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Abstract

Morphogenesis is the remarkable process by which cells self-assemble into complex tissues and organs that exhibit specialized form and function during embryological development. Many of the genes and chemical cues that mediate tissue and organ formation have been identified; however, these signals alone are not sufficient to explain how tissues and organs are constructed that exhibit their unique material properties and three-dimensional forms. Here, we review work that has revealed the central role that physical forces and extracellular matrix mechanics play in the control of cell fate switching, pattern formation, and tissue development in the embryo and how these same mechanical signals contribute to tissue homeostasis and developmental control throughout adult life.

Contents

INTRODUCTION

The embryo forms through a process of self-assembly in which living cells form into complex tissues and organs with highly specialized forms and functions. The long-standing dogma is that soluble morphogens control the spatially oriented changes in cell growth, migration, differentiation, and cell fate switching that mediate morphogenetic control. This paradigm assumes that soluble factors spread from localized cell production sources to generate spatiotemporal concentration gradients, which in turn induce distinct biochemical responses and changes in gene expression in cells located at distant sites that drive tissue patterning.

Although soluble factors clearly are important contributors to developmental control, more recent studies have revealed that mechanical forces generated within the cells and tissues of the embryo can provide regulatory signals that are equally as important as those conveyed by chemicals and genes. More specifically, morphogenesis is mediated by well-coordinated control of tensional force generation within the cytoskeletons of the cells that comprise developing tissues and by associated transmission of these cell-generated forces across transmembrane receptors to neighboring cells and the underlying extracellular matrix (ECM). These physical cues alter cellular signaling and thereby switch cells between different fates (e.g., growth, differentiation, motility, apoptosis, different stem cell lineages) by changing force distributions, modulating cell shape, and activating specific mechanotransduction pathways (Mammoto & Ingber 2010, Mammoto et al. 2012). Thus, developmental control in the embryo is now viewed as a mechanochemical process in which masses of cells are shaped into functional organs through reciprocal interactions between both mechanical and chemical cues. Here we review how cell-generated mechanical forces and local changes in ECM mechanics serve as key epigenetic regulators of tissue morphogenesis, organ development, and body plan determination in the embryo, as well as how these physical signals contribute to tissue development and organ homeostasis throughout adult life.

CONTROL OF EARLY EMBRYONIC DEVELOPMENT

Physical forces are critical regulators of embryological development, starting from the very earliest steps of fertilization. Nanoscale forces generated by the adenosine triphosphate (ATP)-fueled motor protein, dynein, produce rhythmic beating of the sperm flagellum, which generates the

force that enables the sperm to swim through viscous fluid inside the uterine cavity and reach the egg (Allen et al. 2010, Brokaw 1989, Roberts et al. 2012). In mammals, once the sperm penetrates the extracellular zona pellucida and moves through the oocyte membrane, a biochemical process is triggered that mechanically hardens this outer layer by crosslinking its molecular filaments, which physically blocks penetration of other sperm into the fertilized egg (Boccaccio et al. 2012).

After the fertilized oocyte starts dividing, the cellular aggregate physically compacts and increases cell-cell contact areas by generating actomyosin-dependent cytoskeletal traction forces and applying them to adhesion receptors on the surfaces of neighboring cells; this results in formation of a solid ball of cells known as the morula (Ou et al. 2010). Actin and myosin are both enriched in the apical cortex of cells at the eight-cell stage, when cell compaction starts (Sobel 1983a,b). Although most cells divide symmetrically, establishment of the first polarity in the embryo occurs in the morula when an asymmetric cell division generates a polar cell at the periphery and an apolar cell in the central region, resulting in production of two distinct cell populations (Fleming 1987, Johnson & Ziomek 1981) (**Figure 1*a***).

Control of asymmetric versus symmetric cell division is governed by mitotic spindle positioning, which is regulated by physical interactions between cytoskeletal microtubules and contractile actin microfilaments (Grill & Hyman 2005, Kunda & Baum 2009, Reinsch & Gonczy 1998, Wuhr et al. 2009). The dynamic assembly and disassembly of the microtubules physically push and pull the spindle until it reaches its correct position (Desai & Mitchison 1997, Dogterom et al. 2005, Howard & Hyman 2003). However, the forces generated by microtubule polymerization are counterbalanced by myosin-driven tensional forces within the actin cytoskeleton (Woolner & Papalopulu 2012), and forces transmitted from the cell cortex to astral microtubules appear to contribute as well (Grill & Hyman 2005, Marthiens et al. 2010, Siller & Doe 2009) (**Figure 1*a***). This latter point is supported by the observation that cell geometry dictates the positioning and orientation of the spindle in sea urchin egg (Minc et al. 2011). Application of external mechanical stresses also has been shown to modulate spindle positioning by inducing polarization of subcortical actin structures (Fink et al. 2011) and channeling forces over cell surface integrin receptors and microfilaments that link to the mitotic spindle at the cell center (Maniotis et al. 1997).

Thus, mechanical forces generated in the cytoskeleton play key roles in the spindle positioning within symmetrically and asymmetrically dividing cells in the early embryo (Grill & Hyman 2005), and they appear to do this via use of a tensegrity-based, cellular-force balance mechanism that involves opposing microtubules and contractile actin microfilament systems (Ingber 1997). But the contribution of physical cues to embryological development does not stop here. For example, dividing cells in morula centrally secrete a viscous fluid, which generates a central cavity and induces the cell aggregate to transform into a hollow ball of cells, called the blastocyst. This is accompanied by formation of the embryonic-abembryonic axis that spans from the inner cell mass to the opposite region of the developing blastocyst (**Figure 1*b***). Interestingly, although formation of this axis was thought to be prepatterned (Rossant & Tam 2009), it can be redirected by applying external physical constraints (Alarcón & Marikawa 2003, Honda et al. 2008, Kurotaki et al. 2007, Motosugi et al. 2005). For example, when embryos are deliberately compressed into an elongated shape, the blastocoel is positioned consistently at one end of the extended blastocyst (Motosugi et al. 2005); this is consistent with the observation that the natural embryonic-abembryonic axis aligns with the long axis of the stiff zona pellucida, which normally physically constrains the embryo within an ellipsoid form (Gray et al. 2004).

In the mammalian blastocyst, the outer epithelium becomes committed to form the trophoectoderm, which subsequently gives rise to the trophoblast layers of the placenta, and the cells of the inner cell mass differentiate into two cell layers, the primitive epiblast and endoderm. The epiblast forms the pluripotent cell lineage of the blastocyst, giving rise to all of the primary germ layers

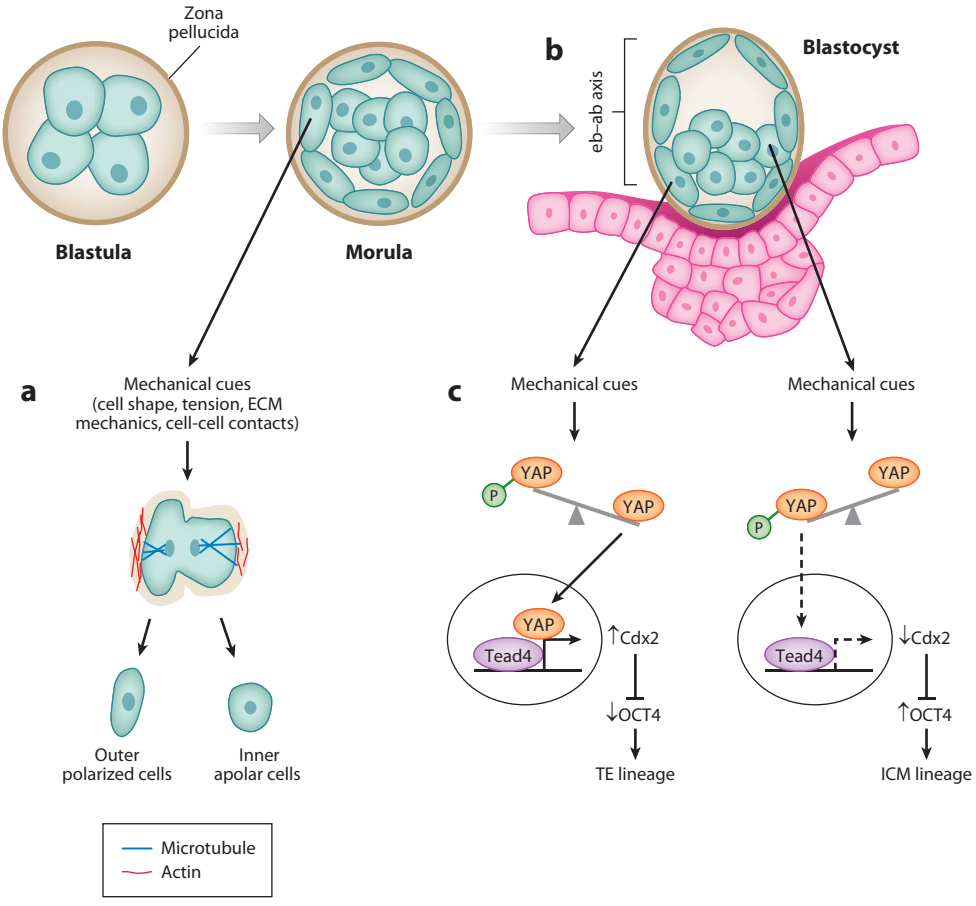


Figure 1

Mechanical control of asymmetric cell division in the early embryo. (*a*) Mechanical tension generated within the cytoskeleton of the first embryonic cells drives cell compaction and modulates spindle positioning through establishment of a cytoskeletal-force balance with resisting microtubules, which is responsible for asymmetric cell divisions in the morula. (*b*) External mechanical constraints by the stiff zona pellucida dictate the embryonic-abembryonic (eb-ab) axis in the developing blastocyst. (*c*) Mechanical cues generated by physical confinement of the blastocyst regulate the expression of OCT4 through Hippo/YAP pathway–dependent regulation of Cdx2 in trophoectoderm and epiblast cells. Abbreviations: ECM, extracellular matrix; ICM, inner cell mass; P, phosphorylated; TE, trophoectoderm; YAP, Yes-associated protein.

of the fetus, whereas the endoderm forms the extraembryonic yolk sac. The emergence of these first epithelial layers corresponds with the appearance of the first organized ECM in the form of a basement membrane containing laminin, type IV collagen, and heparan sulfate proteoglycan, which accumulate within the inner cell mass (Biggers et al. 2000) and under the basal side of the trophoectoderm (Thorsteinsdóttir 1992).

Importantly, local changes in physical forces and in the mechanical properties (e.g., stiffness or compliance) of this ECM appear to actively contribute to the control of gene transcription that drives cell fate switching during blastocyst development. For example, loss of the transcription factor Cdx2 leads to the ectopic expression of inner cell mass markers in trophoectoderm (Niwa et al.

2005) and may induce lineage switching by negatively regulating expression of another pluripotent transcription factor, Oct4. Oct4 expression gradually restricts to the cells of the inner cell mass in the blastocyst, where it drives epiblast formation (Dietrich & Hiiragi 2007), whereas Cdx2 expression is restricted exclusively to outer trophoectoderm (Dietrich & Hiiragi 2007, Ralston et al. 2010). Mechanical forces and physical properties of the ECM appear to modulate cell fate switching through the Hippo pathway (Halder et al. 2012). This evolutionarily conserved signaling pathway, which appears to be necessary for normal organ growth in vertebrates as well as in *Drosophila* (Richardson 2011, Wang & Riechmann 2007, Zhao et al. 2011), is composed of the Hippo and Warts kinases, together with their cofactors, the transcriptional coactivator Yorkie in *Drosophila* or Yes-associated protein (Yap1) in mammals, the scaffold protein salvador, and the MOB kinase activator-like 1 protein (Dick & Mymryk 2011, Zhao et al. 2008). The mechanosensitive Hippo signaling pathway plays a key role in this cell fate switching in that expression of Cdx2 and trophoectoderm formation depend on the transcription factor Tead4 and its coactivator partner, Yap1 (Nishioka et al. 2008, 2009; Yagi et al. 2007) (**Figure 1*c***). Yap1 is localized to the nucleus only in the outer cells that also express Cdx2 (Nishioka et al. 2009), whereas it becomes phosphorylated and sequestered in the cytoplasm of the inner cells in which Cdx2 is downregulated (Nishioka et al. 2009). Similar shifts in nuclear distribution of Yap1 mediate the effects of mechanical forces or ECM stiffness on cell fate switching in other cells (Dupont et al. 2011, Zhong et al. 2013). Thus, differences in physical cues in the local micromechanical environment likely influence cell fate switching in the blastocyst, at least in part via this mechanical signaling mechanism.

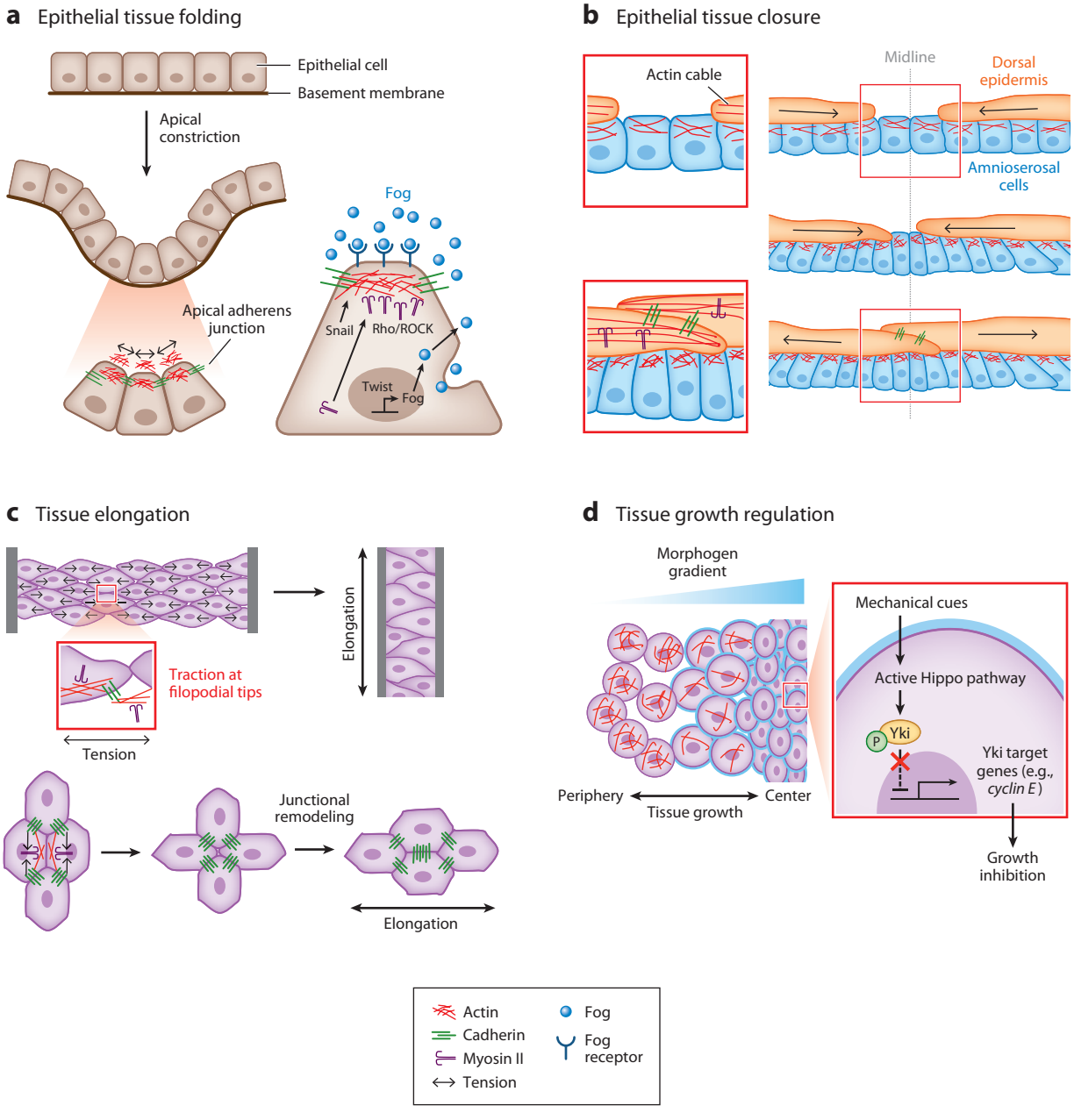
CELL-GENERATED FORCES CONTROL TISSUE MORPHOGENESIS

After the main embryonic axis is formed, cells self-assemble into tissues that undergo growth, bending, and deformation to create organs with characteristic 3D shapes. Again, formation of these specialized structures relies on the ability of their constituent cells to generate mechanical forces within their contractile cytoskeleton and to transmit them across ECM and cell-cell adhesions at the tissue and organ levels. Contractile microfilaments, composed of aligned bundles of actin and myosin II filaments, form a contractile cytoskeletal network that spans from the nucleus to the cell cortex, where it links to the cytoplasmic face of transmembrane integrin receptors and cadherins on the plasma membrane (Backouche et al. 2006; Verkhovsky et al. 1995, 1997). In this manner, inward-directed tensional forces that are generated in the contractile cytoskeleton are exerted on the cell's surface adhesions to underlying ECM and neighboring cells, respectively. These traction forces lead to complicated temporal and spatial patterns of mechanical contraction, which orchestrate various transformations in cell and tissue shape, as well as complex morphogenetic movements.

In developing epithelium, the mechanical linkage between the cytoskeletons of neighboring cells occurs primarily at the apical adherens junctions (Gates & Peifer 2005, Halbleib & Nelson 2006), in which the intracellular domains of transmembrane cadherin proteins form an anchoring complex with β-catenin and its actin-binding partner, α-catenin (Ozawa & Kemler 1992) (**Figure 2*a***). Although the nature of the connection between E-cadherin and the actin cytoskeleton remains unclear (Drees et al. 2005, Yamada et al. 2005), genetic studies suggest that both catenins mediate the mechanical linkage between neighboring cells (Cavey et al. 2008, Dawes-Hoang et al. 2005, Gates & Peifer 2005, Vasioukhin & Fuchs 2001).

Coupling of cell-generated mechanical forces through these cell-cell adhesions results in an apical constriction of epithelial cells, which reduces the size of the apical surface of each cell relative to its base (Sawyer et al. 2010) (**Figure 2*a***). This physical constriction mechanism is used to deform the cells and thereby generate a variety of epithelial patterns during morphogenesis,

including folding, pitting, and tubing (Colas & Schoenwolf 2001, Leptin 2005) (**Figure 2*a***). For instance, during neural tube closure, actin and myosin II, organized within circumferential cables that directly associate with the adherens junctions, drive apical constriction of linked cell populations, resulting in folding of the initially planar neural plate into a hollow tube (Colas & Schoenwolf 2001). Apical constriction also induces invagination of the presumptive mesoderm during *Drosophila* gastrulation (Costa et al. 1994, Kam et al. 1991, Parks & Wieschaus 1991, Sweeton et al. 1991). In this case, myosin II coalesces in aggregates within the apical cortex as a



result of contraction of the actin meshwork (Martin et al. 2009), which exerts traction on cell-cell adherens junctions and thereby induces apical constriction (Dawes-Hoang et al. 2005, Sawyer et al. 2009) (**Figure 2*a***).

Finely tuned mechanochemical coupling regulates morphogenesis in *Drosophila* as well. The mechanosensitive transcription factor Twist (Farge 2003) works in concert with the Snail protein to control mesoderm invagination during *Drosophila* gastrulation through regulation of the folded gastrulation (Fog) protein and the transmembrane T48 protein. Snail induces stochastic pulsed apical constrictions (Martin et al. 2009) that inhibit endocytosis of Fog, thereby increasing its concentration in the extracellular environment, which in turn induces actomyosin-dependent apical constriction of the cells via activation of RhoGEF2 and Rho-associated kinase (ROCK) signaling (Dawes-Hoang et al. 2005, Martin et al. 2009, Pouille et al. 2009) (**Figure 2*a***). In addition to activating Fog expression, Twist targets T48, which promotes adherens junction formation and recruitment of RhoGEF2 to the sites of apical constriction; this in turn reinforces the Snail-induced apical constriction (Kölsch et al. 2007).

Cytoskeletal contractile forces are also critical for closure of the dorsal epidermal opening at the end of gastrulation in the *Drosophila* embryo (Kiehart et al. 2000) (**Figure 2*b***). Closure begins with the formation of supracellular actin cables at the leading edge of the lateral epidermis, which generate traction forces that pull the edges toward the midline (Jacinto et al. 2002). Underlying amnioserosal cells shift from a squamous to a columnar shape and constrict their apical surface, generating additional tugging forces that pull the overlying epidermal tissue toward the midline to produce closure (Solon et al. 2009) (**Figure 2*b***).

Other examples of mechanical control of tissue pattern are the convergence and extension movements that drive the elongation of the anterior-posterior body axis during gastrulation and neurulation in *Drosophila*. These polarized cell movements are produced through interplay between cell protrusive activities (Jessen et al. 2002, Marlow et al. 2002, Shih & Keller 1992, Wallingford et al. 2000) that promote radial cell-cell intercalation and cytoskeletal contraction forces powered by myosin II and dynamic actin meshworks (Rolo et al. 2009, Skoglund et al. 2008) (**Figure 2*c***). The polarity of contractility is due to the oriented transmission of contractile forces through adhesive sites at the protrusive ends of the cells, and cell sliding and intercalation are driven through coordination of the contractile and protrusive activities.

Polarized epithelial tissue elongation, as observed during germ-band extension in *Drosophila*, is similarly influenced by mechanical force–driven assembly and disassembly of cell-cell adherens,

Figure 2

Mechanical control of morphogenetic movements. (*a*) During epithelial tissue folding, coupling of cell-generated mechanical forces through cell-cell adhesions results in apical constriction of the epithelial cells, which produces tissue invagination. In the *Drosophila* presumptive mesoderm, Snail-dependent pulses of apical mechanical constriction inhibit Fog endocytosis through an increase in membrane tension. This activates the downstream-of-Fog/Rho/ROCK/Myo II–signaling pathway, which leads to stable apical constriction and invagination. Fog is expressed under the control of Twist. (*b*) During epithelial tissue closure in *Drosophila*, migrating cells at the leading edge of the dorsal epidermis extend filopodia that promote formation of new cell-cell junctions when they contact cells on the opposing leading edge. The underlying amnioserosal cells also pull the overlying epidermal cells toward the midline by using apical constriction–driven forces to assist the closure. (*c*) Elongation of some tissues in the embryo (*top*) is propelled by myosin II–driven traction forces that are exerted at cell-cell junctions (*bottom*), which elongate the tissue by inducing shortening in the mediolateral direction (convergence) and extension in the anteroposterior direction (extension). (*d*) Growth regulation in the *Drosophila* wing is a result of physical compression of densely packed cells in the central region. This causes actin fiber remodeling in these physically compacted cells, which activates the Hippo pathway and thereby leads to phosphorylation of Yki (the *Drosophila* ortholog of YAP), preventing the nuclear translocation of this transcription factor. As a result, transcriptional activity of Yki target genes, such as *cyclin E*, is decreased, and cell growth is inhibited. At the same time, cells at the periphery slow their proliferation because they have grown beyond the influence of the morphogen gradients; thus, the whole wing tissue grows uniformly. Abbreviation: P, phosphorylated.

which mediate the process of intercalation (Bertet et al. 2004, Blankenship et al. 2006, Irvine & Wieschaus 1994). Myosin II and actin filaments asymmetrically localize to junctional interfaces that shrink, whereas E-cadherin, Armadillo/β-catenin, and the Bazooka/Par-3 junctional proteins are enriched at interfaces that grow (Bertet et al. 2004, Blankenship et al. 2006, Zallen & Wieschaus 2004). ROCK, which stimulates cytoskeletal tension generation, controls adherens junction stability and remodeling, as well as the localization of these molecules (Chen & Macara 2005, de Matos Simões et al. 2010, Harris & Peifer 2004, Sahai & Marshall 2002) (**Figure 2*c***). In addition, high-tension actin-myosin cables (Fernandez-Gonzalez et al. 2009) that span multiple pairs of cells generate multicellular rosette formations, which further promote tissue elongation (Blankenship et al. 2006).

Planar cell polarity (PCP), which governs the orientation of cells within the plane of an epithelial cell layer, is made possible by collective cell movements that generate functionally aligned tissues. The PCP mechanism has been studied in detail in developing *Drosophila* wing, which is covered by a hexagonally packed array of hairs, each constructed by a single wing epithelial cell. During wing development, epithelial cells polarize by using cytoskeletal traction forces to pull against neighboring cells, which results in the alignment of intercellular junctions. This process, mediated by junctional remodeling, is regulated by PCP signaling molecules, such as Wnt and the small GTPase Rab11, which control cell-packing geometry as cells convert from irregular forms into a hexagonal array shortly before hair formation (Classen et al. 2005, Farhadifar et al. 2007). The asymmetric distribution of cytoskeletal and junctional proteins, which are used for tissue elongation in other tissues (**Figure 2*c***), also contributes to polarized cell behavior during hexagonal packing (Blankenship et al. 2006).

Importantly, actomyosin-dependent contractility as well as long-distance mechanical force transmission across the tissue appear to be crucial for the PCP process. For example, myosin II is enriched in a bipolar manner within the aligned cells of the prospective denticle field, and it contributes to cell rearrangements during establishment of PCP in the forming wing by acting in concert with denticle field–specific effectors (Walters et al. 2006). Thus, these epithelial packing patterns, which govern functional wing formation, also appear to be determined by a balance between cytoskeletal pulling forces and resisting adhesive tethers to both neighboring cells and the underlying ECM (Farhadifar et al. 2007). Interestingly, Milinkovitch et al. (2013) showed that mechanical tension fields generated by rapid growth of epithelium also define cracking patterns in crocodile skin. These are all vivid examples of how mechanical forces directly influence development of specialized tissue forms during tissue pattern formation.

Mechanical cues also contribute to the control of cell proliferation, tissue growth, and organ size. For example, models of *Drosophila* wing development (Hufnagel et al. 2007, Shraiman 2005) predict that the tissue will grow uniformly because cell growth at the periphery of the wing slows when cells extend beyond the edge of the morphogen gradient, whereas proliferation becomes suppressed in the central area owing to cell compression (Chen et al. 1997). Interestingly, the mechanosensitive Hippo pathway again appears to mediate this feedback loop for uniform tissue growth. Active Hippo signaling results in phosphorylation of Yorkie and Yap1 and their retention in the cytoplasm, which leads to transcriptional downregulation of other critical target genes, including the cell cycle regulator cyclin E (Dong et al. 2007; Oh & Irvine 2008, 2009). Given that changes in cell shape alter nuclear translocation of Yap1 in mammalian cells (Dupont et al. 2011), local changes in physical forces or ECM mechanics could influence morphogenesis and pattern formation by modulating cell form (**Figure 2*d***), as suggested previously (Huang & Ingber 1999, Ingber & Jamieson 1985, Mammoto & Ingber 2010). Conversely, differential growth between neighboring cells also generates mechanical strain, which modulates various morphogenetic movements (Shraiman 2005, Skalak et al. 1996). For example, growth inhibition of the

local amnioserosa cells, modulated by apoptosis, induces neighboring cells to generate mechanical forces that are required for dorsal closure in *Drosophila* (Toyama et al. 2008).

Mechanical Control of Organ Formation

Once conserved morphogenetic movements have established the basic body plan, embryonic cells start differentiating along organ-specific lineages and self-assemble into mature organs. Mechanical cues also regulate these processes during the later stages of embryological development. For example, though many soluble morphogens play a critical role in control of organ development, some of them manifest their actions by modulating the cellular force balance (Corrigall et al. 2007, Escudero et al. 2007, García Fernández et al. 2007, Lee et al. 2006, Schlichting & Dahmann 2008). During tooth formation in mouse, the dental epithelium produces gradients of opposing attractive and repulsive motility factors—fibroblast growth factor8 and semaphorin 3F, respectively—that cause cells to migrate toward each other and, thereby, generate defined areas of mesenchymal cell compaction in a process known as mesenchymal condensation. Formation of the condensed mesenchyme, in turn, triggers expression of organ-specific transcription factors, such as Pax9 and Msx1, as a result of compression, which induces the cell to round and suppress Rho signaling (Mammoto et al. 2011) (**Figure 3*a***). Compaction of mesenchymal cells in the condensing mesenchyme induces production of collagen VI–containing ECM scaffolds, which stabilize the condensed tissue form and physically induce organ-specific cell lineage specification during tooth organ formation (Mammoto et al. 2011) (**Figure 3*b***). Thus, developmental patterning and organ-specific determination of cell fate are governed through a complex mechanochemical mechanism in which chemical cues manifest their actions largely through changes in the physical microenvironment, which feed back to alter mechanical signal transduction and gene expression.

Mechanical forces are also crucial for the formation of various other organs, including the hematopoetic system (Adamo et al. 2009, North et al. 2009), blood vessels (Chen et al. 2012, Lucitti et al. 2007), heart (Granados-Riveron & Brook 2012, Hove et al. 2003, Voronov et al. 2004), lungs (Cohen & Larson 2006, Gutierrez et al. 2003, Inanlou et al. 2005), kidneys (Serluca et al. 2002, Vasilyev et al. 2012), muscle (Reiser et al. 1988, Zhang et al. 2011), joints (Kahn et al. 2009, Roddy et al. 2011), and bone (Sharir et al. 2011). For example, the heart tube starts pumping blood before formation of the chambers and valves by using dynamic suction force, which is generated by peristalsis movements of the myocytes in zebrafish (Forouhar et al. 2006). The hemodynamic stresses (pressure, flow) generated in this early circulation system feed back to modulate development of the cardiac loop, chamber, and valve (Hove et al. 2003, Voronov et al. 2004), which optimize the efficiency of heart function in the embryo. Fluid shear stress is also required for physiological development of the hematopoietic system in mice and zebrafish; this effect appears to be mediated by the induction of the transcription factor Runx1 through flow-sensitive nitric oxide (NO) production (Adamo et al. 2009, North et al. 2009). This flow-sensitive differentiation of the erythroblasts increases the erythrocyte volume fraction (hematocrit) to maintain fluid shear stress, which modulates vascular remodeling in the mammalian yolk sac (Lucitti et al. 2007). In zebrafish, blood flow also regulates pruning of the vasculature, which is crucial for vascular network maturation in the brain (Chen et al. 2012).

The lung is also exposed to mechanical forces in utero generated by amniotic fluid flow driven by fetal breathing-like movements, which accelerate lung growth and pulmonary cell differentiation required for functional maturation of the lung (Inanlou et al. 2005). Contraction of the embryonic lung smooth muscle, which depends on function of the cystic fibrosis transmembrane conductance regulator, increases amniotic fluid pressure inside the airway and accelerates fetal lung maturation (Cohen & Larson 2006). Importantly, overdistension of the lung in utero, as occurs in congenital

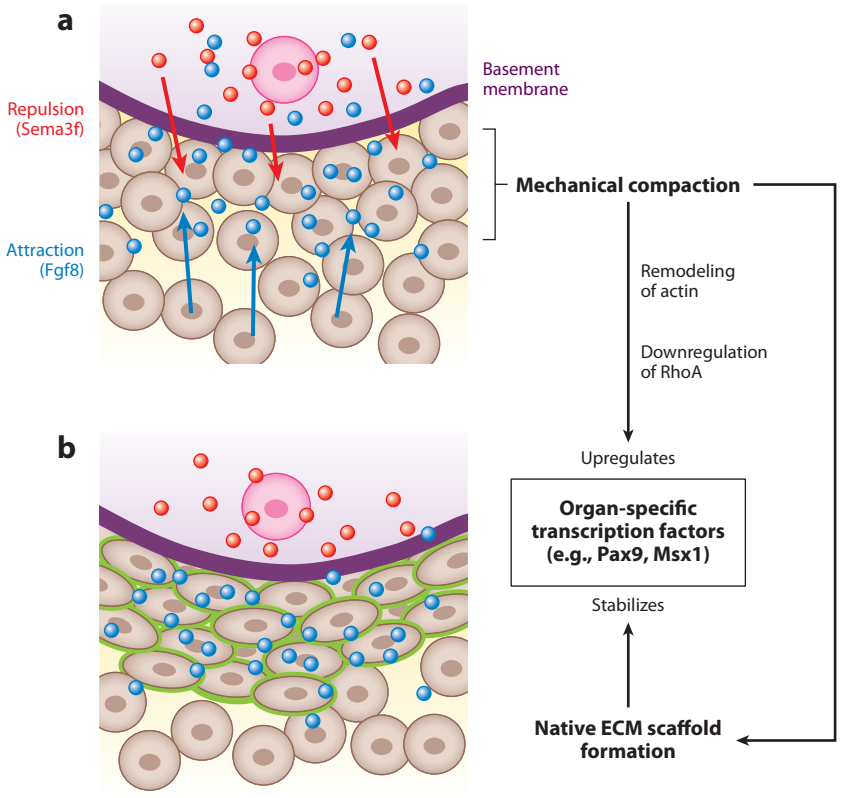


Figure 3

Mechanochemical control of mesenchymal condensation during organ formation. (*a*) During tooth development in the mouse, two antagonistic morphogens, Fgf8 and semaphorin 3f (Sema3f), which are produced by the early dental epithelium, respectively attract and repulse surrounding mesenchymal cells. This causes the mesenchymal cells to pack tightly adjacent to the epithelium and undergo mesenchymal condensation. Resulting mechanical compaction–induced changes in cell shape and associated alterations in RhoA activity and actin organization stimulate expression of transcription factors that are crucial for tooth-specific organogenesis. (*b*) Compaction of mesenchymal cells in the condensing mesenchyme induces production of collagen VI–containing extracellular matrix (ECM) scaffolds that stabilize the condensed tissue form and ensure continued organ-specific differentiation.

laryngeal atresia, results in formation of larger lungs with an increased number of alveoli and more mature architecture than expected for gestational age (Wigglesworth et al. 1987). In contrast, underdistention of the developing lung, which can result from a congenital diaphragmatic hernia, leads to a hypoplastic lung with less surfactant protein (Dibbins 1978, Suen et al. 1993). These findings clearly demonstrate the fundamental role that mechanical forces play in lung development. In kidney, fluid shear forces in capillaries contribute to remodeling of the forming glomerular assembly, which controls blood filtration and tubular flow (Serluca et al. 2002). Shear forces in the tubules also regulate morphogenesis of nephrons by modulating collective tubule cell migration (Vasilyev et al. 2009, 2012), whereas obstruction of flow induces kidney dysplasia (Chevalier 1995).

Mechanical tension exerted by muscles promotes maturation of cell-cell junctions so that they can more efficiently resist mechanical stress, and this contributes to coordinated morphogenesis of tissues during muscle organ formation in *Caenorhabditis elegans* (Zhang et al. 2011). Conversely,

chronic immobilization of muscle leads to a loss of isometric contractile capacity in the skeletal muscle of the chicken embryo (Reiser et al. 1988). Muscle contraction–generated mechanical loads also modulate morphogenesis and strength of developing bone (Sharir et al. 2011). Even after birth, proper physical activity in childhood is crucial for physiological bone development, and decreased compressive loads owing to enforced rest, myopathy, or weightlessness (e.g., in astronauts) result in formation of thinner bones (Nabavi et al. 2011, Schoenau 2005, Ward et al. 2006). Thus, physical forces acting on developing tissues are crucial for proper tissue morphogenesis and organ development.

EXTRACELLULAR MATRIX AND MORPHOGENETIC CONTROL

Organogenesis and morphogenetic movements involve dynamic remodeling of ECM scaffolds in the embryo (Kramer & Yost 2002, Rifes & Thorsteinsdóttir 2012, Rozario & DeSimone 2010, Skoglund & Keller 2007, Yin et al. 2010). In addition to physically connecting cells within tissues, ECMs act as 3D elastic scaffolds that resist cell-traction forces and thereby regulate tissue development by altering physical force distributions, changing the cellular force balance, and modulating cell shape (Beloussov et al. 2000, Huang & Ingber 1999, Ingber & Jamieson 1985). In this manner, physicochemical cues conveyed by changes in ECM mechanics and associated alterations in cell shape can modulate diverse biological functions, including cell migration, growth, apoptosis, differentiation, contractility, lineage specification, and cellular self-assembly (Alcaraz et al. 2008, Chen et al. 1997, Engler et al. 2006, Guo et al. 2012, Hadjipanayi et al. 2009, Ingber & Folkman 1989, Kadler 2004, Lo et al. 2000, Mammoto & Ingber 2010, McBeath et al. 2004, Parker et al. 2002, Polte et al. 2004).

Many morphogenetic movements, such as convergence extension and oriented cell division, depend on assembly of ECM (Davidson et al. 2006; Marsden & DeSimone 2001, 2003). For example, fibronectin (FN) fibrillogenesis is necessary to maintain oriented cell division and cell polarity required for epiboly in the zebrafish embryo (Rozario et al. 2009), and inhibition of FN assembly interferes with epiboly and axial extension in the *Xenopus* embryo (Davidson et al. 2004; Marsden & DeSimone 2001, 2003). These findings suggest that proper spatiotemporal expression and assembly of ECM structures play key roles in the regulation of morphogenetic cell movements.

Cell traction forces exerted on ECM via bound integrins also induce physical unfolding of some ECM molecules, such as FN and collagen. These force-dependent changes in molecular conformation expose cryptic sites that promote ECM fibrillogenesis (Baneyx et al. 2002, Gao et al. 2003), which can feed back to activate intracellular signaling pathways that alter cell proliferation and ECM turnover (Graham et al. 2004, Hocking & Kowalski 2002, Orgel et al. 2011, Sechler et al. 2001, Vogel & Sheetz 2009). Mechanical forces exerted across cell-cell and/or cell-ECM adhesions also can modulate morphogenetic movements by altering ECM remodeling. For example, mechanical tension exerted at cell-cell junctions modulates *Xenopus* morphogenesis by altering FN assembly (Dzamba et al. 2009). Cell-ECM interactions also modulate morphogenesis of the ventral node—a pit-like structure on the ventral side of the embryo that plays a crucial role in organ patterning—by promoting FN assembly, and this is required for establishment of asymmetric gene-expression patterns in early mouse development (Pulina et al. 2011).

Proper control of ECM-driven cell migration is essential for directing cells to their appropriate destinations in the embryo, where they differentiate along organ-specific lineages and assemble into specialized tissue forms. For example, spatiotemporal deposition of FN at the midline of the zebrafish embryo modulates coordinated migration of the myocardial precursor cells to form polarized epithelial sheets, which are crucial for heart tube formation (Trinh & Stainier 2004). When neural crest cells in the dorsal portion of the neural tube migrate in streams through the

embryo to reach their ultimate phenotype-specific sites, they give rise to a diverse cell lineage, including neurons, glia, craniofacial cartilage and bone, pigment cells, and smooth muscle and sympathoadrenal cells (Knecht & Bronner-Fraser 2002). These cells are guided toward their final sites during organogenesis by assembly of conserved sets of ECM components, including FN, laminin, and aggrecan (Perris & Perissinotto 2000, Pietri et al. 2004).

Dynamic remodeling of the ECM also contributes to the process of organ looping, by which heart and gut become positioned asymmetrically with respect to the midline. Spatiotemporal remodeling of ECM regulated by matrix metalloproteinase 2 activity modulates asymmetric patterns of cell proliferation to dictate the direction of cardiac looping in the chick embryo (Linask et al. 2005). In zebrafish, hand2-dependent dynamic remodeling of laminin scaffolds induces asymmetric migration of mesodermal cells, which pushes the developing gut leftward; this allows correct gut looping as well as the proper positioning of the liver and pancreas (Yin et al. 2010). Although the precise role of ECM in this process is not known, mechanical forces generated by rapid growth of the pliable gut tube over the anchoring soft mesenteric sheet determine the looping patterns of embryonic gut, which suggests that the elastic properties of the ECM are critical for organ patterning (Savin et al. 2011).

Epithelial branching morphogenesis is an example in which spatial differentials in ECM remodeling play a central role in determining final tissue form, as well as in amplifying the total tissue surface area available for molecular exchange in organs, such as lung, kidney, pancreas, salivary gland, and mammary gland. These epithelial tissues exhibit complex, 3D, treelike structures that are built through interactive rounds of budding, branching, and bifurcation, which are controlled through mechanical interplay between cells and their ECM adhesive scaffolds. Formation of epithelial branching patterns in the embryonic mouse lung, for example, is governed by a mechanical balance between cell-generated traction forces and differences in the ability of the underlying ECM to resist these stresses in different regions of the growing organ. Cell proliferation and epithelial budding are enhanced in regions of ECM thinning that should exhibit increased compliance (flexibility), whereas growth is suppressed in cleft regions that exhibit a thicker and more rigid basement membrane (Moore et al. 2005). These local variations in ECM mechanics should alter physical force distributions that regulate cell shape and growth (Chen et al. 1997, Huang & Ingber 1999, Ingber & Jamieson 1985), and this possibility is supported by the finding that altering the cytoskeletal force balance by modulating Rho-ROCK signaling can either enhance or suppress morphogenesis in the developing mouse lung (Moore et al. 2005). A similar mechanical feedback loop, involving long-range interactions between cell-generated traction forces and collagen fibers that physically resist these stresses, also directs tubulogenesis in mammary epithelial cells (Cassereau et al. 2012).

The rigidity of the ECM not only stabilizes and mechanically strengthens various tissues and organs but also controls stem cell self-renewal and lineage switching, which are crucial for organogenesis and regeneration. Studies with cultured cells have shown that variations in ECM mechanics direct mesenchymal cells along different stem cell lineages. For example, mesenchymal stem cells (MSCs) differentiate into a neuronal-like lineage when grown on soft ECM gels, but they differentiate into osteoblasts on stiff gels and into myoblasts on ECMs with intermediate stiffness (Engler et al. 2006). Interestingly, cell shape and associated changes in RhoA activity appear to be responsible for MSC lineage commitment in response to the physical cues: RhoA activation induces osteogenic differentiation, whereas inhibition of RhoA leads to adipogenesis (McBeath et al. 2004). Furthermore, RhoA-mediated osteogenic or adipogenic differentiation depends on cell shape distortion in that MSCs allowed to spread on a stiff substrate undergo osteogenesis, whereas rounded MSCs form adipocytes (Bhadriraju et al. 2007). Mouse embryonic stem cells are also highly mechanosensitive, as they rapidly lose pluripotency (as measured by the suppression

of *Oct3/4* gene expression) and differentiate along organ-specific cell lineages when exposed to mechanical stress (Chowdhury et al. 2010).

The stem cell microenvironment, or niche, plays a key role in maintaining tissue homeostasis, in addition to regulating tissue repair and regeneration (Walker et al. 2009). To accomplish this task, adult stem cells must perform asymmetric division in which the cells generate one identical copy of themselves that retains stem cell characteristics and another daughter cell that differentiates into organ-specific cells (Morrison & Kimble 2006). Mechanical adhesive interactions between stem cells and surrounding supporting stromal cells (or their intervening ECM) promote asymmetric cell divisions that are crucial for the maintenance of stem cell niches in embryonic *Drosophila* testes (Tanentzapf et al. 2007) and neurons (Siegrist & Doe 2006). Compromise of cadherin and integrin functions that disrupts cell-cell or cell-ECM adhesion among germline stem cells has been suggested in subsequent loss of organ-specific stem cells in *Drosophila* ovaries and testes, respectively (Song et al. 2002, Tanentzapf et al. 2007), and in mice (Karpowicz et al. 2009, Shen et al. 2008). However, these mechanical cues must be integrated with other chemical signals, such as Fgf or insulin-like growth factor, to exert effective developmental control (Bendall et al. 2007). ECM elasticity also can act in concert with cytoskeletal tension to regulate release of ECM-bound growth factors, such as dissociation of latent TGFβ from integrin-bound TGFβ-binding protein-1, which can then direct cell fate specification, tissue remodeling, and various developmental processes (Akimov & Belkin 2001, Fontana et al. 2005, Wells & Discher 2008). These findings suggest that stem cells are exquisitely sensitive to their physical microenvironment and that mechanical cues are as important as soluble factors for the control of stem cell growth and function.

MECHANICAL SIGNAL TRANSDUCTION

Cell-generated mechanical forces exerted on cell-cell junctions and cell-ECM adhesions not only drive morphogenesis but also establish tensional homeostasis both inside individual cells and within the mechanically coupled tissue and organ. Cells sense changes in this physical force balance, whether produced by externally applied stresses (e.g., owing to movement or gravity) or through alterations in cell contractility or shape, and they transduce these mechanical signals into changes in intracellular biochemistry and gene expression—a process known as mechanotransduction (Ingber 2006). Importantly, intracellular signals generated by this mechanosensation response can feed back to alter cytoskeletal tension generation, and this feedback loop appears to be crucial for morphogenesis as well as homeostasis of adult organs. Thus, to fully understand how physical forces regulate tissue development and functions of adult organs, it is necessary to understand the process by which individual cells sense and respond to mechanical signals at the molecular level.

Transduction Through Cell–Extracellular Matrix Adhesions

Mechanical forces exerted on the membrane surface can be converted into intracellular biochemical signals through various molecular signaling pathways. Forces applied to cell-ECM adhesions are transmitted across the cell surface transmembrane integrin receptors and to the cytoskeleton via molecular linkages with the specialized anchoring complex known as the focal adhesion (Wang et al. 1993). Within the focal adhesion anchoring complex, integrins physically associate with multiple adaptor proteins involved in signal transduction, such as focal adhesion kinase (FAK), vinculin, talin, p130Cas, and paxillin (Cukierman et al. 2001, del Rio et al. 2009, Friedland et al. 2009, Sawada et al. 2006) (**Figure 4**). Thus, both internal forces generated within the actin cytoskeleton and external forces transmitted across ECM adhesions focus on these focal adhesion sites.

Because the focal adhesion orients much of the cell's signal transduction machinery, it serves as a mechanochemical signaling center, in which changes in the local balance of forces are sensed

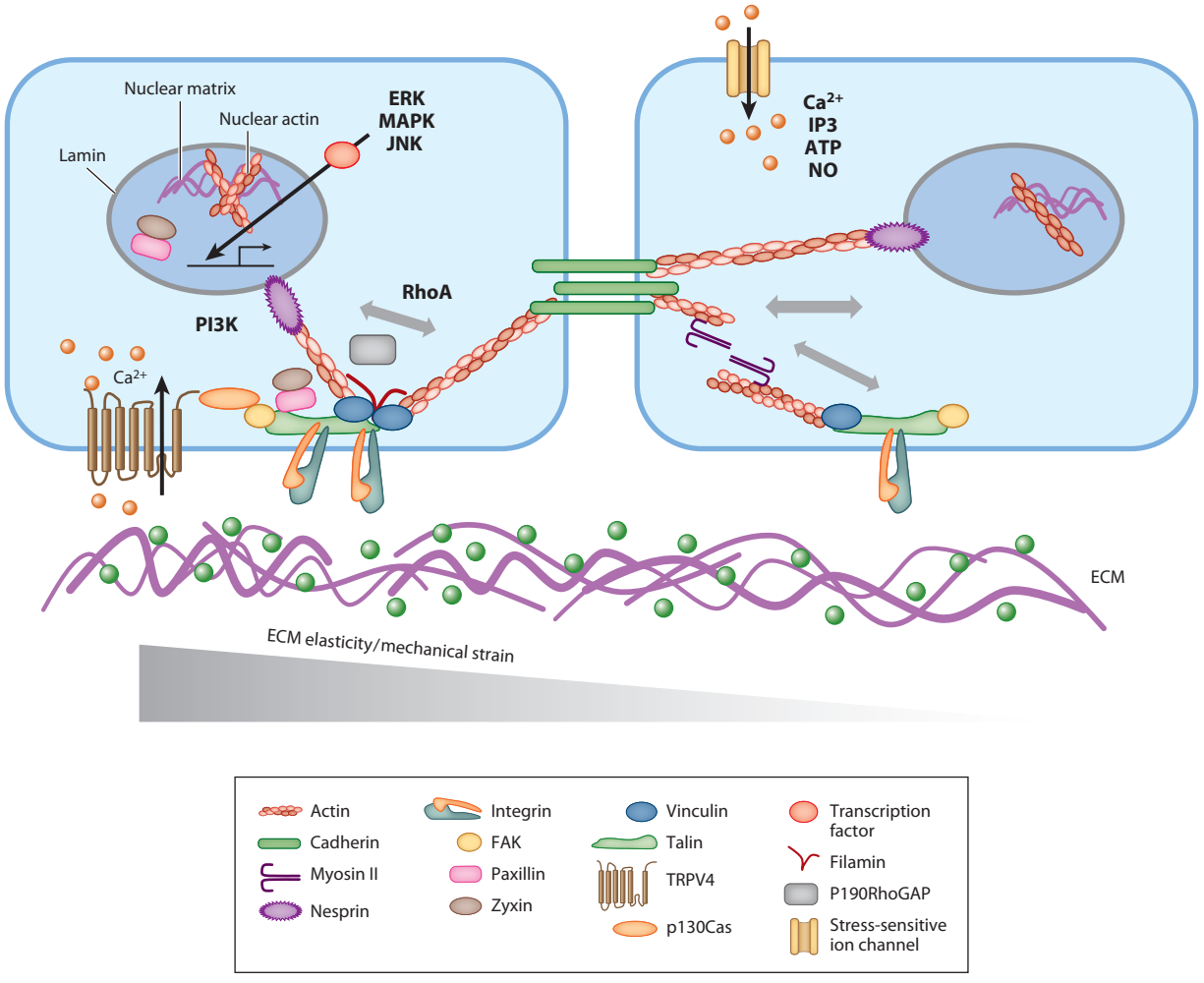


Figure 4

Cellular mechanotransduction pathways. Cells sense changes in physical force balances produced either by externally applied stresses (e.g., owing to movement or gravity) or by alterations in cell shape or contractility via various molecular mechanisms. These mechanical signals are sensed by transmembrane integrin and cadherin receptors that physically couple the cytoskeleton to the extracellular matrix (ECM) and neighboring cells, respectively. Forces conveyed across these receptors can be transduced into changes in intracellular biochemistry and gene transcription by physically distorting molecules with focal adhesion and junctional anchoring complexes that link these surface receptors to the internal cytoskeleton. For example, when cells and tissues experience mechanical strain, forces transmitted through integrin receptors and cadherins modulate intracellular signaling pathways by altering the conformation or binding kinetics of focal adhesion proteins (e.g., FAK, zyxin, paxillin, vinculin, talin) and Rho small GTPases and their regulators [GEFs and GAPs (e.g., p190RhoGAP)], as well as by changing the expression and activity of protein kinases (e.g., MAPK, ERK, and JNK). Mechanical tension exerted on integrins also modulates mechanosensitive ion channels (e.g., TRPVs) and phospholipases, which activate PI3K and PKC, respectively. Physical forces exerted on surface adhesion receptors are transmitted directly from surface adhesion receptors along cytoskeletal filaments and across molecules, such as nesprin, that connect the cytoskeleton to nuclear scaffolds and can also directly influence gene transcription.

and transduced into the biochemical signals to modulate various crucial cell behaviors. At the same time, the focal adhesion itself is stress sensitive in that it increases its assembly when stressed and disassembles when force is dissipated (Geiger et al. 2009, Wolfenson et al. 2011). This immediate mechanical responsiveness is mediated by changes in Rho-ROCK-mDia signaling (Geiger & Bershadsky 2001) as well as force-dependent changes in unbinding kinetics of focal adhesion proteins, such as zyxin (Lele et al. 2006). In this manner, cells and their ECM connections continuously sense changes in their physical microenvironment through focal adhesions and respond by strengthening their ECM scaffolds and adhesions along applied tension field lines.

Focal adhesion proteins mediate mechanosensation by undergoing conformational changes when mechanical forces are applied to integrins. Stress-sensitive ion channels, such as TRPV4, become rapidly (<5 ms) activated when forces are applied to cell surface integrins (Matthews et al. 2010), and the resulting calcium influx appears to trigger a downstream mechanical signaling cascade involving activation of phosphatidylinositol-3-OH kinase (PI3K) and Rho, as well as activation of additional integrin receptors (Thodeti et al. 2009). A key integrin-binding protein, talin, also undergoes stress-dependent unfolding and stretching to expose a cryptic binding site for vinculin when it is mechanically stressed (del Rio et al. 2009, Lee et al. 2007). Consequent changes in talin-vinculin binding trigger integrin clustering, which further enhances signal transduction in the focal adhesion. Mechanical forces also extend the domain of p130Cas that is phosphorylated by Src family kinase (Sawada et al. 2006), which activates the small GTPase RAP1 and thereby initiates a sequence of intracellular signaling events (Hattori & Minato 2003, Tamada et al. 2004).

FAK is a nonreceptor cytoplasmic protein tyrosine kinase that plays an important role in mechanotransduction through its association with various signaling proteins, including Src family RTKs and PI3K (Orr & Murphy-Ullrich 2004, Schlaepfer et al. 1999, Xia et al. 2004). Stress-dependent changes in these molecular interactions involving FAK and its partners enable mechanical forces to activate MAPK pathways, including the extracellular regulated kinase 1/2 (ERK1/2), p38 MAPK, and Jun N-terminal kinase pathways, in endothelial cells, osteoblasts, and fibroblasts (Boutahar et al. 2004, D'Addario et al. 2002, Huang & Ingber 2002, Ishida et al. 1996). Mechanically activated ERK1/2 and/or JNK signals are transmitted into the nucleus, where they activate the transcription factor AP1 and thereby upregulate expression of molecules that regulate tissue formation and remodeling, such as type I collagen and osteopontin in bone (Hong et al. 2010, Jeon et al. 2009, Kook et al. 2009). FAK also plays essential roles in cardiac looping and development of the chambers of the heart during *Xenopus* development (Doherty et al. 2010).

Integrins are also essential for vertebrate, fly, and worm development (Bokel & Brown 2002, Meighan & Schwarzbauer 2008), because they act as both mechanosensors (Papusheva & Heisenberg 2010, Parsons et al. 2010) and morphogenetic regulators that alter cell-ECM adhesion. For example, integrins switch between relaxed and tensioned states in response to myosin II–generated cell-contractile forces and control integrin-FN binding strength (Friedland et al. 2009). Dynamic short-term integrin adhesions regulate cell migration and rearrangements, whereas long-term integrin adhesions support contractility and maintain tissue homeostasis (Bokel & Brown 2002, Meighan & Schwarzbauer 2008).

Transient integrin-ECM adhesions are required for several dynamic morphogenetic processes, including germband retraction and dorsal closure (Bokel & Brown 2002), which involve large-scale epithelial migration, lamellipodia formation, and cell shape changes (Brown et al. 2000, Schock & Perrimon 2002). At the end of embryogenesis, integrins are also required for the maintenance of a diverse array of tissues, including myotendinous junctions (Brown et al. 2000) and terminal tracheal branches in the lung (Levi et al. 2006). To provide stable adhesion, integrins at myotendinous junctions recruit a large, specialized focal adhesion complex that includes proteins such as talin (Brown et al. 2000) and PINCH (Clark et al. 2003). This complex enables stable attachment of

tensile muscles to the epidermis by linking the muscle cytoskeleton via transmembrane integrins to ECM deposited between the muscle and tendon cells; disruption of the adhesion complex or interference with their interactions with integrins results in detachment of the muscle from the tendon (Brown et al. 2000).

Extensive structural analyses and biochemical experiments have shown that the overall strength of integrin adhesion (avidity) is regulated by conformation-dependent alterations in integrin-binding affinity (Askari et al. 2009) or changes in integrin-clustering-dependent binding to ECM (Carman & Springer 2003). Disruption of these regulatory mechanisms results in gross abnormalities in cell architecture and tissue morphology. Together, these molecular binding activities help to organize cells into distinct tissues and organs. In addition, mechanical coupling between integrins and ECM can produce changes in the microenvironment that can feed back to alter cells via other transduction mechanisms. For example, mechanical forces applied to bone cause fluid flow through the lacunar-canalicular network surrounding the osteocyte (Fritton & Weinbaum 2009), which stimulates additional cellular responses that involve integrin receptors and their associated intracellular signaling pathways (Bonewald 2006). This mechanically induced signaling cascade leads to the expression and release of important bone anabolic molecules, such as prostaglandins and ATP, through connexin 43 hemichannels expressed on the cell surface (Cherian et al. 2005, Genetos et al. 2007). Integrin can interact directly with connexin 43, and this interaction is required for mechanical stimulation–induced opening of these channels (Batra et al. 2012).

Forces applied to the apical cell surface also can induce transmembrane ion flux and cytoskeletal distortion by shearing the surface membrane (Lansman et al. 1987, Martinac 2012) or deflecting primary cilia (McGrath & Brueckner 2003, Oh & Katsanis 2012). Interestingly, shear stresses applied to the apical cell surface can be channeled through the cytoskeleton to the cell's basal ECM adhesions and thereby can induce near-instantaneous remodeling of focal adhesions at the opposite pole of the cell (Davies et al. 1994). In fact, even fluid shear–dependent activation of mechanical signaling by bending of apical primary cilia is sensitive to mechanical interactions between integrins and ECM scaffold at the cell base because they govern the cytoskeletal force balance that determines cell mechanics (Alenghat et al. 2004) and, hence, the degree of mechanical deformation that is produced by any external cue (e.g., the primary cilium will exhibit little resistance to distortion in a floppy cell). It is important to note that signal transmission across integrins and stiff cytoskeletal linkages can reach the nucleus much faster than chemical signals can (e.g., microseconds versus seconds) (Na et al. 2008, Poh et al. 2009, Wang et al. 2005).

Transduction Through Cell-Cell Adhesions

Traction forces exerted on cell-cell adhesions that link adjacent cells also play an important role in development. Intercellular contacts, in particular cadherin-based intercellular junctions, are the major means of transmitting force within tissues. Similar to cell-ECM adhesions, cell-cell adhesions act as both force transmitters and mechanosensors that modulate various cell behaviors during morphogenetic movements.

The extracellular domain of classical cadherins forms intercellular bonds with cadherins on neighboring cells, whereas the cytoplasmic domain recruits catenins, which in turn associate with additional cytoskeleton-binding and regulatory proteins. Cadherin/catenin complexes appear to play a key role in the transduction of mechanical forces that shape cells and tissues during morphogenesis. For example, in N-cadherin mutants of zebrafish, convergent cell movements in the neural tube are severely compromised (Lele et al. 2002). Paraxial protocadherins functionally interact with components of the Wnt/PCP pathway in the control of convergence and extension

movements in *Xenopus*, and the protocadherin functions as a signaling molecule that coordinates cell polarity and thereby promotes tissue elongation (Unterseher et al. 2004).

Myosin II–driven increases in intercellular tension induce conformational changes in α-catenin and expose a cryptic binding site that recruits vinculin to cell-cell contacts (Drees et al. 2005, Yonemura et al. 2010). This, in turn, reinforces E-cadherin adhesions (Huveneers et al. 2012, le Duc et al. 2010, Sumida et al. 2011), which mediate force transmission that drives morphogenesis at the tissue level. Assembly and disassembly of cadherin adherens junctions are regulated by Rho/Rock/MLK signaling that controls generation of actomyosin-driven cell-traction forces in endothelial cells (Huveneers et al. 2012). The level of force transmitted from the cytoskeleton over cadherins is also sensitive to the extracellular mechanical environment in that these forces rise as ECM stiffness is increased (Chopra et al. 2011, Ladoux et al. 2010, Tsai & Kam 2009). These mechanochemical mechanisms appear to be used during epithelial polarization, cell sorting, and cell migration in the developing embryo (Gumbiner 2000).

Cell-cell adhesions also interact with cell-ECM attachments to orchestrate collected cell movements (Weber et al. 2011) and contractility at the tissue level (McCain et al. 2012, Tsai & Kam 2009), and this cross talk can be modulated by changes in actomyosin activity (de Rooij et al. 2005). Integrin-mediated cell-ECM adhesions also can modulate the composition (Tseng et al. 2012, Yamada & Nelson 2007) and tension (Martinez-Rico et al. 2010, Maruthamuthu et al. 2011, Weber et al. 2011) of cell-cell junctions. For example, changes in cell-traction forces applied to cell-ECM attachments can modulate mechanical tension exerted on cell-cell adhesions in cultured MDCK cells (Maruthamuthu et al. 2011). Conversely, physical cohesion mediated by intercellular adhesions can influence cell-ECM traction forces in cultured keratinocytes (Mertz et al. 2013). Integrin-ECM adhesions also control mediolateral interactions and axis extension during *Xenopus* gastrulation by modulating cadherin-mediated cell-cell junctions (Marsden & DeSimone 2003).

Force transmission across cell-cell junctions also appears to contribute to control of vasculogenesis in the developing embryo. During this process, endothelial cells differentiate from the mesoderm and coalesce into solid cords that interconnect to form a seamless, primitive vascular network and subsequently form lumens (Blum et al. 2008, Kamei et al. 2006, Strilic et al. 2009). In the mouse embryo, formation of the lumen space of the developing aorta is mediated by colocalization of the cytoskeletal protein moesin with the actomyosin machinery at the endothelial cell-cell adhesions; this defines the luminal cell surface, and resultant tension-dependent changes in endothelial shape lead to lumen formation (Strilic et al. 2009). These early vasculogenic events occur before the onset of circulation, and blood flow is generally not required for lumen formation during vasculogenesis and angiogenesis. However, stabilization of newly formed lumens (Isogai et al. 2003, Wang et al. 2010), aortic arch morphogenesis (Wang et al. 2009), and arterial-venous cell fate switching (le Noble et al. 2004) all depend on blood flow and associated hemodynamic forces.

Platelet endothelial cell adhesion molecule-1 (PECAM-1) is an endothelial cell–specific cell adhesion molecule that localizes to adherens junctions and is rapidly tyrosine phosphorylated to activate ERK signaling in response to shear stress (Osawa et al. 2002). PECAM-1 forms a mechanosensory complex with vascular endothelial–cadherin and vascular endothelial growth factor receptor-2 at cell-cell adherens junctions, and forces transmitted among these three surface proteins stimulate PI3K activity (Tzima et al. 2005). Active PI3K, in turn, phosphorylates Akt to modulate vascular tone through NO production (Dimmeler et al. 1999, Jin et al. 2003). Active Akt also alters integrin conformation and modulates the avidity of its adhesion to ECM, which in turn induces GTPase-dependent remodeling of the cytoskeleton to dynamically control tensional homeostasis in response to fluid shear forces (Tzima et al. 2001, 2002, 2003).

Other Membrane Transduction Events

Primary cilia are solitary and microtubule-based organelles that grow from the centrosome and project from the cell surface in many vertebrate tissues (Wheatley et al. 1996). Importantly, cilia are also highly sensitive mechanosensors that, for example, sense extremely weak unidirectional fluid flow at the ventral node and thereby break left-right (L-R) symmetry during organogenesis in the developing vertebrate embryo (Hirokawa et al. 2006, 2009; Shinohara et al. 2012; Shiratori & Hamada 2006). Two populations of nodal cilia exist in the cavity: Motile cilia at the center generate leftward nodal fluid flow, and immotile cilia on the remaining cells sense the shear stresses produced and activate polycystin-2 calcium channels, which break L-R symmetry through production of an asymmetric calcium signal in the mouse embryo (McGrath et al. 2003, Yoshiba et al. 2012). In addition, the nodal flow generates a directional morphogen gradient by transporting nodal vesicular parcels that encapsulate morphogens, such as Sonic hedgehog (Shh) and retinoic acid, which induce changes in tissue and organ morphology responsible for L-R organ patterning (Tanaka et al. 2005). Primary cilia also mediate the process by which mechanical signals, including compression and fluid flow, regulate ECM synthesis underpinning tissue homeostasis. Bone cells possess primary cilia that project from their cell surfaces and deflect during fluid flow; these primary cilia are required for osteogenic and bone resorptive responses to dynamic fluid flow (Malone et al. 2007). Kidney epithelial cells similarly sense glomerular filtrate fluid flows as a result of deflection of apical primary cilia (Weinbaum et al. 2010).

Endothelial cells respond to shear stress with an inwardly rectifying ultrashort potassium current, which leads to polarization of endothelial cells and regulates vascular tone (Olesen et al. 1988). The opening of the mechanosensitive TRPV4 calcium channels is also important for shear stress–induced NO production, likely via calcium/calmodulin/Akt activation and eNOS phosphorylation in small arteries (Loot et al. 2008, Mendoza et al. 2010). TRPV4 also regulates mechanical force–induced intracellular calcium oscillation, which is crucial for osteodifferentiation and the adaptation of the bone to mechanical loads (Berridge et al. 1998, Godin et al. 2007, Suzuki et al. 2013). In addition, mechanical strain and cell shape distortion activate membrane-associated phospholipases and, thereby, increase the metabolism of inositol lipids and arachidonic acid in the cytoplasm, which results in the release of Ca^{2+} from intracellular stores; activation of protein kinase C; and the remodeling of cardiomyocytes through activation of mechanosensitive transcription factors, such as EGR1 and AP1 (Bishop & Lindahl 1999, Komuro et al. 1991, Sadoshima & Izumo 1993, Tseng et al. 1994).

Caveolae-mediated membrane signaling and the distribution of caveolin 1 protein also can be affected by external mechanical cues. When cells are mechanically stretched, caveolae flatten over the plasma membrane to dampen membrane tension, although this is quickly recovered by actin/ATP-dependent caveolar reassembly in endothelial and muscle cells (Sinha et al. 2011). Disassembly and reassembly of caveolae appear to be regulated by cytoskeletal tension regulated by mDia (Echarri et al. 2012). In endothelial cells, chronic shear exposure activates the ERK pathway in a caveolae-dependent manner (Boyd et al. 2003, Park et al. 2000, Rizzo et al. 2003), and cyclic stretching can cause association of the kinases with caveolin 1 in smooth muscle cells (Sedding et al. 2005). Lipid rafts are also essential for hydrostatic pressure–induced activation of ERK1/2 and c-fos expression in osteoblasts (Ferraro et al. 2004). Interestingly, cytoskeleton-dependent inactivation of RhoA, which regulates cytoskeletal tension generation, is mediated by p190RhoGAP in lipid rafts in endothelial cells (Mammoto et al. 2007). β1-Integrin is also recruited to caveolin 1–containing lipid rafts in response to shear stress, and this results in phosphorylation of myosin light chain by the Src-like kinase Csk in these cells (Radel et al. 2007).

Transduction Through Cell Shape Distortion

The cytoskeleton is not a passive conduit for mechanical signal transmission; it also senses alterations in cell shape and converts them into changes in intracellular biochemistry. For example, the effects of cell shape distortion on cell proliferation are mediated by actin cytoskeleton–dependent control of Rho GTPase activity through p190RhoGAP, which alters the balance between ROCK and mDia activities (Mammoto et al. 2004). When cells round and the actin cytoskeleton is disrupted, filamin A (an actin-binding protein that crosslinks F-actin) binds to p190RhoGAP and its GAP activity is inhibited, leading to activation of RhoA (Mammoto et al. 2007). By contrast, in spreading cells, filamin A is cleaved by calpain, and p190RhoGAP dissociates from filamin A. Subsequently, RhoGAP moves to lipid rafts, where it inactivates RhoA (Mammoto et al. 2007).

Mechanical signals induced by cell shape alterations are also relayed through YAP1 and TAZ (transcription coactivator with PDZ-binding motif), which requires Rho GTPase activity and tension generation within the actomyosin cytoskeleton (Dupont et al. 2011). Several studies have highlighted the interactions between force, Rho signaling, cell shape, and histone acetylation (Destaing et al. 2005, Kim et al. 2005). For instance, modifying fibroblast adhesion and changing cell shape alter cytoskeletal organization and shrink the nucleus and nuclear lamina of cultured cells, which are associated with impaired polymerase access to chromosomal territories and a concomitant reduction in gene transcription (Dalby et al. 2007a,b; Molenaar et al. 2003). Rho-family GTPases also indirectly regulate histone H4 acetylation by shifting the balance of cellular and nuclear pools of F- and G-actin, which, in turn, modify the association between serum response factor and its coactivator MAL (Alberts et al. 1998, Posern et al. 2004, Vartiainen et al. 2007).

These and other results suggest that mechanical forces regulate gene expression to alter cell behavior, either by directly altering DNA or by modulating chromatin remodeling. Interestingly, the perinuclear microenvironment appears to be crucial for transcriptional reprogramming of the nucleus. For example, inserting somatic nuclei into eggs or oocytes is sufficient to reactivate silenced pluripotent genes, such as OCT4 (Pou5f1), in the transplanted nucleus (Kim et al. 2010, Stadtfeld et al. 2008), and this is a more efficient way to reprogram cells into pluripotent stem cells than the forced induction of OCT4, SOX2, MYC, and KLF4 in somatic cells (Kim et al. 2010, Pasque et al. 2010). Nuclear actin polymerization plays an essential role in transcriptional reactivation of the gene encoding OCT4 in transplanted nuclei (Miyamoto et al. 2011), and decreased cytoskeletal tension destabilizes transcriptional regulation of pluripotency and, hence, compromises long-term survival of embryonic stem cells (Li et al. 2010). In addition, nuclear actin can regulate gene transcription through changes in cytoskeletal actin dynamics (Sotiropoulos et al. 1999). These findings suggest that modulation of the perinuclear micromechanical environment by environmental mechanical signals that are transmitted across cell-surface adhesions and linked cytoskeletal connections might contribute significantly to nuclear reprogramming.

DEREGULATED MECHANOBIOLOGY AND DISEASE DEVELOPMENT

Although we focus here on the importance of physical forces for developmental control in the embryo, mechanical forces are equally important regulators of tissue function and organ homeostasis throughout adult life. Examples include the effects of compressive or tensile stresses induced by exercise or weight bearing on the musculoskeletal system, blood pressure and shear stress generated by blood flow on the cardiovascular system, and cyclic strain owing to inspiratory and expiratory forces on pulmonary function. However, cells within all organs are also constantly exposed to isometric tension as a result of establishment of a dynamic force balance between cytoskeletal contractile forces and resistance to cell-cell and cell-ECM adhesions. Moreover,

dysfunctional mechanotransduction or abnormalities in the micromechanical environment of tissues can contribute significantly to pathogenesis in various organs.

The human skeleton dynamically remodels in response to mechanical loads. Reduction in these forces, as can occur with chronic bed rest, cast immobilization, or exposure to microgravity conditions during space flight, leads to loss of bone mineral density and osteopenia, which result in increased risk of fracture (Krasnoff & Painter 1999, Ozcivici et al. 2010), whereas increased mechanical loading enhances bone matrix deposition (Ebbesen et al. 1997, Rittweger et al. 2006). The skeleton also depends on mechanical loads generated by muscle contraction that establish a tensegrity force balance at the level of the entire musculoskeletal system (Ingber 2006). This tensional homeostasis guides the resident cell populations toward regeneration, adaptation, and maintenance.

Similarly, homeostasis of the cardiovascular system is largely maintained by hemodynamic forces (Davies 1995, Takahashi et al. 1997). For example, cardiomyocytes respond to a wide range of mechanical loads and maintain circulatory homeostasis. When the heart is exposed to pressure overload, it undergoes hypertrophy (Barry et al. 2008), which is initially beneficial because it normalizes ventricular wall stress (Grossman et al. 1975, Lammerding et al. 2004). However, sustained mechanical overload shifts homeostasis toward maladaptive remodeling of the myocytes, which may result in cardiac failure (Barry et al. 2008). Although precise mechanisms remain incompletely understood, cardiac myocytes respond to mechanical loads through several internal mechanosensors, including stretch-sensitive ion channels; integrins and integrin-associated proteins, such as melusin or integrin-linked kinase; sarcomeric proteins, such as titin, myosin, or the small LIM-domain protein MLP; and cell surface receptors, such as G-protein-coupled receptors or angiotensin II type 1 receptors (Jacot et al. 2010). These mechanosensors activate multiple and overlapping cellular signaling pathways (Barry et al. 2008) that trigger expression of hypertrophic genes (Heineke & Molkentin 2006). Importantly, these mechanotransduction pathways overlap with neurohormonal mechanisms (for example, G-protein-coupled-receptor signaling activated by angiotensin or catecholamines) and allow the heart to adapt to prolonged changes in mechanical workload with an increase in cardiac myocyte size (hypertrophy) and modification of the surrounding ECM, referred to as cardiac remodeling. The giant elastic protein titin is involved in strain sensing and adaptation in response to changes in mechanical strain (Hoshijima 2006). The C-terminal kinase domain of titin unfolds in response to mechanical strain, leading to the exposure of an ATP-binding site for autophosphorylation; in this manner, titin might serve as a strain-sensing molecule for force adaptation in muscle (Puchner et al. 2008). Hence, organs appear to adapt to changes in their material properties caused by alterations in mechanical loading, and these adaptive responses can be modulated by cytoskeletal prestress (isometric tension in the cytoskeleton) and mechanosensing molecules that regulate tensional homeostasis at the organ level.

Mechanotransduction in vascular cells in response to fluid shear stress and mechanical strain from vessel expansion is a critical protective mechanism against arteriosclerosis, and it can regulate apoptosis, proliferation, and ECM secretion in healthy vascular smooth muscle cells (Jaalouk & Lammerding 2009). Importantly, atherosclerotic lesions occur at focal sites in arterial vessels that relate to disturbed blood flow patterns. Moreover, although disturbed flows in vascular branches and curved regions are proatherogenic, laminar flows in the straight parts are protected against fatty plaque formation. By interacting dynamically with ECM proteins, mechanosensitive integrins activate RhoA and other signaling molecules in focal adhesions and the cytoplasm in response to laminar fluid shear stress; this upregulates genes involved in antiapoptosis, cell cycle arrest, morphological remodeling, and NO production, thus contributing to their atheroprotective effects (Shyy & Chien 2002).

Tightly controlled remodeling of ECM, and hence of force distributions in tissues, is essential for organ homeostasis, and life-threatening pathological conditions, such as fibrotic diseases

and cancers, arise when ECM remodeling becomes excessive or uncontrolled. In skeletal muscle, forces generated in the sarcomeres are transmitted to the ECM through a specialized protein complex that consists of dystrophin and the dystrophin-associated proteins in the plasma membrane, which serve to increase muscle fiber strength and prevent muscle fiber injury. In Duchenne's muscular dystrophy, mutations in the *dystrophin* gene deregulate force transmission between the ECM and cytoskeleton, resulting in progressive muscle degeneration and myopathy (Heydemann & McNally 2007). Importantly, the disruption of cytoskeletal-ECM coupling not only renders cells more susceptible to membrane damage but also causes aberrant activation of MAPK ERK1/2 signaling in response to stretch (Kumar et al. 2004), which could further compromise the function and viability of the muscle. Investigating the relative contributions of ECM mechanics to these pathological conditions could have important clinical implications, as mechanosensitive signaling pathways associated with deregulated ECM mechanics could potentially be attenuated with pharmacological reagents to treat these diseases.

ECM structure is also deregulated in cancer, and the resultant changes in cytoskeletal tension and mechanical signaling may enhance malignancy (Huang & Ingber 2005, Lu et al. 2012, Suresh 2007). Much effort has been devoted to determine how changes in the physical environment might promote cancer development (Bhowmick et al. 2004), and deregulated ECM remodeling that results in compromise of ECM continuity is one of the hallmarks of cancer (Cox & Erler 2011). In addition to a combination of oncogenic mutations, alterations in tensional forces generated by the actomyosin system and changes in ECM structure and mechanics play pivotal roles in cancer formation and progression. This appears to be driven at least in part by changes in cytoskeletal tension generation by Rho and ROCK signaling that increase myosin II light chain phosphorylation through inhibitory phosphorylation of myosin phosphatase (Paszek & Weaver 2004, Paszek et al. 2005). The cellular force balance in cancers is also influenced by ECM stiffness (Huang & Ingber 2005, Paszek & Weaver 2004, Paszek et al. 2005), and tumors are generally much stiffer than the surrounding normal tissue.

The physical microenvironment of cancers is also influenced by increased cell compaction owing to high proliferative rates and by elevated interstitial fluid pressure (Sarntinoranont et al. 2003). This altered physical environment can modulate the behavior of these cells by altering mechanical signaling in the cells (Iwanicki et al. 2011, Sodek et al. 2009, Tse et al. 2012). For example, higher ECM stiffness can result in disruption of normal epithelial cell polarity, causing mammary epithelial cells to fill the lumen ducts during breast cancer progression (Paszek et al. 2005). It also can feed back to increase Rho/ROCK-mediated cell contractility (Wozniak et al. 2003) and thereby promote survival and proliferation of the cancer cells through an integrin-dependent ERK-signaling cascade (Paszek et al. 2005). Increases in ECM rigidity further enhance tumor progression by promoting focal adhesion assembly and ERK-PI3K signaling (Levental et al. 2009). Moreover, reducing cytoskeletal tension by disrupting Rho or ERK signaling results in a significant reduction in tumor cell proliferation and repression of the malignant phenotype. Both integrins and Rho-mediated regulation of intracellular tension also promote invasiveness of fibroblasts and cancer cells in cocultures (Gaggioli et al. 2007, Hebner et al. 2008).

Cancer metastasis also has a mechanical component. For example, adhesion of melanoma cells to the endothelial cell lining of blood vessels is sensitive to the hydrodynamic shear rate because it alters melanoma cell–leukocyte aggregation (Liang et al. 2008). Interestingly, although tumors are generally stiffer than normal tissues, metastatic cells can be distinguished from noninvasive cancer cells and normal cells by reduced cytoskeletal stiffness and increased deformability (Cross et al. 2007, Guck et al. 2005, Suresh 2007). Moreover, cell deformability strongly correlates with passage time through narrow pores and with enhanced metastatic potential in mouse melanoma cells (Ochalek et al. 1988). Thus, increased cellular and nuclear deformability could enable metastatic

cancer cell passage through size-limiting pores and blood vessels, which would result in enhanced metastatic spreading.

IMPLICATIONS FOR CELL AND DEVELOPMENTAL BIOLOGY

Although the importance of genes and chemicals for developmental control is well accepted, there is clearly a resurgence of interest in the role of mechanical forces as biological regulators, ranging from how cell-traction forces govern growth and migration to how tension, compression, shear, and ECM elasticity influence stem cell lineage switching. Taken together, the findings reviewed here suggest that mechanical forces are as crucial as chemical factors for control of developmental processes during embryogenesis and throughout adult life. Thus, there is a great need to integrate physical techniques and modeling approaches from other disciplines, such as engineering, physics, and computer science, into the fields of cell and developmental biology for meaningful advances to be made in the future. These efforts are critical for the forward motion of basic research and for developing new and improved therapeutic and diagnostic strategies for a wide range of diseases.

DISCLOSURE STATEMENT

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