension at scales from many cells to entire tissues as demonstrated in *D. melanogaster* development, organogenesis and wound healing[80–88].

Important determinants of force propagation and tissue dynamics are the overall levels and turnover rate of adherens junctions, their

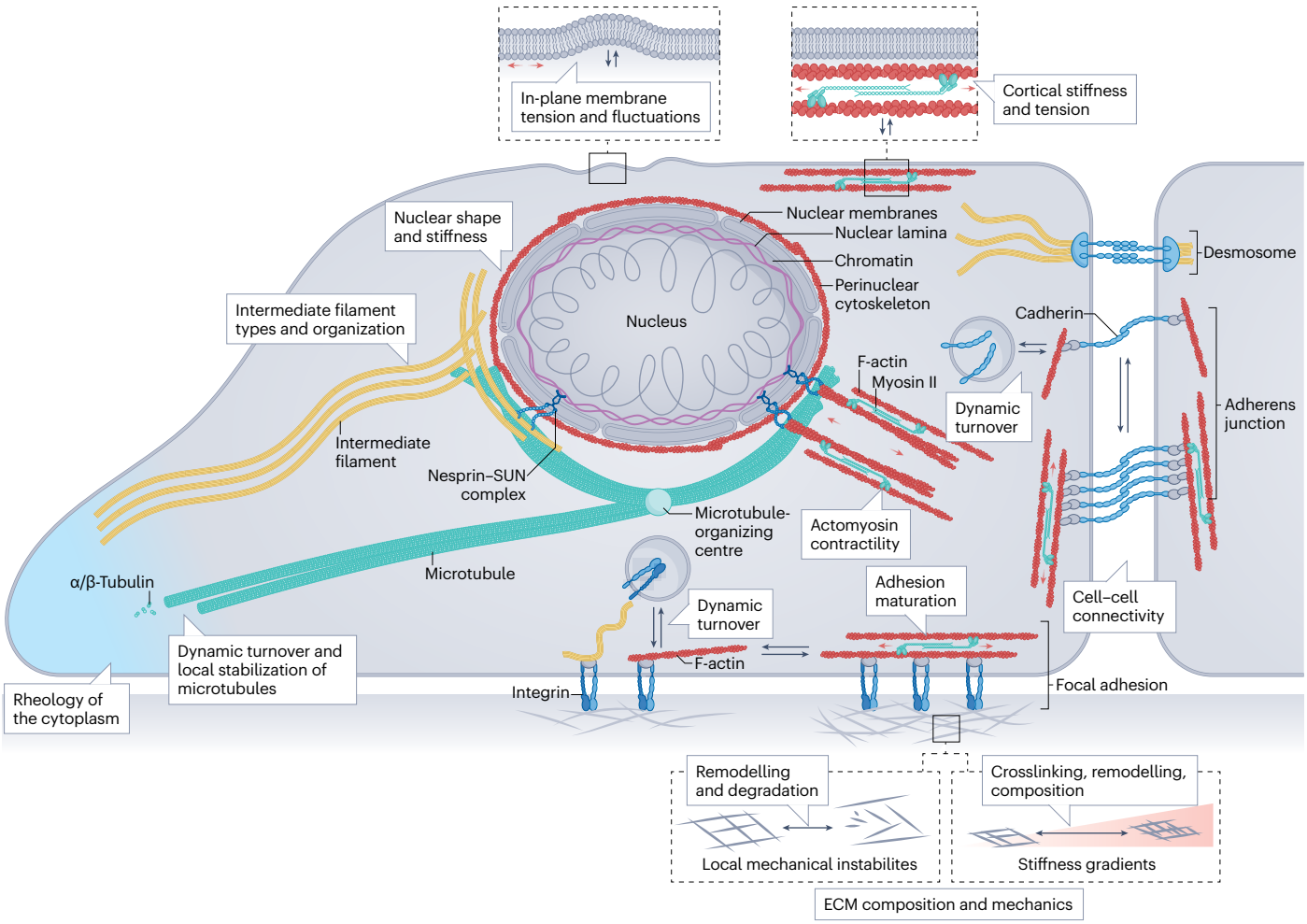

Fig. 2 | Cellular machineries and mechanisms that determine cell and tissue mechanical states. The fluidity of a tissue is influenced by the mechanical properties of the cells within the tissue. These are defined by the contractile actomyosin cytoskeleton that links to cell–matrix (integrin-based adhesions) and cell–cell (cadherin-based adhesions) contacts. Their maturation state and turnover rates contribute to tissue fluidity in addition to the rigidity and composition of the extracellular matrix (ECM). Intermediate filaments and microtubules contribute to the ability of cells to resist compressive loads. This property is regulated by their local dynamics and organization. The rheological properties of the cytoplasm also influence cell mechanics through their effect on microtubule dynamics. Additional important mediators of cell mechanical properties are nuclear shape and stiffness, determined by a combination of chromatin organization, nuclear lamina composition and the structure of the perinuclear cytoskeleton. The sub-plasma membrane actomyosin, regulated by adhesion signalling, provides the strongest contribution to cell cortex tension. Actomyosin cortex tension acts together with plasma membrane tension to propagate membrane tension to regulate cell shape and adhesion. F-actin, filamentous actin.

cluster size and their specific remodelling mechanisms[89]. High levels of tissue fluidity have been associated with low levels of adhesion or increased turnover of adhesion molecules, often promoting cell rearrangements whereas, at low levels of tissue fluidity, cells are less likely to exhibit dynamic changes in and express higher levels of adhesion molecules[5,25]. For example, lowering cadherin levels in a breast cancer model, where cell–matrix adhesions are abundant, increases fluidification and enhances overall migration speed, thus potentially increasing the likelihood of metastasis[90]. Similarly, in an in vitro epithelial model, maturation of cell–cell and cell–matrix adhesions drives a jamming transition independent of cell density[21]. Conversely, mechanical stresses, such as those generated by tissue contractions, have been shown to destabilize E-cadherin complexes and elevate endocytic turnover of E-cadherin in the *D. melanogaster* wing blade to increase tissue fluidity[91]. However, moderately increased cell–cell adhesion results in higher tissue fluidity in the wing disc as it facilitates cell intercalation and rearrangement[24,92]. This notion is supported by theoretical studies suggesting that the levels of adhesions can have non-linear effects on tissue mechanical properties. This is akin to the effects of adhesion on cell migration, where too much adhesion can cause cell contacts to become fixed but too little will also hinder efficient force generation, with both preventing cell rearrangements and tissue fluidization[17] (Fig. 2).

Finally, although the basement membrane provides passive tensile strength and mechanically stable adhesive strength, its dynamic remodelling can alter patterns of force transmission to drive tissue morphogenesis. Several studies indicate that dynamic remodelling of the basement membrane, for example, by generating changes in basal tension or mechanical instabilities such as stiffness gradients, can direct morphogenesis and thus help sculpt the final shape of tissues[93–95] (Fig. 2).

Tissue density, geometry and topology

An emergent property of intracellular and extracellular interactions in tissues is cell geometry and topology (or connectivity), which also affect tissue state transitions. Geometry refers to cell or tissue shape and size, whereas topology refers to tissue organization and cell connectivity. In most biological contexts, cells are organized and confined within specific structures, often referred to as boundary conditions[96]. From the perspective of tissue biology, boundary conditions can be classified into the external constraints that cells encounter such as the tissue size and shape. In vitro, these constraints can be mimicked using microfabrication or micropatterning that limit the dimensions of the structure[97]. A second relevant type of boundary conditions involves interfacial constraints generated by intrinsic factors such as differential adhesion or contractility. An intra-tissue difference between these factors can generate an energy barrier between compartments through interfacial tension and is relevant in processes such as cell sorting[96,98]. Depending on the context, these boundaries may either be static, as is the case for quiescent adult tissues such as the brain, or they may move as new tissue is formed during development. Cell division within fixed boundary conditions, such as in confined epithelial spaces, results in increased cellular crowding, enhancing the likelihood of jamming transitions[7,17,99]. Simulations of self-propelled particle models showed that increased density drives jamming[17]. As density increases, particle–particle interactions grow in number and progressively constrain the range of possible motions. Similarly, in a biological system, each additional cell–cell contact removes one or more degrees of freedom from the system, progressively slowing down motility[17,99,100].

Most tissues are continuous and do not display gaps, and thus contact density is already maximized and not substantially changed even upon increased confluency[17]. Yet, these tissues also display jamming upon confluency. Theoretical work, especially using 2D and 3D vertex models, predicts that cortical contractility, cell–cell adhesion strength and motility are heavily influenced by geometric constraints rather than by changes in adhesion density to determine epithelial rigidity transitions[17,99,100]. In this scenario, where jamming is a tissue-scale phenomenon, it arises from the degrees of freedom of every single cell that becomes constrained in a gradually decreasing space, where movement is limited, for example, by high junctional tension. As the motion of one cell becomes blocked by its neighbours, which in turn are blocked by their neighbours, immobile cell clusters become large enough to span the entire system. As a result, cells can no longer rearrange their position and the tissue becomes frozen and rigid in a process known as rigidity percolation[18,19,101,102]. Thus, although cell divisions, through their ability to increase confluency, can enhance jamming, at the scale of single cells, both cell division and apoptosis (controlled cell death), through their ability to dynamically reorganize junctions and generate mechanical fluctuations, are predicted by theoretical work and demonstrated by experimental studies to trigger fluid-like behaviour[20,102,103].

Theoretical and in vitro studies suggest that increasing tissue-scale curvature promotes epithelial unjamming by favouring cell intercalation and overall mobility[104–107]. However, theory suggests that this relationship is biphasic and, as the epithelial cells expand, the high curvature will halt motion and promote epithelial rigidification[104–107]. In conclusion, tissue mechanical properties are influenced by the dynamics of intracellular and extracellular factors, including cytoskeletal remodelling, membrane mechanics, cell–cell and cell–ECM adhesion, ECM composition, and cell geometry. Although dominated by the above cell-intrinsic and cell-extrinsic factors, tissue mechanics can also be highly responsive to external mechanical forces (Box 2) and biochemical stimuli as well as by the time scales by which these forces act on the tissue, which can change depending on the developmental state of the tissue. During development tissue morphogenesis, patterning and growth involve changes in cell size, shape, position and number whereas, in homeostasis, changes in tissue architecture and size are minimized. Upon injury, cell loss needs to be compensated for and tissue architecture restored. This simple notion implies that, in addition to biochemical signals, patterns of force generation and transmission are different depending on the life stage of the tissue and organism (Fig. 3). The nature and functional role of life stage-specific tissue mechanical transitions will be discussed in the following sections.

Development and morphogenesis

During development, changes in cell size, shape, position and number, either directly or indirectly, involve force generation and propagation that coincide with changes in the mechanical state of the tissue to facilitate the generation of organs and tissues with specialized shapes and functions (Fig. 3a,b).

Early embryonic development

During gastrulation, the embryonic epithelium, facilitated by a cell division-associated reduction in adhesion[79] as well as increased motility[108,109], flows like a fluid in response to active forces generated by actomyosin contractility to form the early embryonic shape. The spreading of the blastoderm in early zebrafish development also requires a rapid and patterned unjamming (or fluidization) in the centre of the

blastoderm tissue, controlled by local Wnt signalling[110]. Although jamming was not directly addressed, studies in the head mesoderm of *Xenopus laevis* showed stiffening in response to increased cell density, which promoted neural crest cell migration[111]. Studies in invertebrates have also shown the roles of jamming–unjamming transitions in distinct developmental stages. In particular, an unjamming transition is required for epithelial gap closure during gastrulation in *Tribolium castaneum*[112] whereas ventral furrow formation in *D. melanogaster* embryos shows a progressive jamming transition as cells become less elongated and less variable in shape[99]. Fluid–solid jamming transitions are also evident during zebrafish body axis elongation as posterior tissues undergo a jamming transition from a fluid-like behaviour at the extending end to a solid-like behaviour in the presomitic mesoderm[22,113].

Tissue mechanics in folding and patterning

During development, many tissues acquire complex shapes through folding. Differential growth between two adherent tissues generates in-plane mechanical stress and instability at this interface. This in-plane stress can be dissipated by bending the tissues[114,115]. An interesting example is the vertebrate gut tube, which has a looped morphology[116]. As shown in chicken, cell proliferation within the gut tube is higher than in the dorsal mesentery it adheres to, creating differential in-plane stress. The gut loops form to relax this stress[117,118], where the final looping pattern depends on tissue-specific mechanical properties and is driven by asymmetric distribution of mechanical motors[119]. Although having comparable growth strains as in chicken, the quail mesentery showed higher tension and a greater elastic force, producing a smaller loop but more loops per tissue length, explaining the scaling of the number of gut loops with organism size[118]. Interestingly, the same principles of an interaction between growth-driven mechanical instability of two adjacent tissues and differential mechanical properties also drive the formation of the microscopic gut patterns, the intestinal villi[120]. Further, similar mechanisms have been proposed for airways, arteries, skin fingerprints and brain fold development indicative of a general mechanism of tissue folding[121–124]. However, it should be noted that the alternative hypothesis of signalling reaction–diffusion patterns (also known as Turing patterns) driving tissue folding cannot be ruled out at this point[125,126]. In this two-component reaction–diffusion model, a signalling activator with low diffusivity promotes its own synthesis and that of an inhibitor with higher diffusivity, which in turn inhibits the activator and itself. This feedback loop is theoretically sufficient to give rise to a periodic tissue pattern[127]. In addition, more recent work on cerebellar brain folding indicates that, although initiation of folding involves faster expansion of the outer layer of proliferating progenitors than the core layer, no stiffness differential between the layers or compressive forces were detected[128]. Instead, the expansion of the outer layer is uniform and fluid-like, and the cerebellum is under radial and circumferential constraints, leading to tissue folding[128,129]. Besides folding, branching can also be driven by tissue mechanical transitions as has been shown for the chick airway, where mechanoresponsive basement membrane thinning coincides with mesenchymal fluidization at branch tips[130] (Fig. 3b).

A diverse set of defined tissue structures, such as the intestinal villi, cartilaginous rings of the trachea, rugae of the palate (tissue folds that are located in the oral cavity palate), skeletal elements of the limb, and feathers, scales or hair follicles, also develop in a periodically patterned manner, requiring coordinated morphogenesis over length scales[131]. Interestingly, these tissue patterns frequently emerge in one specific region and then progressively propagate across the entire tissue[132]. Although progress has been made in understanding the role of active mechanical forces in driving tissue invaginations[133], the role of tissue-scale mechanics in coordinating tissue patterning in animals is less well understood. In the examples of chicken feather bud and mouse hair follicle development, mechanical forces have been proposed to coordinate the patterning process: here, motile mesenchymal cells beneath the epithelium generate periodic foci of high cell density, generating local mechanical deformation[134–136]. At the same time, biochemical signals, orchestrated by morphogens such as Wnts, trigger patterned cell-shape changes and mobility of the epithelium to drive self-organization of the follicle precursors, the placodes[134]. Interestingly, simultaneously with the initiation of hair follicle patterning, the surrounding epidermis undergoes a jamming transition to initiate epidermal cell delaminations and formation of a multi-layered, stratified epithelium[7]. Concomitantly, the hair follicle fluidifies through localized cell divisions, initiating the downward budding[137]. To conclude, tissues can transition from more solid-like to more fluid-like states when dynamic morphology changes are required during active morphogenesis but become more solid-like in fully developed tissues in order to stabilize and fix tissue structures during adult life (Fig. 3), as will be discussed in the next section.

Maintenance of adult tissue

Post development, tissues obtain and maintain a steady state to continue to function optimally throughout adult life. To maintain this steady state, tissues have acquired properties that allow them to 'buffer' extrinsic mechanical forces (Box 2) by stress dissipation or relaxation. The homeostatic properties of a tissue will depend on its function: self-renewing and quiescent organs have different requirements. In self-renewing organs, the maintenance of homeostatic tissue size and architecture can be divided into three main components, (1) regulation of cell division rate, (2) regulation of cell growth rate, and (3) activation of apoptosis, cell extrusion or cell motion[138,139]. The stress

Box 2

Extrinsic mechanical forces in tissues

Cells, tissues and organelles are exposed to various tissue-specific extrinsic mechanical forces, and this exposure has fundamental effects on cell behaviour. These mechanical forces include compression, shear, stretch, fluid flow and hydrostatic pressure. Compression is abundant in tissues that bear extrinsic loads due to body movements, including skin, bones, articular cartilage, muscle and teeth[256]. Shear forces, which occur when adjacent layers of cells or fluid move parallel to each other with different velocities, are abundant in all mechanically active tissues, including skin, cardiovascular system, respiratory and digestive systems as well as synovial joints, tendons and ligaments. Stretch is particularly abundant in the lungs due to breathing as well as in heart muscle, whereas fluid flow is highest in the cardiovascular system[257,258]. Hydrostatic pressure is the pressure exerted by a fluid due to the force of gravity. In the human body, hydrostatic pressure is particularly high within blood vessels, specifically in arteries, as well as in articular cartilage[259].

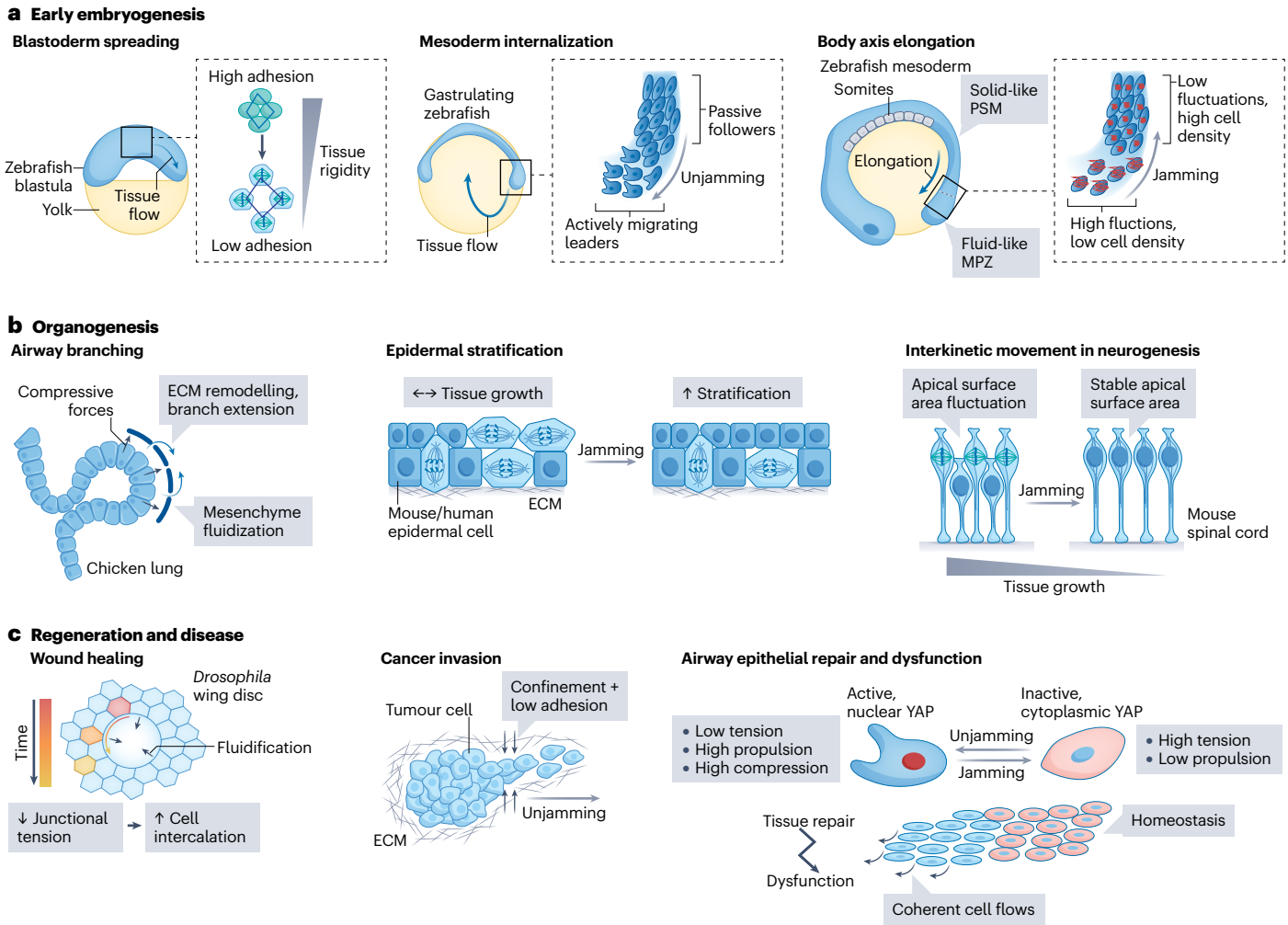

Fig. 3 | Examples of tissue state transitions in development, homeostasis, disease and ageing. a, Fluidization promotes various collective tissue movements during development. In the zebrafish blastoderm, metasynchronous cell divisions lead to decreased cell–cell cohesion and fluidification to promote tissue spreading (shown here for blastoderm spreading)[102]. During gastrulation, a tissue mechanical state transition from a solid-like to a fluid-like state (unjamming) of actively migrating leader cells facilitates mesoderm internalization[108] whereas a jamming transition (change from a fluid-like to a solid-like state) driven by reduced cell-shape fluctuations and increased cell density facilitates efficient body axis elongation[22]. Blue arrows represent the direction of tissue flow or elongation. **b**, During chicken airway branching, the elongating epithelial branch compresses adjacent mesenchymal cells, and this pressure triggers mesenchyme fluidization to facilitate efficient extracellular matrix (ECM) remodelling and airway branching[130]. In the mouse and human epidermis, a jamming transition during embryonic development drives stem cell compartmentalization into the basal layer and stratification of skin layers[7]. Cell division rates during mouse spinal cord development decline over time, and the resulting decrease in interkinetic movements attenuate fluctuations and solidify the tissue[20]. **c**, During wound healing of the *Drosophila melanogaster* wing disc, an increase in intercalation rate increases tissue fluidity and reduces in bulk viscosity. The resultant fluidification of the tissue accelerates wound healing[24]. Genetically reducing junctional tension can further increase intercalation and tissue fluidity to drive fast wound repair. Timescale indicates that a cell initially at the wound edge (pink) will move away from the wound edge via cell intercalation as time progresses (adopting the orange cell position, then the yellow cell position). In cancer, increased confinement and decreased cell–cell adhesion through reduced E-cadherin expression promote fluidification and subsequent invasive behaviour[90]. In vitro studies of the airway epithelium showed that low junctional tension, high cell propulsion and tissue compression, along with high Yes-associated protein (YAP), activity promote fluidification and tissue repair. However, when dysregulated, the same phenomenon can promote aberrant tissue states in asthma and pulmonary fibrosis[23,233,234]. MPZ, mesodermal progenitor zone; PSM, presomitic mesoderm.

dissipation and/or relaxation that is required for maintenance of tissue integrity can involve any of these components. Importantly, a number of mature tissues do not undergo self-renewal and thus engage different mechanisms to dissipate the stresses that they experience. Both of these mechanisms will be discussed in this section.

Relaxation and dissipation of local stresses

Non-uniform growth in a layer of cells that are mechanically integrated through cell–cell adhesion or adhesion to the ECM can lead to stress-induced tissue folding during development. By contrast, in mature tissues, permanent deformation is not a desirable outcome and has not

been observed. This indicates that cells within self-renewing tissues, such as the skin epidermis or the gut epithelium, possess mechanisms that can regulate local cell behaviours to avoid excessive local compression and buckling and that a key property of healthy tissues is to tolerate or react to changes in tissue packing and cell density (Fig. 4).

To preserve tissue integrity as cells divide or die, epithelia can acquire fluid-like properties to enable efficient adhesion remodelling and resolve packing irregularities and defects[92,140,141]. Loss of an adhesive contact between two neighbouring cells results in the emergence of a new four-way vertex. This is resolved in a process called a T1 transition, where a new adhesion interface connects the two cells in this cell quartet that were previously separate from one another[2,142] (Fig. 4a). These processes are well studied during development in processes involving convergent extension to drive tissue elongation[2]. However, studies in a mature, non-dividing tissue that has reached its final homeostatic size, such as in the *D. melanogaster* notum (that is, the dorsal portion of its thorax), show that the rate of neighbour exchanges decline due to an increase in junctional actomyosin[31]. Collectively, these studies indicate that the local variance in tension between junctions determines whether actomyosin-based forces will inhibit or drive the topological transitions that either deform a tissue, such as during development, or refine tissue packing.

In vitro studies have shown that, when subjected to compressive, tensile and shear forces, cells can flatten to dissipate the force over a larger surface area[143,144]. Uniaxial stretching of cell monolayers causes supracellular orientation of cells and polarization of actomyosin in the direction of or perpendicular to the force, depending on the cell type and the arrangement of their ECM. For example, endothelial cells, fibroblasts, mesenchymal stem cells and keratinocytes all orient perpendicular to cyclic stretching on 2D stretchable substrates but many of them orient parallel to stretching in vivo and in 3D culture[144–147]. These differences are likely due to variations in how deformations transverse through the substrates. The combined actomyosin remodelling and re-orientation stiffen the tissue and minimize strain on organelles such as the nucleus, hence buffering mechanical stress[13,143,145–147]. Re-localization or increased production of adhesion proteins through mechanosensitive molecular positive feedback mechanisms allow cells to strongly attach to the ECM and/or to each other[148,149] to resist deformations. Alternatively, tissue stability can be achieved by increasing cellular density[150]. Although tissues have certain elastic properties, they can only resist a certain amount of force (called yield strength), which is dependent on various factors, including the magnitude and duration of the applied force[151]. Beyond its failure point, the tissue can fracture or tear leading to injury. Overall, a combination of factors affects tissue mechanics during tissue homeostasis and their dysregulation can lead to disease and contribute to ageing.

Cell divisions, death and extrusion

Strong adhesion and tension at junctions seem to prevent fluctuations of cell shape and neighbour contact in non-dividing tissues[1,25]. Therefore, barrier tissues, such as skin epidermis or intestinal epithelium, that require tight adhesions and limited neighbour exchange for barrier maintenance but display frequent divisions for tissue self-renewal must use alternative stress dissipation mechanisms. These mechanisms involve the regulation of timing, frequency and position of cell division and death. Importantly, cell death and/or survival are regulated by the mechanical state of the cell and its surrounding tissue: several studies suggest that high hydrostatic pressure and reduction in cell volume or spreading area can trigger caspase activation and cell death[152–154]. For example, restricting the cell adhesion area by micropatterned surfaces or reducing the cell volume to 70% of the original volume using a hypertonic medium are both sufficient to initiate apoptosis in the absence of death ligands[152,154].

Theoretical work suggests that cell division and apoptosis trigger a reorganization of elastic tissues that leads to liquid-like behaviour characterized by dynamic cell rearrangements[103,155]. When such simulated tissue reaches a homeostatic state, cell divisions and apoptosis become balanced, and stress relaxation is driven by cell rearrangements that prevent build-up of compression[103]. Notably, this work further suggests that imposing extrinsic pressure onto the cells leads either to the complete disappearance of the tissue through apoptosis in case of pressure higher than in the homeostatic state or, on the contrary, to a complete invasion of tissue space by dividing cells in case of low extrinsic pressure[103]. This indicates that increased pressure promotes mechanical cell competition, where cells physically compete for a finite amount of space, resulting in the build-up of compression force and elimination

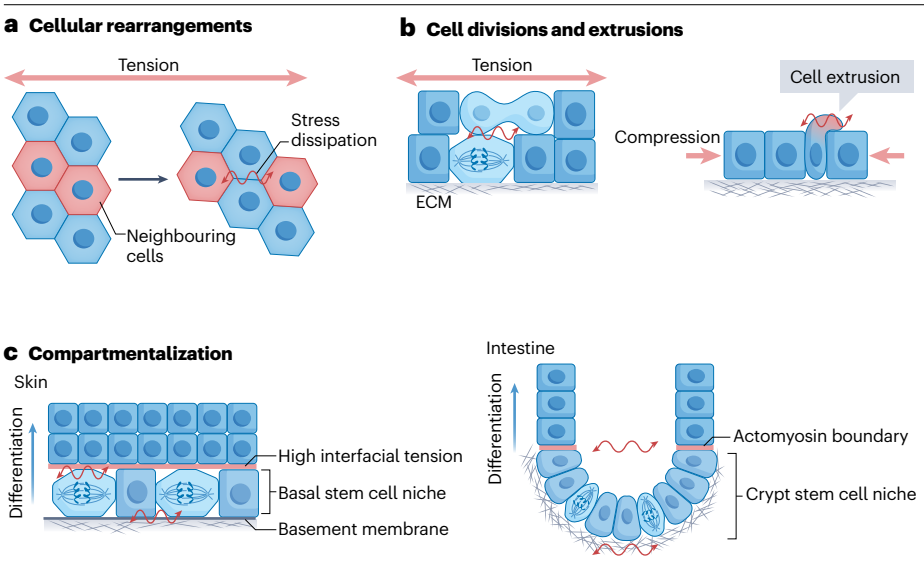

Fig. 4 | Strategies for dissipating mechanical stress and fluctuations at the tissue scale. a, A fluid-like tissue state with low junctional tension enables exchanges of neighbouring cells, which dissipates mechanical stress in epithelia. **b**, Various epithelia use cell divisions that are oriented in the direction of tissue strain, cell extrusions and/or delaminations in response to crowding or compressive stresses to counteract tissue tension generated, for example, by local tissue growth. **c**, In a homeostatic tissue, separation of proliferative activities through tissue compartmentalization and generation of specialized extracellular matrix (ECM) environments, exemplified by stem cell niches, allows insulation of mechanical fluctuations. These fluctuations arise, for example, from local cell divisions of stem cells surrounded by non-dividing tissue.

Glossary

Blastocyst
A fluid-filled sphere of cells that forms during the first 5–9 days of mammalian embryonic development and generates all embryonic and extra-embryonic tissues.

Blastoderm
The single layer of embryonic epithelial tissue that makes up the blastula, the early embryonic stage characterized by a hollow, spherical structure, with a fluid-filled cavity called the blastocoel.

Cell extrusion
This term describes the controlled elimination or removal of cells from an epithelium while maintaining epithelial barrier integrity.

Cortical tension
This describes the sustained contraction of the cortical cytoskeleton. It is largely but not exclusively based on actomyosin contraction and depends on the density of the cortex as well as on its structure and composition.

Emergent properties
New property or behaviour of a system that results from the combination of or interaction between two or more different components or processes, none of which displayed the behaviour individually.

Friction
A force that resists motion when the surface of one object (such as a cell) comes into contact with the surface of another object (for example, a cell or extracellular matrix). In cells, this force is typically generated by adhesion molecules.

Interfacial tension
The tension at the boundary between two objects such as a junctional interface between two cells.

Presomitic mesoderm
This is a region of the embryo also known as paraxial or somitic mesoderm that flanks the neural tube and gives rise to somites.

Shear stress
A stress that is applied parallel or tangential to the surface of a material, as opposed to stress that is applied perpendicularly.

Tensile forces
A force that has two components — tensile stress and tensile strain — that act on a material to stretch it while it is under tension.

Ventral furrow
This is an invagination generated by the first large-scale morphogenetic movement in the *Drosophila melanogaster* embryo, where the morphogenetic movement transforms a single layer of columnar epithelial cells into a multi-layered structure by triggering internalization of the most ventrally positioned cells of the embryonic epithelium.

Vertex models
A type of statistical mechanics model used to model the behaviour of adherent cell collectives, mostly epithelia. In vertex models, cell shape is represented by a set of vertices that mark the common point of three or more neighbouring cells and on which forces from within cells and in between cells act. These models can be two-dimensional or three-dimensional.

Wetting force
An adhesive force between a liquid and a solid, resulting from intermolecular interactions between the two and keeping the surfaces of both materials in contact with each other.

Yield strength
The stress at which a material ceases elastic deformation and undergoes plastic, permanent deformation.

of the physically 'weaker' cells. This is consistent with another theoretical study that proposes that differential growth could lead to the accumulation of mechanical stress in epithelial tissues. Faster dividing cells will push on their neighbours, leading to a local increase in pressure[156]. This theory further predicts that, if the fast-growing population is also less sensitive to pressure than the neighbouring cells, slow-proliferating cells will be eliminated.

Indeed, reducing tissue growth inhibits cell extrusion in the *D. melanogaster* notum, whereas increasing tissue growth enhances extrusion[6]. Cell extrusion also happens in regions where cells converge at high density such as in zebrafish fins[157]. Further, it has been experimentally demonstrated that cellular crowding due to excessive proliferation can lead to a solid-like state of the tissue, especially in the presence of strong cell–cell adhesions[21,158], and that this crowding promotes cell delamination or live cell extrusion[6,7,157]. Collectively, these studies suggest that, in mechanically homogeneous tissues, stresses generate pressure that leads to cell competition and extrusion whereas, in tissues with mechanical heterogeneity, stress is dissipated through cell movements and rearrangements. These observations emphasize the role of tissue rheology in dictating the response of the tissue to both external and internal forces with potentially profound implications for how disruption of homeostatic tissue architecture in disease might influence cell behaviour.

Mechanical insulation of tissue compartments

A general feature of most tissues is their distinct organization into cellular compartments of different cell states and behaviours. The interfaces between two tissue compartments, called compartment boundaries, often maintain clear separation of cell states and behaviours such as proliferation rate, with stem cell niches providing a useful example. In 1963, Steinberg suggested that the maintenance of compartment boundaries is based on differential cell adhesion[159,160] whereas more recent in vivo work proposed that cell segregation is rather governed by differential interfacial tension at the boundary[98,161,162].

Given the differential mechanical properties of the compartments due to differences in cell lineage or behaviour, stresses are non-homogeneously distributed. In the rapidly growing trichome cells of *Arabidopsis thaliana*, the proliferating cells are capable of distorting organ shape. Here, the cortical microtubule alignment in adjacent cells along the growth-derived maximal tensile stress axis mechanically isolates the trichome cells and thereby limits their impact on overall organ shape[163]. Whereas direct experimental access to forces is difficult in intact mammalian tissues, in vitro systems, such as organoids, have provided interesting insights into the relationship between tissue-scale forces, stresses and compartmentalization. In flattened intestinal organoids, mechanical compartmentalization of the stem cells enables niche folding and physically separates stem cells from differentiated cells[164]. Furthermore, rather than being pushed out of the niche by proliferative pressure, differentiating stem cells are being 'pulled out' by tension generated by migrating differentiated cells[165]. The niche curvature is further defined by substrate rigidity[164]. Although definitive experimental evidence for the role of mechanical compartmentalization of the in vivo crypt is lacking, it is still interesting to note that establishment of the mature adult stem cell population

in the mouse coincides with establishment of the crypt structure and formation of a mechanical boundary between stem cells and differentiated progeny[166,167]. Similarly, in the mouse epidermis, proliferation is restricted to the stem cells that become compartmentalized into the basal layer[168]. Only the stem cells retain direct contact with the basement membrane (Fig. 4c). This adhesive boundary separates the epithelial skin compartment from the underlying dermal compartment but also generates a negative-tension 'wetting force' that retains stem cells in their basal position[169]. In vitro studies indicate that cell cycle-driven fluctuations and junctional tension serve as a key source of active stress within this epithelial stem cell monolayer[170]. These studies further show that the cell density-induced jamming transition triggers the delamination and/or extrusion of differentiating stem cells from the basal to the suprabasal cell layers[170]. These findings suggest that the compartmentalization of epithelial tissues arises from a critical interplay between two mechanical variables — stresses from cell cycle dynamics and stresses from substrate rigidity that regulate the mechanical state and/or curvature of the tissue (Fig. 4).

The role of the ECM and the basement membrane

As highlighted above, an important component of stress insulation is the ECM, and a highly organized ECM supports the tissue architecture. The basement membrane in particular provides the mechanical stress insulation that is crucial for the functional integrity of tissues. Interestingly, pressure-controlled inflation and/or deflation to measure the stress–strain behaviours of an intact basement membrane have shown that it exhibits a highly non-linear elasticity with a strong strain stiffening effect, that is, an increase in stiffness upon reaching a certain deformation threshold[171]. This non-linear stiffening behaviour of the basement membrane is essential for maintaining the integrity of tissues during homeostasis by providing the necessary confining stress[171]. Stem cell niches frequently have a unique basement membrane composition and are softer than the surrounding differentiated tissue[172,173] (Fig. 4c). Although the role of basement membrane mechanics has frequently been attributed to rigidity sensing through mechanisms such as Yes-associated protein (YAP) signalling[174–177], the role of ECM viscosity and viscoelastic properties in these systems remains largely unexplored. In fact, recent work suggests that cell responses to substrate energy dissipation, as defined by YAP activity, outweigh rigidity sensing[178]. Thus, the role of the energy-dissipating properties of stem cell niche-surrounding ECM in tissue function remains an intriguing open question.

Repair and regeneration

The reparative and regenerative capabilities of tissues are critical for adult life. Extreme extrinsic insults, such as physical injury, can alter tissue mechanics to trigger and facilitate repair and compensatory growth to restore already fully developed tissue. Tissue mechanical transitions during wound repair are crucial in changing the mechanical properties of cells in the vicinity of the wound to close the gap[179,180]. Contraction and tension around the wound help pull wound edges closer until the gap is closed, but excessive tension can lead to scarring and over-healing, resulting in cellular overgrowths at the wound site[181,182]. Conversely, increased tissue fluidity allows cells to intercalate from the wound edge to facilitate cellular remodelling and promote more efficient wound closure[24] as observed in the *D. melanogaster* wing disc (Fig. 3c, left). Hence, a delicate spatial and temporal control of tissue mechanical state transitions is needed for efficient repair.

A damaged tissue can be restored through one of two distinct processes: regeneration or repair. The occurrence of each process is determined by various factors. Regeneration is the replacement of damaged tissue through the proliferation and differentiation of tissue-specific stem cells. This process is commonly observed during prenatal life and postnatally in only some organisms like amphibians and some invertebrates. Most organisms have limited or no regenerative ability in adulthood[183]. By contrast, tissue repair occurs during milder tissue damage and aims to restore tissue integrity and continuity[184]. The wound-healing phases in regenerative organisms, such as zebrafish and some amphibians, are inherently different from wound healing in non-regenerative organisms such as mammals. Some key differences include re-epithelialization rate and ECM composition and deposition[183], which may lead to differences in tissue mechanics driving different rates of wound closure.

Cell migration is a common mechanism for wound closure across various species, but different cytoskeletal rearrangements may explain why re-epithelialization in mammals occurs via different modes of proliferation, contraction and migration, compared to, for example, zebrafish[185–187]. Consistent with the different modes of re-epithelialization, wound closure rate is considerably slower in mammals. For example, zebrafish skin can close wounds at a rate of 250–500 μm h^{-1} (refs. 188,189), whereas the rate in human skin is only 100 μm h^{-1} (ref. 190). Rapid re-epithelialization, a reduced immune response and differences in ECM remodelling are all key characteristics observed in regenerative organisms such as *X. laevis*[191,192]. These key differences suggest that regenerative organisms are in a more fluid mechanical state than non-regenerative organisms. However, tissue fluidity may result in increased inflammation, caused by an influx of inflammatory cells, and delayed wound closure[193]. Therefore, for optimal wound healing, there needs to be precise regulation of tissue mechanical transitions in conjunction with regulation of inflammation.

Fundamental to re-epithelialization, two types of behaviour are typically observed from wound-edge epithelial cells: cell crawling and purse-string contraction. Cell crawling is characterized by protrusion extensions towards the centre of the wound to close it[194]. These protrusions are driven by the actin cytoskeleton, which provides both structural support and contractile forces[195,196]. Purse-string contraction involves the formation and contraction of a supracellular actomyosin cable around the wound edge, particularly in concave regions of a wound[85,197,198].

Often in parallel with re-epithelialization, a proliferative phase of wound healing repopulates cells within the damaged tissue and forms a new, disorganized provisional ECM network (fibrogenesis)[199]. The primary cells involved in fibrogenesis are fibroblasts, which secrete ECM proteins, such as collagen and fibronectin, to increase tissue stiffness[194]. As cells can undergo durotaxis, that is, migrate up stiffness gradients, this local increase in wound stiffness could provide a mechanism for cell migration towards the stiff wound site[200] and provides better traction forces for migration than soft substrates[201,202]. During the final repair phase, proteolytic enzymes remodel the disorganized ECM into an ECM that more closely resembles the pre-injury state, thus restoring the normal tissue mechanical state[199].

Ageing and disease

Ageing is associated with changes in the mechanical properties of tissues, such as reduced elasticity, leading to altered mechanotransduction and mechanosensitivity, which compromises tissue form and function (one example being a decline in repair capacity)[203]. In addition, diseases such as cancer or fibrosis, which are sometimes the consequences of chronic wounds, can reactivate embryonic-like

programmes and mechanical states by disrupting compartment boundaries to facilitate uncontrolled growth and formation of new, abnormal tissue structures and/or deposition of new ECM.

Decline in repair capacity

Tissue mechanical changes during wound healing can be influenced by age. Injuries acquired during prenatal life and postnatal life repair with different dynamics[204]. These changes correlate with differences in the ECM composition in prenatal and postnatal wounds. During prenatal development, the fetus can heal wounds efficiently. Fetal ECM has been shown to have higher levels of hyaluronic acid, higher matrix metalloproteinase (MMP) activity and a greater ratio of type III to type I collagen[205]. These properties of the ECM can all contribute to a more flexible, less stiff and more fluid wound[206]. As ageing progresses, ECM turnover decreases and ECM stiffness increases[19], which can reduce cell intercalation and migration during wound healing. Studies have shown that older individuals often heal wounds more slowly, resulting in an increased risk of chronic wounds[194]. Age-related alterations in tissue mechanics, including augmented ECM stiffness and diminished tissue fluidity, may contribute to this phenomenon in multiple tissue types[207–210].

Ageing-associated tissue stiffening impacts regeneration and repair also by reducing the proliferation capacity of tissue-resident stem cells. In the skin, stiffening of the ECM attenuates the ability of hair follicle stem cells to become activated and to initiate regeneration of the hair through force-mediated effects on chromatin and gene silencing[208,209]. Stiffening of the ECM is also observed in the brain, which attenuates the regenerative capacity of oligodendrocyte progenitor cells[211] (Fig. 3c).

Transition from repair into disease

The consequence of a 'non-healing wound', which can be exacerbated by ageing, is often the transition into diseased states such as fibrosis and cancer. Further implicating tissue mechanics as a driver of healing outcomes, acute and chronic wounds exhibit different mechanical properties, reflected by their distinct pathophysiology. Acute injuries are characterized by a rapid and robust immune response, which efficiently clears debris and infection and results in resolution of the wound. However, when the injury fails to resolve properly, it persists and becomes chronic[212]. Chronic wounds are often characterized by changes in the ECM, such as increased stiffness through altered MMP activity or excessive ECM deposition (also known as fibrosis)[213]. The precise balance between matrix synthesis and degradation is important to avoid prolonged inflammation and excessive turnover and synthesis of the ECM, which can contribute to fibrosis and cancer progression[214].

Beyond wound repair, fibrosis is a hallmark of many chronic diseases such as liver cirrhosis, multiple cancers and pulmonary diseases[215,216]. Liver cirrhosis is a chronic and progressive disease that can be caused by various factors, both genetic and environmental, including long-term alcohol abuse, hepatitis B or C infections, non-alcoholic fatty liver disease, and autoimmune diseases[217]. Such factors cause an accumulation of ECM proteins in the liver that leads to increased tissue stiffness, also known as liver fibrosis[218]. As liver fibrosis progresses, the tissue becomes more rigid and less flexible as the collagen networks become disorganized and more densely packed. This can lead to liver failure and increased risk of liver cancer development[217,219].

It has also been shown that continuous ECM production and tissue stiffening are linked to the development of mutations and genetic alterations that can increase the risk of cancer, for example, by altering integrin signalling[220–222]. Increased tissue stiffness is often a defining characteristic of solid tumours[215,223]. In many cancers, the activation of stromal cells, such as cancer-associated fibroblasts, causes excessive production of ECM components, leading to fibrosis[224] and stiffening of the tissue. As the ECM becomes stiffer and denser, it limits normal cell mobility but promotes tumour growth and invasion, for example, by inducing epithelial–mesenchymal transition in cancer cells[225], by increasing the viscosity of malignant cells[223] to enable them to more easily squeeze through tighter spaces[226], or by triggering confinement and compression to promote unjamming and invasion[90] (Fig. 3c, middle). Additionally, cancer cells and cancer-associated fibroblasts can enzymatically or physically (by pulling and stretching) remodel the ECM to facilitate cancer cell migration from the primary tumour site and cause metastasis[227–229].

Oncogenic mutations, such as Ras^{V12}, are also known to stiffen cancer cells via downstream MEK–ERK signalling, particularly during mitotic rounding, enabling the cells to round up and divide in crowded environments[230]. However, collectively, cancer cells can also display tissue-scale fluidization and expansion. For example, activation of Ras GTPase or of Ras-related protein Rab5A in cancer cells can remodel the actomyosin network, which changes cell rheology and promotes tissue deformations and the flow and spread of malignant cells[231,232].

In the lung, mechanical transitions are often associated with the progression and pathophysiology of several respiratory diseases such as asthma[23] and chronic obstructive pulmonary disease. Airway epithelial cells can undergo a solid–fluid (unjamming) transition upon a compression force or injury (Fig. 3c, right), which may aid repair as the cells move into new positions relative to their neighbours until they jam again into a new solid-like state[233,234]. However, in cells from patients with asthma, the unjamming–jamming transition is delayed significantly, which may hinder repair[23]. In patients with chronic obstructive pulmonary disease, tissue unjamming-associated ECM remodelling occurs due upregulation of proteases that degrade its components resulting in reduced tissue elasticity following repair and remodelling[235].

Overall, it is becoming clear that tissue mechanical transitions are often drivers of disease progression and, as such, prevention of such mechanical transitions may provide solutions to delay, or indeed prevent, these pathologies.

Conclusions and perspectives

Despite the complexity of functional and mechanical transitions throughout development and adult homeostasis, organisms can consistently and robustly grow and develop into their correct size and morphology and, in most cases, are able to buffer the daily chemical and mechanical insults from their environments during adult homeostasis. How is such robustness achieved? The cellular processes discussed in this Review that regulate tissue mechanical states and their transitions are, in fact, highly noisy and stochastic. For example, it is still challenging to deterministically predict the exact 2D or 3D shape of a cell or the exact topology, geometry, and contractile patterns of any epithelium[236] or when and where cells will divide or die[237]. To add to this intrinsic stochasticity, tissues are not mechanically isolated entities but are subjected to constant fluctuations from their extrinsic environment, whether from the movement of the fetus or mother in development[238], or the variable contractions of the lung and heart in the adult animal. Yet, at the emergent tissue level, such 'mechanical noise' is seamlessly buffered and the control of the system is almost perfect.

To understand how such robustness is achieved, better tools are required for faster in vivo imaging, especially in moving organisms such

as a swimming fish or a crawling worm. We must also vastly increase the resolution and throughput of our microscopy image analysis by using artificial intelligence and machine learning approaches to quantify variations in nature and across whole populations of animals or plants. Importantly, we still do not understand precisely how the macroscopic rheological properties (viscosity and tension) of a tissue are derived from molecular-level regulation. Bridging the scales from molecule to cell and tissue would require improved in vivo force sensors that can track and quantify stresses throughout the life of an organism to characterize regimes of mechanical stresses experienced by such. We can then integrate the data with stochastic dynamic models of cell and tissue morphogenesis, specifically in 3D, to fully investigate system stability and control across the relevant scales. Hence, a fully quantitative insight into this mechanochemical control network is essential for our future understanding of developmental robustness and steady-state tissue maintenance, especially as we live longer and are hence more susceptible to pathological changes associated with ageing and disease.

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