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Mechanoreciprocity in cell migration

Sjoerd van Helvert[1], **Cornelis Storm**[2], and **Peter Friedl**[1,3,4]

[1]Department of Cell Biology, Radboud Institute for Molecular Life Sciences, Radboud university medical center, Geert Grooteplein 28, 6525 GA Nijmegen, The Netherlands [2]Department of Applied Physics and Institute for Complex Molecular Systems, Eindhoven University of Technology, Groene Loper 5, 5612 AE, Eindhoven, The Netherlands [3]David H. Koch Center for Applied Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston 77070, Texas, USA [4]Cancer Genomics Center, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands

Abstract

Cell migration is an adaptive process which depends on and responds to physical and molecular triggers. Moving cells sense and respond to tissue mechanics and induce transient or permanent tissue modifications, including extracellular matrix stiffening, compression and deformation, protein unfolding, proteolytic remodelling and jamming transitions. Here we discuss how the mechanoreciprocity of cell-tissue interactions allows cells to change position, and to define single-cell and collective movement, structural and molecular tissue organization, and cell fate decisions.

Introduction

Most cells in multicellular organisms are able to move during defined phases of tissue formation, maintenance, regeneration and immune defence, but also during diseases such as chronic inflammation and cancer[1,2,3]. To exert force for movement, cells interact with tissue structures such as the extracellular matrix (ECM) and other cells. The molecular organization and function of these interactions are adaptive, and vary between cell types and tissues. Although commonly studied as separate biophysical domains, ECM and cell functions are strictly interdependent and coevolve in all tissues. The resulting bi-directional crosstalk, termed dynamic reciprocity[4,5] results in a gradual evolution of both the cell and the tissue through which it migrates[6].

Well-defined in vitro models allow direct probing of isolated physicochemical parameters of cell migration, including the role of dimension, ECM stiffness, confinement and barrier function by the tissue, and their consequences for individual or collective cell migration[7]. In vivo models, such as Drosophila and zebrafish embryos and adult mice allow cross-referencing of those ECM aspects that influence cell migration in physiological and disease contexts[8]. These approaches have revealed that cells and engaged tissue can be regarded as multi-component viscoelastic units, subject to reciprocal mechanochemical interactions that

Correspondence should be addressed to PF (peter.friedl@radboudumc.nl).

induce, guide or limit cell migration in a context-dependent manner[2,3,7]. These relationships between the cell and its ECM context are inherently bi-directional, and aptly described by the term 'mechanoreciprocity'[9]. We here review the force-responsive elements involved in cell-ECM interactions in the context of cell migration, summarizing the fundamental physical and molecular properties of tissues and cells that determine cell-tissue interaction and migration and we develop a framework for direct and indirect mechanoreciprocity between migrating cells and their extracellular environment. As an emerging concept, mechanoreciprocity controls the migration mode, the ECM remodelling responses and the outcomes for assembling and remodelling tissue structures.

Mechanical properties of ECM

Cells respond to tissue organization and mechanics at subcellular[10], cellular[11] and multicellular[12] scales through interactions between the plasma membrane and the substrate This process, called mechanotransduction, involves different structural and functional parameters, here termed 'modules'. The mechanical modules of tissues are determined by their constituent materials. Physical modules of tissues that jointly influence cell migration include ECM stiffness, confinement and topology (reviewed in[2]). Modules evolve and vary with cell type, tissue context and cell activation state. They depend on their spatial ECM arrangement, degree of crosslinking and other chemical modifications, as well as hydration state and stresses induced by cells or extracorporeal forces, as discussed in more detail below. Additional mechanical modules controlling cell migration include tissue porosity and nanotopology (Box 1).

Material stiffness measures the amount of force required to induce a change in length. Technically, stiffness is not the same as the elastic modulus; it is common practice in tissue- and cell mechanics to use the terms interchangeably, and we here refer to both as stiffness. Stiffness depends on the composition, architecture and momentary forces acting upon the tissue. When analysed at micrometre scale, tissue stiffness varies from soft and deformable, such as brain or provisional ECM, to very stiff and non-deformable like in bundled collagen or bone (Fig. 1a). At micro- and nanoscales, ECM mechanics vary even more; single collagen fibres are multi-fold stiffer than fibrillar collagen networks[13]. Cells can sense substrate stiffness in the range from 0.1 to at least 25 kPa[14] through integrin adhesion receptors[15], and respond to stiffer substrate with preferential protrusion and alignment parallel to the substrate. Notably, this stiffness response is well established for fibroblasts and epithelial cells, but may vary for other cell types. This interaction between cellular and substrate mechanical modules is a principal component of the reciprocal relation between cell and matrix.

The structural organisation of the ECM influences cell behaviour at different levels. ECM comprises both randomly and oriented, fibrillar or sheet-like protein polymer networks. Fibrillar networks provide both space (pores) and anchorage sites (fibrils) for moving cells, and typically pervade tissue designed to support moving cells[16,17] (Fig. 1b). Tissues with highly demanding mechanical functions, such as tendons and bones, are often highly ordered, as are the collagen-rich tissues of scars and deposits resulting from chronic inflammation or fibrosis[18,19]. Sheet-like interfaces composed of a basement membrane

adjacent to interstitial connective tissue provide linear-configured shape and efficient guidance for moving cells[20,21]. Cells rapidly sense and respond to these structural modules at different dimensionalities: interactions with ECM in interstitial tissues occur in three dimensions (3D), with simultaneous interaction to two-dimensional (2D) structured basement membranes (Fig. 1b), and sparse collagen fibrils sensed as one-dimensional (1D) substrate. These dimensions likely coexist in 3D tissues and jointly determine other mechanical tissue properties, including porosity and nanotopology, and their responses to external pressure and changes in hydration (Box 1)[21–23].

By interpreting ECM stiffness, order and porosity, migrating cells adapt their own mechanochemical repertoire of mechanically integrated cell functions, including adhesion, traction, protrusion, deformation and directional persistence. In addition to transient alterations of ECM modules through cell migration, permanent ECM remodelling takes place by enzymatic tissue remodelling (Fig. 1d). At the cellular level of integrating these cell modules, the actin cytoskeleton defines adhesion strength and cell shape to generate pulling or pushing force and induce tissue remodelling and different migration modes (Fig. 2a, b). At the molecular level, integration is mediated by mechanically responsive proteins which can unfold when pulled, and develop mechanically adhesive or signalling functions in response to tension[24]. Both levels of adaptive responses are discussed in more detail below.

Cellular responses and mechanotransduction

By combining pushing and pulling, cells can adapt their shape and exhibit complex mechanocoupling responses to achieve migration (Fig. 2b). The actin cytoskeleton mediates both pushing and pulling. Polymerizing actin filaments push and protrude the membrane, under the control of Rho GTPases[25,26], whereas pulling depends upon myosin motors which crosslink, bundle and contract actin filaments under the control of Rho-associated protein kinase (ROCK)[27], transmitting force to the substrate[28,29]. Adaptor proteins play an important role in this context by connecting actin filaments towards extracellular structures, transmitting both signals and force: talin links actin filaments to focal adhesions and podosomes[30], ezrin/radixin/moesin (ERM) proteins connects to the plasma membrane[31]; nesprins engage with the nuclear membrane[32], and α-catenin and afadin bind adherens junctions[33]. Adaptor protein functions are dynamic, transient and contribute to pulling[1,13], and further cooperate with intermediate filaments and microtubules. Moreover, adaptor proteins mediate a direct structural and mechanical interaction between cell and matrix.

Actin-based force transmission occurs at adhesion sites, mediated by integrin adhesion receptors[13,34]. Molecular bridges, provided predominantly by talin and vinculin[34], transiently connect actin filaments with integrins and function as a ‘molecular clutch’, which translates retrograde actin flow into traction force towards the substrate[35] (Fig. 2c). Strong forces result from longer-lasting actin-rich focal adhesions connected to bundled and contractile actin filaments[36], and low forces are transmitted by small integrin foci or diffusely organized integrin contacts[13]. Adhesion maturation and regulation of traction force in mesenchymal cells depends on myosin II motors contracting actin filaments[37], and involves talin[28,38] and filamin-A linking integrins to actin[39].

As a consequence of such plasticity of actin dynamics and adhesion regulation, actin networks and adhesion sites can respond to substrate geometry and stiffness. ECM geometry can guide actin orientation and cell alignment[40]: adhesion sites and actin nucleation preferentially grow along substrate edges[13,36,41]. At low substrate stiffness, cell adhesions are labile with cortical actin diffusely distributed[13,28,42,43], but at higher substrate stiffness, adhesion strength increases, the actin cytoskeleton develops bundled and aligned filaments which contract and generate higher force[42,43]. For efficient migration, cells locally form and resolve adhesions, adjusting their degree of adhesion to the amount of available ligand and substrate stiffness[13,24]. In parallel, non-integrin adhesion systems, such as cell-surface heparan sulfate proteoglycans (HSPGs such as CD44v3, syndecans, glypicans and betaglycan) engage with fibrillar protein networks, provide additional, weaker adhesions and thereby co-regulate focal adhesion strength and cytoskeletal organization[44]. In addition to cell-matrix adhesion, adhesive coupling to neighbouring cells is achieved by cadherin-mediated adhesions, which connect to the actin cytoskeleton and allow stress distribution through cells, and sustain a force of approximately 100 nN perpendicular to the cell surface[45]. Importantly, besides regulating cell-ECM and cell-cell interactions, the actin cytoskeleton anchors the nucleus and co-regulates cell shape, volume and membrane tension.

The nucleus, the largest and stiffest organelle[46], is mechanically linked to cytoskeletal filaments which determine its shape and position[47], protecting nuclear content from mechanical assault. The shape and stability of the nucleus is provided by nuclear lamins, which stabilize the nuclear envelope,form a 3D network inside the nucleus[46] and connect to all three cytoskeletal networks (Fig. 2d, 1). The stiffness of the nucleus ranges from 0.1 to 10 kPa[48]; this stiffness range is cell-type dependent and regulated by expression levels and assembly state of lamin A[48]. There is a direct link between nuclear mechanics and cell migration: reducing lamin A expression increases nuclear deformability (Fig. 2d, 2) and permits migration through smaller pores, whereas increased lamin A levels limit cell deformation and migration speed in 3D environments[49,50] and protect the DNA from mechanical damage[49,51].

There is also an interplay between the cell membrane and cytoskeletal dynamics in the migrating cell. Cytoskeletal polymerisation or hydrostatic pressure (discussed below) pushes the cell membrane outwards, leading to membrane deformation and increased tension (Fig. 2e)[25]. Membrane tension is defined as the surface free energy per unit area, and is measured by determining the force required to displace a membrane-bound bead with optical tweezers[52]. Values range between 0.2-1.6 mN/m in single cells[53]. Membrane tension further depends upon the net amount of membrane at the cell surface (Fig. 2e). Consequently, extension-retraction cycles in migrating cells cause and depend upon cell surface- and membrane tension regulation, and membrane tension, in turn, regulates the speed of actin polymerization by acting as a physical barrier. In protruding lamellipods, membrane of high tension is pushed by a dense actin network with filaments growing at steep angles, whereas the actin network at lower membrane tension has a lower density and contains more filaments oriented perpendicularly to the membrane[54]. In migrating neutrophils, increasing membrane tension impedes actin nucleation[25] through phospholipase D2 (PLD2) and mammalian target of rapamycin complex 2 (mTORC2) signalling[55]. Conversely, low

membrane tension triggers actin assembly, and enhances cell spreading and polarization[56]. As a consequence, any shape change during migration imposes fluctuations in membrane tension which, in turn, regulate actin networks and motility.

During cell shape change and migration, cells regulate their internal hydrostatic pressure through contraction of the actomyosin cortex, membrane tension and mechanosensitive channels. Intracellular pressures range from ~20-100 Pa, and, during cytokinesis, may rise to ~400 Pa[53]. High intracellular pressure pushes the plasma membrane outward in regions of low actin density, generating bleb-like protrusions or lobopodia, a hybrid of an actin-rich pseudopod and a membrane bleb[57], which are crucial for migration. In confined space and channels, cancer cells polarize transmembrane ion and water channels to the leading and trailing edges, and move through anterior expansion and rear membrane shrinkage[58]. To form lobopodia, fibroblasts migrating in confining 3D tissue increase intracellular pressure towards the leading edge by moving the nucleus forward. This causes a rear-to-front hydrostatic pressure compartmentalization that enhances front protrusion and movement[59]. Both, actin protrusion and hydrostatic pressure are counteracted by membrane tension, together forming a balanced system with strong self-regulatory kinetics.

In summary, tissue and cell modules both function interdependently, forming a dynamic network of activities which occur in parallel or in series, depend upon each other and require coordination in the same cell to adhere, polarize and migrate.

Modes and mechanics of cell migration

In an ongoing process of sensing and execution, moving cells interpret multiple physical ECM parameters in parallel and translate them into an integrated response which involves multiple cell moduli and determines cell shape, polarity, stiffness, and other functions. By adjusting multiple moduli, cells regulate their cytoskeletal organization and the force balance towards ECM substrate and neighbouring cells and adapt both migration strategy and efficacy.

Cells generating low traction towards the substrate adopt rounded shapes, so called ‘amoeboid’ morphology (Fig. 2a) and displace their cell body predominantly by cortical actin flow and contractility[60]. Mechanotransduction through poorly assembled or non-focalized adhesions occurs by low-level friction[61] or mechanical intercalation between extracellular structures by cell deformation and lateral protrusions[62]. When adhesion and traction forces are higher, migrating cells adopt spindle-like shapes, or ‘mesenchymal’ morphology (Fig. 2a)[3,13]. Here, integrin-based adhesions are more focalized and generate higher traction towards the substrate[13,28,36]. In 3D environments, amoeboid-moving cells tend to push, whereas mesenchymally moving cells pull on the substrate[63], indicating distinct force-generating principles between migration modes. When cell-cell junctions remain intact, cells migrate collectively (Fig. 2a) and generate a combined force towards the substrate, resulting in substrate deformations beyond single-cell dimensions[12,64,65]. Consequently, the range of traction forces generated by moving cells is higher in collectively moving cells[64,65].

The strength of traction force generated by cells is further sensitive to microenvironmental conditions, including substrate stiffness[66], ligand density[67], the intracellular processing of focal adhesion adaptor proteins by calpains[68], and substrate organization[41]. By integrating these microenvironmental modules, moving cells regulate adhesion and contractility, transit between high- and low-traction force levels, and switch between migration modes[69] (Fig. 2a, arrows). Switching between amoeboid and mesenchymal migration modes occurs in tumour cells in response to experimental regulation of cell protrusion and actomyosin contractility[70], varying integrin availability or substrate stiffness[71,72]. Thus, moving cells can be viewed as multi-component viscoelastic units which constantly adjust their mechanochemical networks to navigate through heterogeneous tissue.

Contact guidance provides cell orientation by combining ligand binding and mechanocoupling with cell alignment along an anisotropic solid structure, linear or curved, which guides the moving cell body[36,73]. Contact guidance depends upon alignment of actin-rich protrusions and/or focal contacts along the substrate, with notable edge effects along curved or discontinuous substrate countours[36]. Moving fibroblasts and tumour cells form precisely aligned focal contact-like structures along the edges of fibrils of oriented collagen gels[74,75] or the ridges of grooved surfaces[36,76]. In a cell-type dependent manner, the efficacy of contact guidance depends upon optimal spacing between parallel fibrillar or linear patterns, integrin-mediated and integrin-independent adhesions[77], and myosin-mediated traction force[78]. The precision of guidance decreases when cell-substrate adhesion diminishes[77], or when other forces counteract cell alignment such as those from cadherin-based cell-cell junctions during collective migration[36]. In 3D environments, contact guidance along nanotopologies is combined with cell gliding along paths of least resistance. Moving T cells precisely follow collagen fibre textures bordering complex-shaped pores[79], and tumour cells align and migrate collectively along tracks of least resistance which are constitutive or pre-patterned by leader cells[80,81]. In all migration modes, physical and molecular ECM cues likely cooperate for contact guidance in anisotropic environments.

Stiffness directly guides cell migration in durotaxis, the movement of cells towards substrate regions of higher stiffness[82]. Single cells discern stiffness gradients from ~1 Pa/μm[83] up to ~400 Pa/μm[84] and depend on focal adhesions and actomyosin contractility to sample ECM stiffness and durotax[11]. In collective durotaxis, stiffness gradients are sensed through actomyosin force transmission between both ends of the cell group[84]. Single-cell durotaxis may depend upon differential stiffness sensing and tugging action between adhesion sites[85] and stiffness-dependent differential integrin clustering[86]. Collective durotaxis may result from differential binding and unbinding rates of integrins and differential molecular clutch to actin flows, which jointly generate preferential mechanocoupling and movement towards stiffer higher substrate[84].

Haptotaxis directs moving cells towards a gradient of increasing density of immobilized ligand, such as dendritic cell navigation towards tissue-bound chemokine CCL21 to navigate towards lymph vessels[87], or cancer cell movement towards increasing ECM concentrations[88]. However, haptotaxis could also be a consequence of differential mechanical force coupling as both the Arp2/3 complex, which branches actin filaments in lamellipodia, and fascin, which bundles actin in filopodia, support haptotaxis along

fibronectin gradients[89,90] and differential actomyosin contractility defining front-rear asymmetry[91].

Modelling of cell migration mechanics

This astounding parameter range for ECM and cell states, their interactions and adaptations, is challenging to fully control and co-register in cell-based experiments in vitro or in vivo, which is why often only a handful of parameters are tested. To complement wet-lab experiments, in silico modelling can recapitulate cell-based experiments and predict outcomes with broadened parameter space. Modelling allows dissection of mechanistic dependencies in time and space, which define the type, efficacy, decision making and steering of cell migration in response to tissue organization[92,93]. We describe principles of modelling in Box 2 and provide examples of recent efforts to model decision making in cell migration.

Single-cell migration models predict quantitative parameters of migration from mechanical models for mechanosensory pathways, adhesion and force generation. Cell motions can be modelled as different types of Random Walks (RWs), in which a motile agent migrates with defined average velocity along its path. Inputs are rules for velocity and randomness of the trajectory and modulators such as polarization or chemical gradients (Table 1). Linking RWs with mechanical models generates diverse modes of force generation (amoeboid, pseudo/filopodial or mesenchymal) and cell shapes[94,95] (see Table 1). Further, single cell durotaxis was recapitulated by a RW model which linked persistence of movement to substrate stiffness[96]. Cell sensitivity to substrate geometry can be modelled by representing the cytoskeleton as a series of linear, ‘Hookean’ springs responding to small deformations, which can be shortened by myosin intercalation[97]. The resulting traction increases cell spreading on convex substrates, but collapses laterally and thereby increases directional persistence on concave substrates[97].

The collective behaviour of cell aggregates can be predicted by the cellular Potts model (CPM) and cell jamming models (CJM). CPM, supplemented with information about adhesion receptor and ligand density, predicts increasing cell and ECM strains when ECM remains space-limiting, as in tumour growth and invasion[98]. CJM apply the principles of jammed granular solids[99] (like sand piles) to describe multicellular stiffness and collective motions[100]. CJM recapitulate transitions between stationary and dynamic states, similar to the ‘glass-jamming transition’, by which disordered packing of discrete units transition between stationary, solid-like and flowing, liquid-like states[100,101]. CJM take as input the strength of cell-cell contacts and the membrane and cortical tensions to predict cell motions. Strong connections suppress motions between cells (cells are ‘jammed’), but when migration is inducted by a stimulus cell elongation and coherent motions result. Coupling the CPM to continuum-mechanical models for 2D and 3D ECM allows to understand directional collective cell movement as a function of ECM alignment[102]. As a mechanical mechanism for collective cell durotaxis, a generalized clutch model predicts differential force transmission along the cell edge facing the softer substrate[84]. Differential strength of adhesion and the actin clutch may thus be sufficient to mediate collective durotaxis. In the future, combining physical and chemo-dynamical models with genomic and even

population-based evolution models will provide a systemic understanding of the hierarchies that underpin cell fate, aggregation and migration decisions.

Mechanoreciprocity of cell-tissue interactions during cell migration

We here define mechanoreciprocity as an iterative, cyclic process in which cells modify the organization and elastic response of the environment and reciprocally adjust their behaviour[9]. As a consequence, cell function states and tissue topology underlie structural and molecular coevolution (Fig. 3a, 1). Mechanoreciprocity is thus an adaptive process which occurs at different time- and length scales and magnitudes, and whereby any cell-induced change of tissue composition, architecture, or tensional condition results in altered tissue mechanics, reversibly or irreversibly, locally and/or globally. At the molecular level, fibrillar ECM and cytoskeletal protein networks, including fibrillar collagen, fibrin, vimentin and neurofilaments, undergo reversible stiffening when tensile or shear forces are applied[103]. By pushing and pulling on ECM, moving cells induce ECM compression and densification or strain stiffening and thus exert elastic forces. Subsequently, cell detachment may be followed by viscoelastic substrate relaxation. Additionally, permanent ECM remodelling by deposition, crosslinking and degradation of ECM, may impose more long-lived responses. When two properties coevolve, three outcomes are possible (Fig. 3a, 2)[104]: convergence to steady state, such as quiescent cell and tissue function; periodic behaviours, such as the extension-retraction cycles in moving cells; or irregular outcomes, such as destabilized epithelial cohesion, perpetuated ECM remodelling and further deteriorating cohesion[101]. Thus, steady-state and oscillatory behaviours underlie predictable and often self-limiting physiological interactions, whereas chaotic coevolution may cause pathological processes.

Epithelial, endothelial and mesenchymal cells restructure tissue while moving, and these alterations iteratively impact cell function. Beyond position change, cell migration thereby contributes to tissue building and maintenance, as discussed further below, but also to tissue regeneration and chronic disease.

Cells can generate traction force upon ECM networks, reversibly deform ECM architecture and locally increase stiffness and ligand density[42,65] to transiently impact cell function. Moving epithelial and mesenchymal cells locally stiffen collagen networks by up to 1 kPa[42,65], and similar stiffening can induce invasive behaviour in breast cancer cells[105]. Beyond stiffening, moving cells induce ECM network alignment and densification in the direction of force[64,65], and this augments the cellular force response and cell stiffness[42] (Fig. 3b, 1). Cell-induced strain stiffening depends upon β1 integrin and actomyosin-mediated mechanocoupling, as well as activation of focal adhesion kinase (FAK), p130Cas and nuclear myocardin-related transcription factor-A (MRTF-A)[64]. In concert, strain stiffening with locally increased ligand density may reinforce duro-/haptotaxis and contact guidance[75,82,106,107], as a cell-autonomous mechanical mechanism for directional self-steering[64].

Furthermore, moving cells push against tissue structures. Actin-based cell protrusions, including the leading edge and podosomes, generate protrusion forces and compress deformable substrate very locally[30]. Larger, cell-scale tissue deformation occurs when the

moving cell body and particularly the nucleus move in 3D confined space and push against mechanically confining boundaries[20,21] (Fig. 3b, 2). T-cells crawling through 3D tissue deform their cell body, but also displace ECM fibrils in a mechanically integrated process[79]. Tumour cells moving along engineered microtracks in 3D collagen push against and condense the collagen interface, without degrading collagen by matrix metalloproteinases (MMPs), and thereby widen the track in which they move[20]. Within expanded tracks moving cells can rearrange as a collective strand[20], representing a mechanically reciprocal step towards self-organization.

The ECM can also be remodelled in a non-reversible fashion by biochemial modification and external mechanical stresses. Examples include proteolytic ECM degradation by MMPs[108] and ECM deposition and crosslinking[109] to first alter and then stabilize the altered structure (Fig. 1d). In addition, contractile cells can permanently deform, densify and align ECM networks between cells by stress-induced tension[110], alter ECM porosity and nanotopology, ligand type and density, and these changes reciprocally define whether and how the cell migrates[111,112]. Contact-dependent regions of cell confinement by ECM structures, including fibrillar barriers, are preferentially cleaved by MT1-MMP, and loose ends of fibrils become realigned along adjacent structures[112,113] (Fig. 3b, 3). As a consequence, a path largely cleared of ECM allows cells to move through originally much denser, impenetrable tissue (pores <5-10 μm^2)[111]. The cleared ECM path represents a confining interface for contact guidance of follower cells and transition to collective movement[112,114]. For cell passage through basement membranes, localized ECM remodelling by podosomes, invadopodia and stromal cells likely cooperate with mechanical pushing and pulling to form a structural gap through which the cell migrates[115,116]. Breaching the basement membrane is critical in vascular sprouting[117], and supports cancer metastasis to distant organs[118]. Proteolytic movement thus introduces ECM remodelling, with functional consequences for the cell itself and follower cells.

Further, forces occurring between cell surface and ECM may conformationally unfold strain-sensitive ECM, adhesion and cytoskeletal proteins[24]. When deformed, strain-sensitive proteins expose previously cryptic epitopes and alter function, such as the number of exposed adaptor sites, enzymatic activity, or signalling state. Strain-sensitive cytoskeletal adapter proteins include talin[38] and p130Cas[119], and increasing load can prolong the substrate bond lifetime of integrins[120], actomyosin[121], and cadherin-catenin complexes[122] (Fig. 3c, 1). When stretched by cells engaging α5β1 and αvβ3 integrins, anchored fibronectin fibrils unmask previously cryptic adhesion sites for further integrin binding and fibronectin assembly[123]. Through a similar mechanical process, integrin αvβ6 exerts tension upon the prodomain of latent transforming growth factor beta 1 (TGF-β1), which liberates TGF-β1 from latency-associated peptide (LAP), an anchor protein covalently linked to ECM[124]. TGF-β is released by as little as 40 nN pulling force[125], and its release is facilitated on pre-strained ECM, such as during tissue remodelling by myofibroblasts[126] (Fig. 3c, 2). Tissue stiffening enhances TGF-β activation and TGF-β activates cytoskeletal contractility, and both events cooperate to additional release of TGF-β. Thus, mechanical protein unfolding is fundamental in converting forces into biochemical signalling and, again, actomyosin based force transmission, in a reciprocal cycle[24].

In stationary epithelia with isotropic force distribution, connected cells adopt polygonal shape and cease migration with high cell density (‘jamming transition’). Physical or molecular stimuli may, however, initiate collective migration of confluent epithelia with cell-cell junctions retained[3,6], and transition from stationary to collectively migrating states is supported when cell-cell adhesions are strong[101]. Dysfunctional regulation of cortical tension, observed in freshly isolated asthmatic epithelium, facilitates unjamming with extensive cell flows and disrupted epithelial stability[101]. Besides cell-cell interaction stability, confined space may force loosely connected cells to establish cell-cell junctions, undergo a partial jamming transition and move collectively along joint paths[80]. The jamming transition concept provides a multi-parameter framework defining transitions of cytoskeletal interactions across cell boundaries and pressure conditions during collective movements in confined tissue space.

Mechanoreciprocity in disease

Tissue regeneration initiated by, for instance trauma or inflammation aims to reinstall the integrity and function of epithelia, connective tissue and blood vessels. After wounding, provisional fibrin- or fibronectin-rich ECM is colonized by fibroblasts and endothelial cells from adjacent intact tissue which jointly recreate vascularized connective tissue[127] (Fig. 3d, 1). Interstitial fibroblasts secrete proteases which dissolve the provisional ECM while depositing fibrillar collagen networks[128]. Initially loose collagen networks become aligned by contact-dependent collagenolysis mediated by MT1-MMP[129]. Concurrent with collagen deposition, fibroblasts co-engage collagen-binding α1β1, α2β1 and α11β1 integrins, together with fibrin- and fibronectin-binding αVβ3, αVβ5, α5β1 and αVβ1[130], and these multi-ligand engagements mediate focal adhesion strengthening, stress fibre formation, and contractility to reinstall collagen bundling and tissue tension[13,39,131]. This leads to a step-wise transition from randomly textured fibrin to comparably ordered collagen ECM, while fibroblasts transit from migratory and secretory to resident and contractile state[128] (Fig. 3a, 2: stable coevolution). Concurrently, endothelial cells collectively sprout into the wound bed from intact neighbouring vessels. Endothelial tip cells are initiated by proteolytic invadopodia which focally degrade the vascular basement membrane of intact vessels to enable cell penetration through the gap of least resistance[117]. Tip cells engage with fibrin predominantly via αVβ3, α5β1 integrins[132], realign ECM by tension[133], and engage MT1-MMP for fibrin and collagen degradation[114,134]. Follower cells connect through VE-cadherin and tight junctions[127], move actively[133] and deposit basement membrane along the cell-ECM interface[117,135] (Fig. 3d, 1). Thus, endothelial sprouts create their own path of least resistance while depositing substrate for collective guidance.

After acute trauma, this canonical program to tissue regeneration is self-limiting, reaching an equilibrium of stable microanatomy of ECM and vascularization. However, when the defect persists in chronic wounds, perpetuation of fibrosis and/or inflammation can result in divergent outcomes. When the myofibroblast response dominates, collagen deposition and stiffening may perpetuate, as in vascular fibrosis in atherosclerosis[136], the foreign body response[18] or the reactive tumour stroma (see below). Network modelling of pulmonary fibrosis suggests that collagen deposition by preactivated fibroblasts and stiffening of lung tissue coevolve, with fibrosis as outcome[137]. When (sub)acute inflammation dominates,

perpetuated proteolytic ECM remodelling and collagen degradation may ultimately destroy tissue (ulceration)[138]. Fibrotic encapsulation versus lytic tissue degeneration thus represent differently composed mechanoreciprocal progression and distinct outcomes of ECM remodelling.

Mechanoreciprocity is also relevant for cancer invasion and metastasis. In cancers, the growing lesion and the reactive tumour stroma coevolve as a self-propagating neo-tissue, including inflammation, fibrosis, neoangiogenesis and cancer cell migration[6]. As organizers of ECM remodelling, myofibroblasts become activated by tumour and stromal cell-derived cytokines[139]. Myofibroblasts deposit and crosslink collagen and other ECM proteins by lysyl oxidase (LOX), and thereby stiffen ECM[118]. High ECM stiffness potentiates mechanical and molecular reprogramming of cancer cells by enhancing growth factor signalling[118]; invadopodia activity[140], tension, deformation and remodelling of basement membrane to support cell transmigration in vitro[116] and metastasis in vivo[141] and integrin signalling[118], which supports survival and stemness. ECM stiffening further enhances TGF-β activation by myofibroblasts, in parallel to increased release of chemokines and matrisome proteins[126,128]. In stiff environments, excess TGF-β aggravates myofibroblast differentiation[15], enhances fibrosis and diversifies cancer cell invasion plasticity by favouring single-cell dissemination[139]. Myofibroblasts and tumour cells jointly rearrange tissue topology, by aligning and bundling collagen, creating new corridors of single-cell width[19] to guide cancer cells along paths of least resistance[142,143] and favour partial cell jamming and transition to collective invasion[80,112] (Fig. 3d, 2). Besides collagen, fibronectin is deposited by both cancer cells and myofibroblasts which provides a bi-modal scaffold for contact guidance of epithelial cancer cells through integrin signaling[107] and for latent TGF-β1 activation by moving tumour cells using α6β4 integrin[77]. In other sub regions, tumour cells may be prevented from invasion by a collagen capsule. The capsule acts as a barrier and increases the intra-tumour pressure, limits blood vessel sprouting and blood supply and impedes delivery of systemic therapy[144,145]. In silico, ECM alignment and stiffening and contractile stresses during cell migration reinforce each other reciprocally, with intermediate ECM stiffness as most conducive to invasion[146]. Similarly, combining cellular Potts with fibrous ECM modelling predicts a biphasic cell response to collagen density, ECM stiffness and pore size, with optimum cancer migration and persistence at intermediate level of each module[102]. Thus, cancer cell invasion depends on both reciprocal interactions and fibrosis which, depending on topology, reprogram tumour sub regions to either promote migration or prevent it through fibrotic encapsulation (Fig. 3d, 2).

Conclusions and outlook

The reciprocity of cell and tissue mechanics generates a situation whereby virtually every step of cell and tissue biology depends upon mechanochemical events. For example, a purely mechanical signal can initiate a developmental program. In the developing *Xenopus* embryo, emigration of neural crest cells is triggered by a mechanical tension signal, which cooperates with preceding EMT signals and chemokine signals present in the stroma, yet neither stimulus alone suffices to induce delamination[147]. To distil cause-consequence relationships from multi-parametric wet-lab analyses, advanced statistics is required to discriminate the role of cell migration from integrated growth, survival and therapy response programs[148]

and such parametric data will allow in silico modelling to successfully combine large-scale tissue analysis with micro- and nano-topological models.

Besides cell migration and tissue remodelling, other intracellular processes respond to mechanical stimuli, including gene transcription, cell differentiation and metabolism[149]. Thus, force-sensitive adhesion signalling may cooperate with mechanosensitive ion channels, chromatin, transcription factors and the protein trafficking machinery. Current strategies of the mechanobiology field, as delineated in this review, focus on understanding complex mechanistic relationships, but ultimately aim to deliver novel insight and rationale for interference strategies. Examples include dampening adhesion signalling or actomyosin contractility, for instance by FAK or Rho kinase inhibitors[148,150,151], to interrupt the ECM stiffness-induced cell programming. However, beyond mechanical functions, molecular effectors also contribute to signalling networks, and the mechanobiology in complex disease models may be complicated by parallel or counteracting networks. As an example, collagen-crosslinking enzymes including LOX increase ECM stiffness which enhances cancer invasion and metastasis[109,118], however LOX can also dampen oncogenic signalling and limit neoplastic progression[152]. Combating chronic tissue stiffening and remodelling effectively may require bi- or multimodal intervention, such as co-targeting of neoangiogenesis and macrophage influx to prevent detrimental fibrotic scarring near biomedical implants[18]. In summary, mechanical mechanisms feed molecular processes, and vice versa, to co-direct cell and tissue homeostasis and pathology. Thus, the framework of mechanoreciprocity mandates us to integrate biomedical disciplines to enhance diagnostic and therapeutic workflows and improve disease control.

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Box 1

Emerging modules of tissue and cell mechanics

Porosity

The porosity of the tissue varies from >100 μm^2 between collagen fibrils in loose connective tissue and lymph nodes, to <1 μm^2 between dense collagen bundles[16,21]. Nearly-impenetrable dense ECM impedes cell migration and requires particular abilities, such as the capacity to strongly deform the nucleus and/or to proteolytically degrade ECM and generate space[111]. Collagen-rich stroma and basement membrane are examples of such high-density environments[158]. Loose to medium-density ECM has pores that match the cell size with pore sizes around the nuclear cross-section (30-70 μm^2, Fig. 1c, arrows) and represent a minimal barrier for migration at maximum speed, without requirement of tissue degradation[36,79].

Nanotopology and curvature

The order of ECM macromolecules and their surface texture provide complex 3D nanopatterns. Cells discriminate aligned from disordered patterns for guidance of migration[22]. Engineered fibrils of 400 nm in diameter support 2-fold faster migration speed compared to 700-1200 nm fibrils[159]. The surface of collagen fibrils provides nanotexture by D-periodic bands[160] (Fig. 1b), and globular patterns from adhering macromolecules[160], yet it is unclear which level of nanoscale can be resolved by cells. The 2D structure of basement membranes is a meshwork of nanoscale pores and fibrils[161] (Fig. 1b), but engineered nanoridges of comparable scales exert no apparent impact on cell migration when compared to a planar surface[162]. Thus, at nanoscale, moving cells likely sense protein substrate as a 3D topology, integrate curvature as either ridge-like or flat surface, and interpret basement membrane nanotopology as ‘2D’. Tissue curvature furthermore induces spatial patterning of mechanical stresses and proliferation of cell sheets, suggesting a role in enhancing proliferation and, likely, guiding migration[163].

Tissue hydration

Tissue hydration is maintained by interstitial fluids, which flow between ECM macromolecules by convection. Both freely flowing and GAG-bound water fill the ECM space and regulate porosity as a dynamic equilibrium[23]. When vascular permeability increases during tissue trauma, inflammation or cancer, interstitial water influx increases hydrostatic pressure by multi-fold, followed by tissue swelling (edema) with increased ECM network porosity and tension by hydrostatic pushing[164,165] (Fig. 1c). Edema accompanies acute and chronic tissue responses with increased migration of infiltrate leukocytes and stromal cells, and hydrostatic regulation of ECM porosity and alignment facilitates cell trafficking[166]. Beyond mechanical effects, edema accelerates interstitial fluid flow, which redistributes chemotactic proteins and contributes to cell guidance[167].

Cell stiffness

Cell stiffness is predominantly determined by the nucleus, cortical actin, and the cytoskeleton[168]. Bundled actin creates higher local stiffness compared to diffuse actin

structures[42,43]. Cell stiffness thus scales with the traction force generated by cells and lowering stiffness facilitates shape adaptation of moving cells[169]. Invasive cancer cells are less rigid than benign or less invasive counterpart cells[169], indicating distinct cytoskeletal organization.

Box 2

In silico modeling

Principles of modelling cell mechanics

At subcellular scales, network models, including open cell foam, beam and cable models, and tensegrity models (Table 1), combine the elastic, force-extension properties of fibrillar cytoskeletal proteins with their spatial organization[170]. Intracellular processes can be modelled as continua[171] or discrete cell structures, including dynamic actin networks or bundles and external mechanical conditions[172]. Network models describe the nonlinear response of heterogeneous filamentous environments and their reciprocal interactions during cell migration. For example, the stiffness response of weakly deformed crosslinked actin networks was predicted to be a linear function of the concentration of single filaments[173], confirmed by mechanical characterization of reconstituted actin protein networks in wet-lab experiments[174]. Network models of transient actin filament bundling, combined with cytosolic liquid models recapitulate higher-order assemblies, such as filopodia[175]. Whole-cell mechanical modelling requires coarser and/or multiphasic mechanical models to capture ECM orientation, bundling, and heterogeneity. The behavioural switch between collective, mesenchymal and amoeboid migration modes, for instance, is modelled as a function of cell-tissue adhesive strength[176].

Importantly, distinct in silico models can be combined and integrated to reach complex mechanical, molecular and outcome predictions. For example, a coarse-grained mechanochemical model for cell, ECM and adhesions, combined with reaction diffusion equations to model mesenchymal chemotaxis, predicts complex behaviours of cancer cell invasion[177]; detailed network models for ECM and cytoskeleton with stochastic reaction diffusion equations reveals filopodial dynamics in leader cells[172], and mechanical models for ECM with CPM reveals the nuclear deformability as rate-limiting in confined cell migration[178], similar to decelerated migration in dense fibrillar collagen[111].

Mechanoreciprocity in silico

To model the dynamic coevolution of migrating cells and ECM requires linking complementary modelling strategies that resolve both cell and ECM states over time. Mechanomechanical models ascribe an overall energy function to coupled FEMs for ECM and cells, physically connected by adhesion sites. The minima of this energy function correspond to (meta)stable cell-matrix equilibria and dynamics are simulated using the evolution of the energy function towards its minima. For example, combining the density and polarization of cells, their contractility and strains at cell-cell and cell-ECM contacts, and the strength and abundance of cell-ECM adhesions reveals that strain stiffening and ECM alignment precede and support the detachment of individual cells from a multicellular cluster[146]. Other approaches combine discrete cell-based CPM polarization and movement, traction forces and durotaxis into an adaptive ECM continuum[179]. Emerging hybrid network models and reaction-diffusion equations resolve the intra- and extracellular spaces down to the fibrillar level to model the production,

redistribution and remodelling of ECM caused by MMPs[172]. Such detailed models, however, generally do not permit simulations spanning longer timescales.

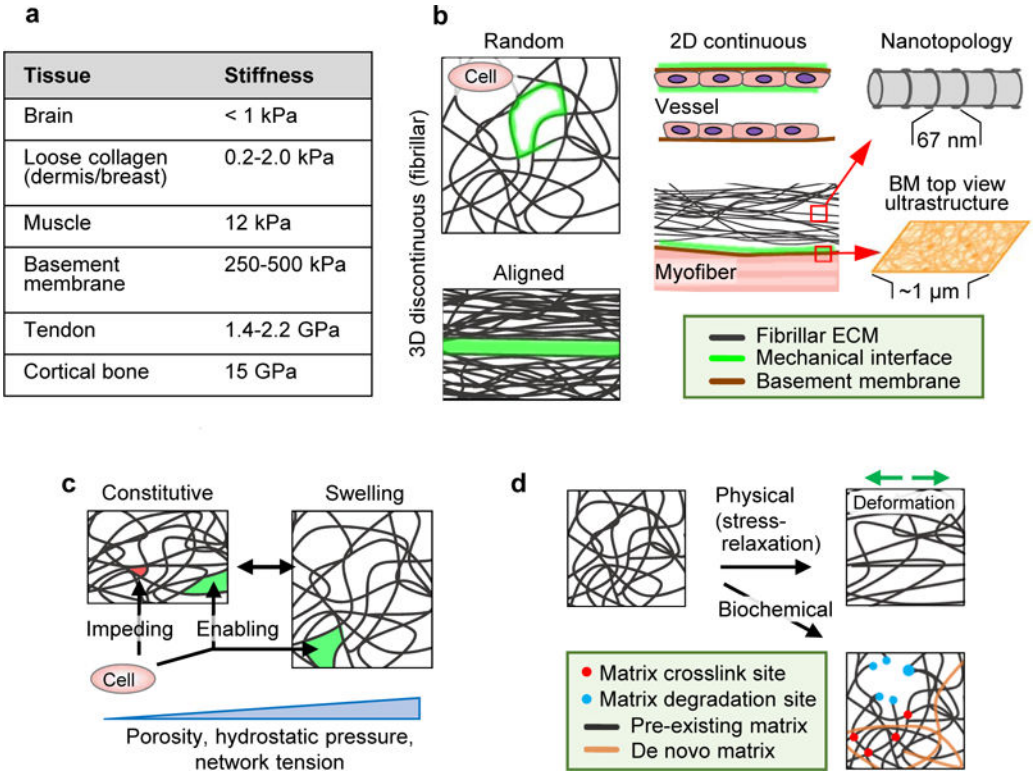

Figure 1. Physical ECM modules determining cell migration

Tissue properties determining cell migration, including topology of the ECM and organization of interfaces between tissue structures. **A** Elastic modulus range present in macromolecular tissue structures. GAG-rich stroma surrounding cell networks, such as brain tissue, is soft (below 1.0 kPa)[48]; loose fibrillar type I and III collagen-based porous protein networks such as dermis and breast scale typically between 0.2 and 2 kPa[111,118]. Thicker, more crosslinked collagen bundles in muscle are substantially stiffer (12 kPa)[48], which reaches the low GPa range in tendon[153]. Basement membranes consisting of type IV collagen and laminins have a stiffness in the higher kPa range, with at least double the stiffness on the epithelial side compared to the stromal side[154]. The stiffness of calcified tissue, including cortical bone, can go up to 15 GPa[155]. **B** Principal ECM geometries defining mechanical cell migration interfaces (green) including 1D, 2D and 3D organization and nanotopology. **C** Baseline porosity range, relative to cell size and deformability, and hydrostatic pressure induced reversible swelling and mechanical alterations in fibrillar ECM. **D** Irreversible changes induced by physical or biochemical factors. Direction of physical deformation denoted by green arrows.

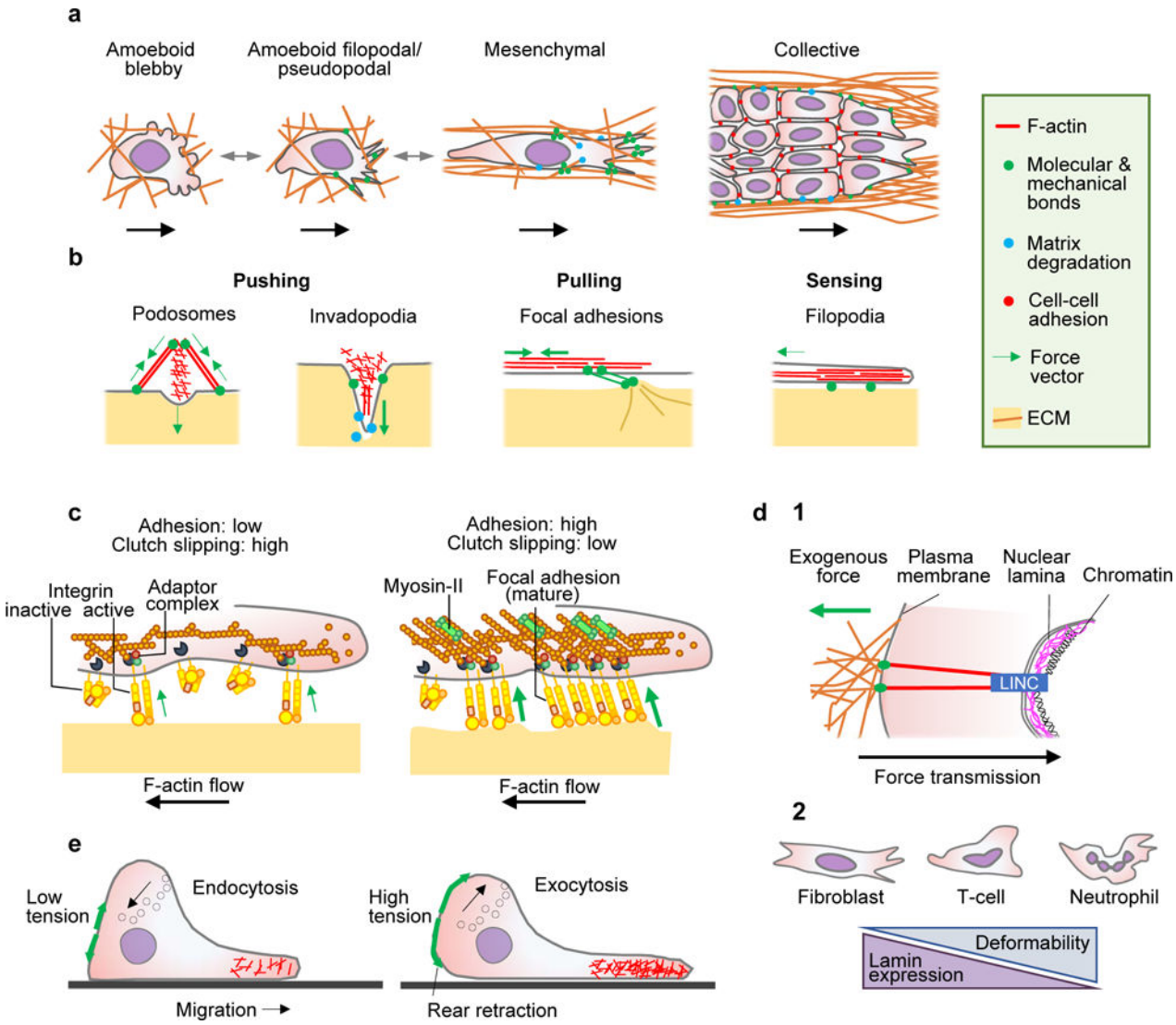

Figure 2. Mechanical cell modules in cell migration

A Cell migration modes in 3D environments, including single-cell and collective migration. **B** Actin-rich cell surface structures mechanically interacting with tissue, including: podosomes probing the substrate vertically; invadopodia protruding and locally degrading substrate in vertical direction by releasing proteases; focal adhesions generating adhesion and pulling force; and filopodia extending along ECM structures and generating traction force in parallel. **C** Differential adhesion regulation. Tension generated by mechanical extracellular interactions of adhesion receptors depend upon intracellular adaptor proteins linking to the actin cytoskeleton, which flows in rearward direction (clutch). The strength and duration of adhesion receptor bonds to substrate increase with force[156] and are regulated by lateral clustering of integrin adhesion receptors, which increases the number of bonds[157]. Diffusely distributed integrins exert weak adhesion and traction force (left). With integrin clustering, adhesions increase the number of engaged bonds to actin filaments and recruit myosin-II, providing stronger adhesion and traction force towards the substrate (right). **D** Nuclear mechanics. (1) Mechanical linkage between ECM, cytoskeleton, nuclear lamina and

chromatin through the LINC complex (linker of nucleoskeleton and cytoskeleton) consisting of nesprins 1-4 and Sun1/2 proteins, which regulate nuclear positioning and deformation in response to cell responses to extracellular cues[47]. (2) Shapes and correlation between nuclear deformability and lamin expression. **E** Membrane tension and cell migration. Left panel, low membrane tension in partly polarized cell facilitating actin polymerization. Right panel, fully polarized cell with high membrane tension limits actin filament protrusion at the leading edge, but supports rear contraction and is counterbalanced by transport of intracellular vesicles to the plasma membrane. Green arrows, force vectors.

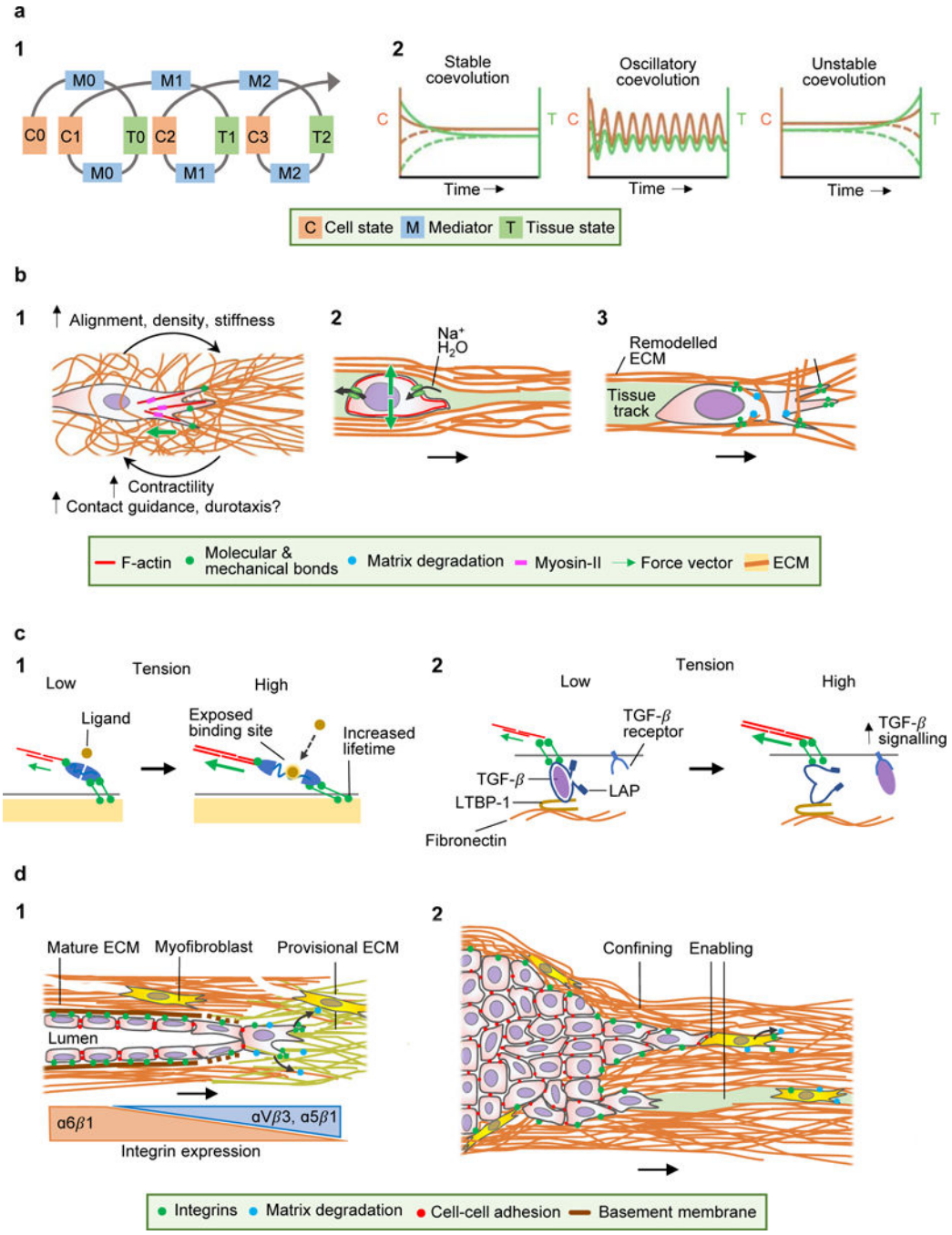

Figure 3. Cellular and molecular mechanoreciprocity in tissue regeneration and disease

A (l) Spiral concept of mechanical cell-tissue interactions, describing coevolution of cell and tissue mechanics. Cells impose ‘mediators’ (pulling, pushing, ECM deposition, ECM degradation) and thereby alter tissue modules. Through iterative reinforcement (indicated by the spiral) or negative feedback, both cell and tissue modules undergo coevolution towards altered morphology and function. (2) Development of cell and tissue coevolution, including acquisition of a stable equilibrium (left), oscillatory coevolution with both positive and negative feedback loops (middle), or unstable coevolution, typically caused by negative

feedback or disruption of co-engagement (right). The dashed lines indicate the temporal coevolution for perturbed initial conditions; in case of stable or oscillatory coevolution, the system converges to well-defined asymptotic behaviour, in the case of unstable coevolution the sensitive dependence on initial conditions typical of chaotic systems is seen. **B** Mechanoreciprocity in cell migration. (1) Strain stiffening of an ECM network by tension at the leading edge, creating a multi-parameter mechanochemical feed-forward loop. (2) Tissue compression by migrating cells, condensing ECM. Intracellular hydrostatic pressure is jointly maintained by stress-sensitive ion and water channels and actomyosin contractility. (3) Structural ECM remodelling. Mesenchymal migration leads to traction and fibre realignment by the leading edge, followed by pericellular proteolysis of collagen fibrils constraining the cell body, which after fibril realignment leaves behind a remodelled tissue track. **C** Molecular mechanoreciprocity. (1) Unfolding of mechanosensitive proteins by force. Actomyosin-contraction and tension exposes bioactive domains in adaptor proteins (e.g., talin, vinculin, p130CAS), which allows further ligands to bind and alter function in a strain-dependent manner (e.g. increased lifetime of catch-bonds). (2) Strain-dependent activation of TGF-β1. Cell adhesion and tension to ECM-tethered LAP induces a conformational change and releases TGF-β to diffuse and bind to its receptor. LTBP-1, latent TGF-β-binding protein 1. **D** Mechanoreciprocitiy in disease. (1) Concordant immigration of fibroblasts and endothelial cells into the wound bed, which realign and degrade provisional ECM and synthesize collagen and basement membrane proteins and undergo a transition of engaged integrin systems. As outcomes, tissue alignment, density and stiffness are reciprocally linked to fibroblast function. (2) Mechanoreciprocity in cancer invasion. Dual function of ECM deposition and stiffening by myofibroblasts in sub regions, leading to encapsulation or invasion along collagen interfaces.

Table 1

Modelling strategies for mapping of cell and tissue mechanics

Modelling approaches (top to bottom) are ranked from lowest to highest resolution. Combinations of modelling approaches, where different structures are resolved at different length- and time scales, are termed Multiscale Models. Models in red employ one or multiple phenomenological parameters, models in green are physics-based.

Modelling approach*	Model scales	Key input	Key output	Modelling principle	Application
Finite Element Modelling (FEM)	Tissue, organ (mm-cm)	Mechanical moduli, constitutive relations, shape	Organ scale shape changes; mechanical rupture	Different elements that represent local mechanical properties are combined, allowing scalable modelling of heterogeneous tissue	Complex, heterogeneous, multicellular systems in tissue
Cellular Potts Model (CPM)	Cell, cell aggregate (μm-cm)	Cell and ECM mechanics, target volume and area, speed	Single-cell and collective dynamics, cell shape, invasiveness, vascularization	Represents cells as domains on a regular lattice, with mathematical rules prescribing their ECM contacts, interactions, proliferation and migration	Cells and cell cluster growth and migration
Multiphasic, active and constitutive (SGR) modelling	Cell, tissue (μm-cm)	Constitutive equations; composition, porosity and anisotropy; energy consumption	Mechanical properties, dynamics and response of entire cells	Mathematical equations dictating the flow and elastic response of cell and environment	Predicting cell deformation, relaxation and shape change under applied stress
Network models (numerical, analytical)	Cell, microtissue (μm-mm)	Fibril (visco-) elastic response, network architecture	Visco-elastic constitutive (dynamic) response fibrils, incl. bundling and alignment; filopodial dynamics	Fibril bending and extension properties are modelled to predict network deformation responses	Cytoskeletal mechanics, ECM mechanics
Coarse grained molecular dynamics (CGMD)	Fibril, bundle (nm-μm)	protein aggregate, arrangement, PMF	Mechanical response of single fibrils; effects of quaternary structural defects and crosslinking	Small particles (i.e. molecules) are aggregated and modelled as single particles, allowing modelling of larger volumes	Protein assembly and mechanical response of single protein fibrils
Atomistic models	Protein (≤100 nm)	Amino acid sequence, chemical composition, force fields	Potentials of mean force (PMF) for CGMD, mechanical effects of mutations and molecular damage	Numerical solution of Newton's equations for the motions of atoms, alone and in molecules	Single protein mechanics and structure