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Wickstroem, Sara A.

Elsevier Ltd.
2018-10

Wickstroem, S A & Niessen, C M 2018, 'Cell adhesion and mechanics as drivers of tissue organization and differentiation : local cues for large scale organization', Current Opinion in Cell Biology, vol. 54, pp. 89-97. https://doi.org/10.1016/j.ceb.2018.05.003

http://hdl.handle.net/10138/260560
10.1016/j.ceb.2018.05.003

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Current Opinion in Cell Biology

Cell adhesion and mechanics as drivers of tissue organization and differentiation: local cues for large scale organization

Sara A Wickström[1,2,3,4] and Carien M Niessen[5]

Biological patterns emerge through specialization of genetically identical cells to take up distinct fates according to their position within the organism. How initial symmetry is broken to give rise to these patterns remains an intriguing open question. Several theories of patterning have been proposed, most prominently Turing's reaction–diffusion model of a slowly diffusing activator and a fast diffusing inhibitor generating periodic patterns. Although these reaction–diffusion systems can generate diverse patterns, it is becoming increasingly evident that cell shape and tension anisotropies, mediated via cell–cell and/or cell–matrix contacts, also facilitate symmetry breaking and subsequent self-organized tissue patterning. This review will highlight recent studies that implicate local changes in adhesion and/or tension as key drivers of cell rearrangements. We will also discuss recent studies on the role of cadherin and integrin adhesive receptors in mediating and responding to local tissue tension asymmetries to coordinate cell fate, position and behavior essential for tissue self-organization and maintenance.

Addresses
[1] Helsinki Institute of Life Science, Biomedicum Helsinki, University of Helsinki, FI-00014 Helsinki, Finland
[2] Wihuri Research Institute, Biomedicum Helsinki, University of Helsinki, FI-00014 Helsinki, Finland
[3] Paul Gerson Unna Group "Skin Homeostasis and Ageing" Max Planck Institute for Biology of Ageing, Cologne, Germany
[4] Cologne Excellence Cluster on Stress Responses in Aging-associated Diseases (CECAD), Germany
[5] Department of Dermatology, Cologne Excellence Cluster on Stress Responses in Aging-associated Diseases (CECAD), Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany

Corresponding authors: Wickström, Sara A (sara.wickstrom@helsinki.fi), Niessen, Carien M (carien.niessen@uni-koeln.de)

Current Opinion in Cell Biology 2018, **54**:89–97

This review comes from a themed issue on **Cell dynamics**

Edited by **Andrew J. Ewald** and **Vania M.M. Braga**

For a complete overview see the Issue and the Editorial

Available online 1st June 2018

https://doi.org/10.1016/j.ceb.2018.05.003

Introduction

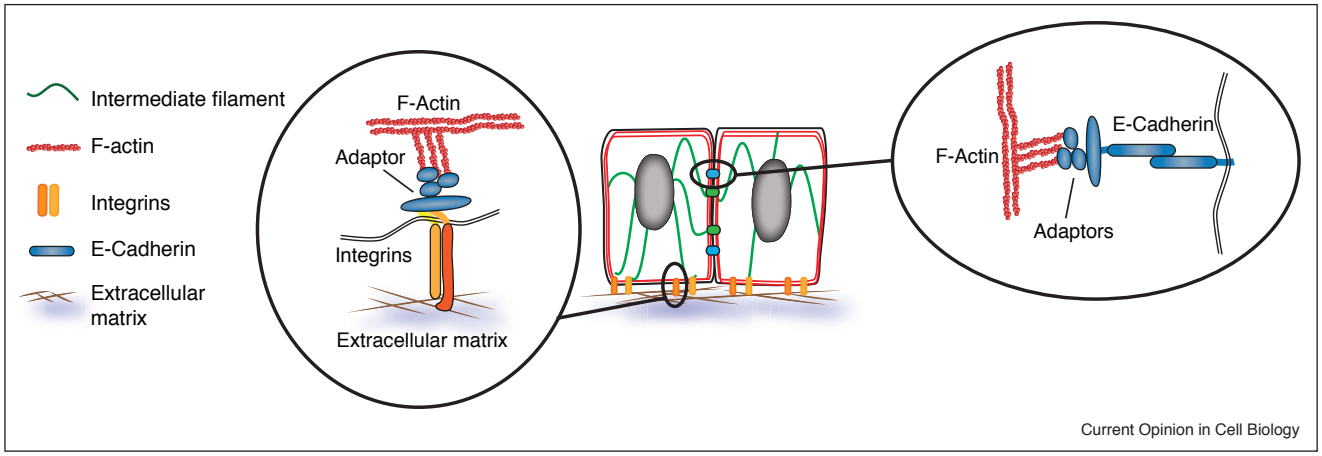
Tissues are formed and maintained in an extremely stereotypic manner. This reproducible patterning necessitates integration of signals that determine cell fate with adhesive and cytoskeletal cues that control cell shape and cellular rearrangements. These shape changes and rearrangements require tightly controlled force generation that occurs through coordinated engagement of the contractile actomyosin cytoskeleton with integrin and cadherin adhesive complexes. Cadherin-dependent intercellular junctions link intercellular adhesion to the organization of the cortical actomyosin cytoskeleton as well as provide landmarks that spatially orchestrate signaling [1,2], thus allowing cells to coordinate their behavior across the tissue [3] (Figure 1). Like cell–cell adhesions, integrin-dependent cell–extracellular matrix (ECM) adhesions link to and regulate actomyosin organization and contractility [4]. What distinguishes integrin adhesions from other adhesive complexes is their ability to bind and dynamically remodel the ECM into a precise configuration (Figure 1). The ECM provides cells with positional and structural information of the surrounding tissues as well as binds and regulates the availability and activation of growth factors, thus acting as a topographical cue and signaling platform [5].

These cell–cell and cell–matrix adhesion receptors can thus recognize and mechanically respond to local changes in their microenvironment. However, how forces generated by adhesion and the cytoskeleton integrate cell fate with the positioning of cells within tissues is less clear. The recent evolution in technology and methods to quantify and experimentally manipulate adhesive and mechanical properties of cells and tissues has revolutionized the field, thus allowing more direct probing of this question. The role of cadherins, integrins and actomyosin in mechanotransduction and tissue morphogenesis has been extensively reviewed, for example in [6–8]. Instead, this review will focus on highlighting recent data on the adhesive and force transduction mechanisms that control cell fate and/or shape to break cellular symmetry within multicellular assemblies, which then drives tissue self-organization.

Triggers of cell shape and force anisotropies

Tissue self-organization and patterning requires the coordinated positioning of cells to couple function with tissue architecture. It is well established that signaling has a key

Figure 1



Cell–cell and cell–matrix adhesions are linked to the contractile actomyosin cytoskeleton. Classical cadherin receptors mediate adhesive binding to cadherins presented on the surfaces of neighboring cells to promote cell–cell adhesion. Integrins bind to extracellular matrix proteins to mediate cell–matrix adhesion. Both adhesive systems mechanically couple to the actomyosin cytoskeleton through cytoplasmic multi-adaptor complexes and regulate its organization and contractility.

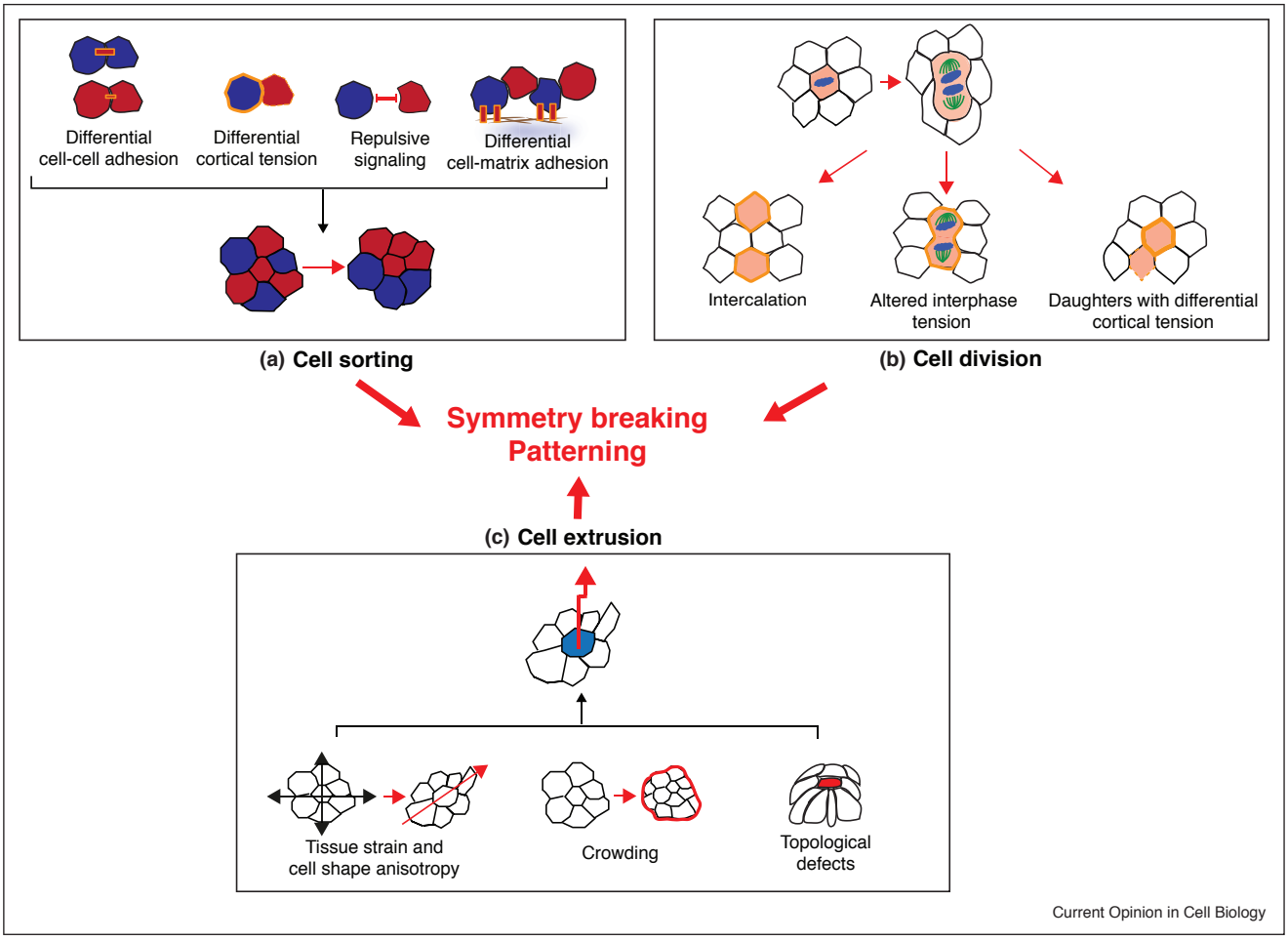
instructive role in patterning with several models, especially Turing's reaction-diffusion model [9], explaining how these signaling systems generate periodic patterns. Recent studies have begun to unravel a critical role for cell shape and tension anisotropies in symmetry breaking to generate and shape signaling gradients and promote the self-organization of tissue patterns [10,11].

Adhesion in forming and maintaining boundaries

Cell sorting is a process in which two or more populations of cells self-organize to create fate boundaries and spatially defined structures [12] (Figure 2a). In principle, the outcome of cell sorting can be predicted using models that consider cell-specific differences in interfacial energies, resulting in a configuration that maximizes the most energetically favorable cell interfaces [13]. Historically, this disparity in interfacial energy was considered to be driven by differences in adhesive specificity and/or strength (differential adhesion hypothesis, DAH) with cadherins as best examples [13]. Later work indicated that sorting was primarily driven through differential cortical tension properties of the two populations (differential interfacial tension hypothesis, DITH) [14,15], with adhesive receptors required to couple tensile forces to the cell membrane [16]. In both cases, the action of so-called repulsive signals, for example of Eph–Ephrin receptors, at heterotypic junctions (defined as between two different cell types [12]) was ignored. In contrast, the Fagotto group recently identified a major role for Eph–Ephrin signaling in establishing high heterotypic interface tension (HIT) that drives the separation of Xenopus ectoderm from mesoderm with little to no role for differential adhesion or cortical tension [17••]. These authors then proposed a unifying model in which the rapid and stable formation of sharp tissue boundaries, for example Xenopus ectoderm–mesoderm boundary, is highly dependent on HIT, whereas DAH and/or DITH are likely more important for situations in which cells sort out during active cell rearrangements, for example during convergence extension movements.

Local differences in matrix composition, resulting in a selective ability of different cell populations to adhere to this matrix, can also provide a dominant cell sorting cue. Such a binary interaction signal of presence or absence of cell–matrix contact may robustly buffer the more dynamic rearrangements and spectrum of interaction energies of individual cell–cell interactions. This concept was recently directly explored using the self-organizing capacity of mammary or prostate gland primary epithelial cell aggregates that consist of two different populations. By combining mathematical modelling and knockdown of key adhesion proteins these authors found that only one cell type was able to interact with and spread on the ECM tissue boundary. This binary interaction was essential for cell positioning and gland self-organization, and robustly buffered alterations in key cell–cell adhesion molecules [18]. The principle of a binary instructive cue deriving from basement membrane adhesion triggering self-organization is further beautifully demonstrated in studies of early mammalian development. During the first stages of post-implantation morphogenesis, the pluripotent epiblast that later gives rise to all tissues becomes organized into a rosette-like structure of highly polarized cells and a central lumen is then formed through hollowing of the apical membranes of these polarized cells. This symmetry breaking is orchestrated by polarization cues from the basement membrane and transmitted through β1-integrin receptors [19] in a manner similar to MDCK cyst morphogenesis [20]. Interestingly, studies on

Figure 2



Adhesion and cell mechanics-dependent mechanisms of symmetry breaking and patterning. Cell shape and tension anisotropies can be generated both locally or on the tissue scale to break symmetries and generate tissue patterns. **(a)** Cell sorting can occur on the basis of differential cell adhesion, cortical tension or repulsive signaling. A common denominator is that all these mechanisms locally maximize differences in interfacial energies to generate tissue internal boundaries. **(b)** Cell division is capable of generating tension asymmetries to promote cell intercalation, to generate interphases with reduced tension or to specifically position daughter cells based on their differential cortical tension. **(c)** Cell repositioning through delamination has been shown to be triggered by tissue-scale stresses such as strain anisotropy, crowding and topological defects.

micropatterned ECM surfaces have shown that cell–matrix adhesions can spatially organize intercellular junctions due to the high intercellular forces generated in the close proximity of these matrix junctions, thus directing cell–cell adhesions away from the ECM [21]. Conversely, the formation of cell–cell adhesions prevents the local formation of cell–matrix adhesions [22], thus coordinating cell–matrix forces [23]. Collectively, this leads to global minimization of the total contractile energy and thereby stabilization of cells in this position, providing a self-organizing mechanism for matrix adhesion-driven cell polarization and positioning.

The presence of a boundary, for example through matrix deposition and/or through differential interfacial tension, may control collective organization and behavior of cells over larger length scales. For example, neuronal stem cells cultured at high density and provided with an artificial boundary form aligning migratory patterns. These patterns show long-range nematic order (behaving like a liquid crystal phase characterized by the arrangement of the long axis of the molecules in parallel lines) that mimick the length scale and organization of the migratory stream of neuroblast cells in rodent brains, in which collective behavior is determined by topological defects [24•]. Interestingly, a very recent paper indicates that, independent of local asymmetry in interfacial energy, these long-lived and long-range mechanical patterns are associated with jamming (the cell layer being in a solid-like state) and contribute to the formation and maintenance of boundaries [25•].

Thus, tissues can employ different strategies to sort and position cells to drive tissue self-organization. A common denominator is that all these strategies locally maximize differences in interfacial energies but, depending on the sorting process, through different molecular mechanisms: whereas acute and strong boundary formation is likely driven mainly by repulsive intercellular interactions and/or differential cell–matrix adhesion, processes that involve large scale cell rearrangements seem to involve dynamic changes in cell–cell adhesion,cortical tension, and the mechanical state of the cell layer. More experimental and theoretical work are, however, required to validate this concept.

Cell division as a trigger of tension asymmetry and tissue patterning

Although oriented cell division contributes to patterning by axial positioning of daughter cells, division itself has only lately been shown to directly generate local tension and adhesion anisotropies necessary for changes in cell shape and rearrangement. Using the gastrulating chick as a model system Firmino *et al.* [26] recently reported that cell division drives intercalation of its neighbors (Figure 2b). These dividing cells have low cortical actomyosin contractility allowing the mitotic cell to remodel their junctions and establish initial contact between the two distant neighbors. Recent other reports indicate that cell division can even locally direct the tension state of its neighbors. In the Drosophila notum cytokinesis-generated forces dynamically reorganize junctions at the mitotic-non-mitotic interface resulting in self-organized actomyosin flows in neighboring cells [27••] (Figure 2b) essential to coordinate cellular shape and dynamics. Similarly, because the mammalian epidermis displays features of a jammed, solid like state, mitosis also locally reduces interphase tension with its neighbors, which is necessary for junctional remodeling that then promotes delamination of these neighboring cells [28•] (Figure 2b). Vice versa, external forces may instruct orientation of division and subsequent daughter cell shape, thus contributing to the patterning of tissues along a certain axis, as demonstrated in Drosophila and Zebrafish [29–31].

Interestingly, mouse blastocysts employ asymmetric division to generate two daughters with low and high contractility, which then triggers their sorting into inner and outer positions (Figure 2b). The inner, more contractile cell also turns on Yap, thus coupling cell position with fate determination, allowing self-organization of the 16 cell stage blastocysts [32,33•].

Cell extrusion in tissue formation and homeostasis

To establish, maintain and restore their functional integrity, tissues, in particular epithelia, have to balance cell proliferation with cell loss and/or differentiation. To do so, tissues employ several mechanisms to either prevent overcrowding or supply new cells upon, for example, cell death induction or injury. Increasing evidence indicate that the dynamic changes in cell shape and tension anisotropies are directly linked to on the one hand to local cell density and on the other hand to cell fate (Figure 2c), and thus play a key role in tissue homeostasis. For example, crowding and/or apoptosis induces local actomyosin contractions in the future extruded cell and subsequently in its neighbors, which promote adhesion rearrangements that are essential for its apical extrusion [34,35]. Interestingly, altered actomyosin tensile activity in apoptotic cells can also actively remodel tissues by promoting tissue folding [36].

In the developing Drosophila Notum crowding induces delamination of living cells that is necessary for patterning the tissue. Delamination correlates with increased cell shape anisotropy, and modeling data suggests that this anisotropy is in fact sufficient to induce delamination [37] (Figure 2c). Crowding-induced cell shape anisotropies also trigger differentiation and delamination in the epidermis [28•]. On the molecular level, E-cadherin-mediated mechanical signals instruct nearest neighbors to remodel junctional actomyosin necessary to drive cell extrusion or delamination [28•,38,39].

Cell density, fate, and extrusion may not only be controlled by local cellular interactions, but also coordinated through tissue-level mechanics. Using monolayers of MDCK cells Saw *et al.* [40••] found that epithelial monolayers, unlike fibroblasts, behaved like active nematic crystals, in which spontaneous stress-induced topological defects occur. These topological defects induce local isotropic compression resulting in apoptosis and extrusion of the compressed cell (Figure 2c). Interestingly, knockdown of α-catenin increased the number of defects as well as extrusion rate, indicating that intercellular junctions are essential to dissipate mechanical compression, and, as a consequence, control the number of apoptotic, extruding cells [40••].

Tissues may furthermore employ increased contractility at the interface of differentially fated cell clones as a mechanical force to shape and maintain tissues. Interestingly, a combination of experimental and computer simulations using a 3D vertex model indicated that the ultimate outcome of this increased interface contractility depends on the clone size of the newly (potentially mis-) specified fate. Whereas a single cell with an aberrant cell fate will be extruded, intermediate sized clones will form a cyst through abscission, thus becoming potentially tumorigenic. In contrast, large size clones are predicted to create a smooth boundary, as also seen in development [41•].

Collectively, tissues thus utilize force and shape anisotropies to control homeostatic cell density and to couple cell fate with position to generate tissue patterns (Figure 2). How mechanical changes integrate with known signal

pathways essential for tissue formation and function and, on the other hand, how cell fate boundaries might remodel contractile forces at these interfaces to regulate/reinforce patterning, are key remaining questions.

Adhesion-dependent mechanics, signaling and cell fate

Local integration of cadherin mechanotransduction and signaling

Genetic studies have long implicated cell adhesion complexes as modulators of tissue growth and cell fate, predominantly through regulating Erk, SHH, Wnt/β-catenin and/or Yap signaling (e.g. [42–45]). However, whether these changes in signaling and cell fate are directly linked to cadherin-dependent mechanotransduction has only recently been addressed. Yap is a mechanosensitive key transcription factor important to coordinate growth and organ size [46,47]. In the epidermis αE-catenin interacts with and inhibits the nuclear activity of Yap in a non-cell autonomous manner that requires adherens junctions [48]. Further support for cadherin-dependent force transduction came from studies in MDCK cells in which external force application promotes nuclear entry of Yap and β-catenin, resulting in cell cycle re-entry [49]. E-cadherin force transmission also activates AMPK, a key metabolic enzyme, which was essential to generate energy for force resistance and transmission [50•]. Activation of AMPK may potentially alter the metabolic state of cells, with implications for cell fate [51].

Two recent papers provide direct evidence that cadherin dependent cell mechanics control cell fate in mammalian tissues. Neurogenesis requires the abscission of an apical cell-process from the ventricular surface. This abscission is driven by apical actomyosin constrictions induced by a reduction in N-cadherin. Detachment of this apical process then results in loss of cilia and SHH signaling that promote cell cycle exit and neuronal differentiation [52]. In the epidermis, E-cadherin dependent control of cortical tension is necessary for basal cell delamination and subsequent differentiation, thus allowing this tissue to couple cell position to cell fate [28•].

Recent *in vivo* evidence further indicates an intimate bi-directional cross-talk between cadherin adhesion and signaling to regulate cell fate. In early Zebrafish embryos only prolonged cadherin-dependent contacts initiate nodal signaling, which then through a positive feedback loop further increased cadherin contact duration. This loop resulted in a deterministic bi-stability of the system in which old contact times are 'remembered' to control mesoderm versus endoderm cell fate [53]. Thus, asymmetries in adhesive contact duration may determine cell fate, with the caveat that it is not clear whether differences in contact duration and signaling strength requires mechanical changes.

More direct evidence for direct feedback mechanisms between force perception and signaling comes from recent studies in vascular endothelial cells and keratinocytes. Shear stress triggers a non-canonical, transcription-independent Notch signal in endothelial cells. Subsequently, the Notch transmembrane domain recruits a complex of VE-cadherin, the transmembrane phosphatase LAR and the Rac nucleotide exchange factor Trio that activates Rac to promote adherens junctions and vascular endothelial barrier function [54••]. In the epidermis different mechanical states of adherens junctions secure the restricted positioning of barrier-forming tight junctions only to the uppermost viable layer through a feedback mechanism that integrates actomyosin activity and EGFR signaling. Adherens junctions are in a low-tension state in layers that do not form a barrier, resulting in increased EGFR activity, which in turn lowers cortical tension as well as increases internalization of a key tight junctional protein occludin. Through as yet unknown mechanisms, adherens junctions in the uppermost viable layer of the epidermis switch to a tension high state that inhibit EGFR activity, which subsequently further reinforces cortical tension and stabilizes tight junctions in the appropriate position [55]. As Notch and EGFR have key roles in differentiation and proliferation, these studies provide a potential mechanism how signaling receptors may integrate the differentiation status of cells with mechanical adhesive and cytoskeletal cues to control their position.

Local matrix remodelling and mechanics

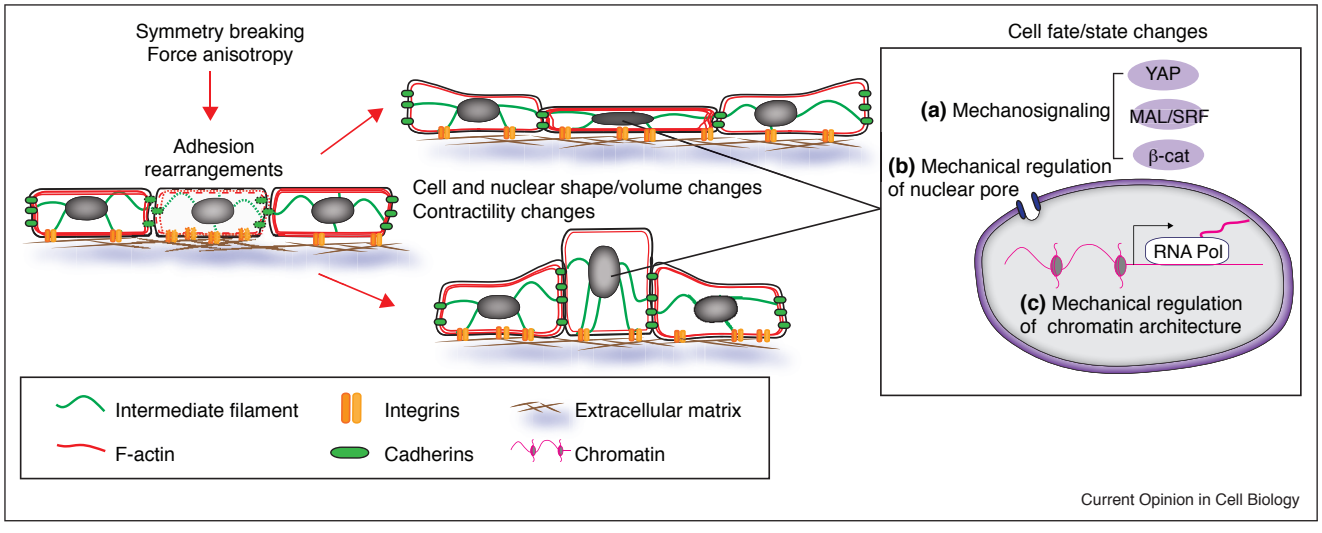
Several recent studies indicate that the heterogeneity in ECM composition and stiffness provide important positional cues for cell fate and patterning. The basement membrane composition within the hair follicle stem cell niche is distinct from the surrounding epidermis and critical for regulating stem cell activation [56]. These stem cells further secrete the basement membrane protein nephronectin, which acts as a specific niche factor for smooth muscle cells, to guide the anchoring of the arrector pili muscle to the niche [57]. Upon injury, this specific ECM patterning may be lost as is, for example, observed in the injured mouse intestinal epithelium. Injury-driven production of various ECM proteins leads to intestinal stem cell reprogramming to facilitate repair. This reprogramming is driven by the increased stiffness of the provisional injury-associated ECM that activates a mechanosensitive signaling pathway involving focal adhesion kinase (FAK) and the mechanosensitive transcription factor YAP [58]. This study highlights the importance of not only the molecular but also the mechanical properties of the local ECM in cell fate determination. The actomyosin contractile stresses exerted on cell adhesions are essential for mechanosensing, but the molecular mechanisms of this are still being worked out. One hypothesis is that responses to changes in rigidity are triggered by local contractile forces that exceed a certain threshold [59].

As for cadherins, the YAP pathway has a prominent role in matrix-rigidity driven signaling [60]. Other key developmental and stem cell pathways, such as Wnt/β catenin and Oct 3/4, also respond to mechanical properties of the matrix to instruct cell fate decisions [61•,62]. In contrast, for neuronal stem cells matrix remodelling but not stiffness seems a key determinant for stemness [63]. Interestingly, some of the effects of matrix stiffness and remodelling may be relayed indirectly by regulating the stability of cell–cell contacts and thereby the availability of β-catenin [61•,63]. Moreover, additional engagement of cadherin adhesion reduces the contractile state of mesenchymal stem cells resulting in less nuclear Yap signaling. This reduction allows these stem cells to perceive matrix stiffness differently, with direct effects on lineage commitment [64]. These studies thus highlight the intimate cross-talk and interdependency of the two adhesive machineries. However, how these local contractile actomyosin rigidity sensors are mechanistically coupled to the biochemical signaling machinery remains one of the key open questions in the field.

Local modulation of substrate viscoelasticity has recently emerged as a further potential key determinant of cell fate. Using alginate, a polymer non-degradable to mammalian cells, in combination with PEG spacers to engineer gels that underwent stress relaxation, it was observed that fast stress relaxation that increased cell spreading and proliferation also promoted osteogenic differentiation of mesenchymal stem cells [65]. Thus, mechanical forces that acutely alter cell shape may impact cell fate. Indeed, modulation of cell adhesion and confinement is sufficient to drive a phenotypic fate switch from mesenchymal to ameboid type of migration [66••]. By experimentally controlling integrin ligand density and cell confinement, the authors observed that a combination of low adhesion, which in general reduced migration speed, and cell confinement, which increased cell contractility, triggered a switch to an ameboid migration mode in a wide range of different cell types [66••]. Analogously, confinement in low adhesion environments was shown to regulate the matrix-producing phenotype of chondrocytes [67]. These results indicate that dynamic changes in the microenvironment that control three fundamental parameters — adhesion, confinement, and contractility — can trigger substantial phenotypic and functional alterations in cell behavior.

The molecular mechanisms by which the three modules — adhesion, confinement, and contractility — locally co-operate and integrate with signaling to control cell fate is still largely unclear. An intriguing recent report described force-driven nuclear flattening to induce opening of nuclear pores, leading to increased nuclear import YAP [68••]. Owing to the direct effect of force on the nuclear pore, this mechanism might apply to nuclear import more generally, and thereby provide a very rapid and efficient mechanism for cellular adaptation to

Figure 3



Model of how adhesion rearrangements trigger mechanosignaling through cell shape changes. In light of recent data we propose a simple model on how force anisotropy - triggered adhesion rearrangements result in cell fate regulation. As both cell–cell adhesions (in green) and cell–matrix adhesions (in orange) couple to the actomyosin (in red) and intermediate filament (in green) cytoskeletons, they balance the contractile forces of the cytoskeleton. Force anisotropies within a tissue represent a symmetry breaking event leading to dynamic adhesion rearrangements, distorting the adhesion force and actomyosin contractility equilibrium. Changes in adhesion forces, ligand-bound adhesion molecules and available adhesive surfaces lead to changes in cell shape and contractility, directly impacting also the shape of the nucleus. All of these factors individually, but possibly also as an integrated signal, impinge on **(a)** activity of mechanosensitive signaling molecules, **(b)** nuclear import through regulation of the nuclear pore, and **(c)** direct effect of mechanical signals on chromatin accessibility and gene expression resulting in changes in cell fate/state.

different mechanical environments. Alternatively, direct effects of mechanical forces on the nuclear lamina and thereby chromatin, have been shown to alter gene expression through epigenetic mechanisms [69–71] (Figure 3).

Concluding remarks

Taken together, a model is beginning to emerge from these recent studies: Adhesions integrate mechanical signals from local differences in matrix ligand density, the topographical features of the environment, cellular crowding state, as well as in the contractile state of the cytoskeleton to regulate cell shape and interactions necessary for tissue patterning and remodeling. At the same time these junction-mediated cell shape changes also control nuclear shape and signaling to drive changes in gene activity that affect cell fate (Figure 3). Together, these biomechanical signaling networks thus integrate cell fate and function with the position of cells within the tissue. Future work is required to understand how these very broad mechanisms are converted into specific gene expression changes to control precise and stable cellular fates and how these mechanical pathways interface with classical biochemical signals to mediate tissue self-organization and patterning.

Conflicts of interest statement

The authors declare no conflicts of interest.

Acknowledgements

We thank the Niessen and Wickström labs for many fruitful discussions. CMN is supported by DFG SFB 829 A1, A5 and Z2, The German Cancer Aid and DFG SPP 1782, NI 1234/6-1. SAW is supported by Helsinki Institute of Life Science, Wihuri Research Institute, Max Planck Society, and DFG SFB 829 A11.

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- •• of outstanding interest

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