Cell

Leading Edge
Review

Forces in Tissue Morphogenesis and Patterning

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During development, mechanical forces cause changes in size, shape, number, position, and gene expression of cells. They are therefore integral to any morphogenetic processes. Force generation by actin-myosin networks and force transmission through adhesive complexes are two self-organizing phenomena driving tissue morphogenesis. Coordination and integration of forces by long-range force transmission and mechanosensing of cells within tissues produce large-scale tissue shape changes. Extrinsic mechanical forces also control tissue patterning by modulating cell fate specification and differentiation. Thus, the interplay between tissue mechanics and biochemical signaling orchestrates tissue morphogenesis and patterning in development.

Introduction

The processes by which multicellular organisms take shape are driven by forces that are typically generated by molecular motors and transmitted via cytoskeletal elements and adhesion molecules within and between cells. The study of forces in embryo morphogenesis has a long history, starting with the movement of Entwicklungsmechanik (developmental mechanics)— which described how forces exerted by cells shape the embryo—in the second half of the 19th and first half of the 20th century and continued by seminal contributions from Holtfreter, Steinberg, and others, who analyzed how specific cell affinities and cell behaviors coordinately drive morphogenesis (for review, see Keller, 2012). One major challenge in analyzing the role of forces in morphogenesis is to monitor in vivo mechanical forces in the order of pN to nN and to link them to the cellular and biochemical processes by which they are generated, propagated, and received within the organism. In recent years, considerable progress has been made in the development of image acquisition tools to record dynamic changes in cell and tissue shapes at high spatial and temporal resolution and in the development of image analysis tools to quantify cell/tissue dynamics (Montero et al., 2005; Kwon et al., 2008; Keller et al., 2008; Blanchard et al., 2009; Olivier et al., 2010; Bosveld et al., 2012; Tomer et al., 2012; Gao et al., 2012; Krzic et al., 2012). Furthermore, the use of various biophysical tools, such as laser cutting devices and micropipettes to analyze mechanical and adhesive properties of cells and tissues, have provided novel insight into the processes by which forces are generated and propagated within cells and tissues (Kiehart et al., 2000; Chu et al., 2004; Farhadifar et al., 2007; Rauzi et al., 2008; Mayer et al., 2010; Maître et al., 2012; Movie S1 available online). An important step in this direction has also been the successful construction and implementation of molecular force sensors, which made it possible to "visualize" forces acting on specific molecules of the force-transducing machinery (Grashoff et al., 2010). Last but not least, various physical models have been implemented that allow simulation of morphogenetic processes at both the cell and tissue scale and thus test the plausibility and predict the outcome of certain mechanistic models (for review, see Morelli et al., 2012).

Integral to cell/tissue morphogenesis is the ability of cells to perceive mechanical forces and physical constraints modulating their specification and differentiation. Although the influence of shear force due to fluid flows on endothelial cells forming the vasculature has been extensively analyzed (for review, see Freund et al., 2012), more recent advances in the development of microfabricated devices has also provided evidence for a critical function of static forces in cell fate specification and differentiation (for review, see Kobel and Lutolf, 2011). The challenge ahead is now to integrate the roles of mechanical forces in tissue morphogenesis and cell fate specification with the aim to understand how the interplay between cell/tissue morphogenesis and cell fate specification and differentiation is realized in embryo development.

There are numerous excellent reviews on how specific morphogenetic processes are achieved on a cell and tissue level and the function of various signaling pathways therein (Solnica-Krezel, 2005; Leptin, 2005; Hopyan et al., 2011; Suzuki et al., 2012). Here, we aim at highlighting recent advances made in identifying fundamental and common mechanisms by which mechanical forces function in tissue morphogenesis and cell fate specification/differentiation. Specifically, we will focus on recent findings in which mechanical forces play a pivotal role in both cell/tissue morphogenesis and patterning. We will begin the Review with a short description of the basic cell dynamics that entail tissue shape changes, followed by a discussion of tissue self-organization driven by the adhesive and contractile properties of their constituent cells. We will then summarize key findings on the spatiotemporal control of cell/tissue morphogenesis by subcellular actin-myosin dynamics and will describe

how planar cell polarity (PCP) pathways coordinate cell behaviors within a tissue to generate large-scale tissue changes. Finally, we will discuss how the mechanical coupling of cells leads to force integration at the tissue scale that, in turn, influences individual cell behaviors. On short timescales, such feedback will primarily lead to the coordination of cell behaviors, whereas on longer timescales, it can also modulate gene expression. We will conclude the Review with an outlook on future directions to unravel the role of forces in integrating tissue morphogenesis and cell fate specification/differentiation during development.

Forces in Tissue Self-Organization

Tissue morphogenesis describes the processes by which a tissue takes shape. Such processes typically involve changes in cell number, size, shape, and position. Changes in the number of cells within a tissue are achieved by cell proliferation and death. Proliferation of cells is driven by cell divisions, which distribute the two daughter cells along the orientation of division. Cell death usually results in the disappearance of the dying cell, vacating the position of the cell taken before its death. Changes in cell size and shape can have manifold expressions—cells can increase their size, e.g., by metabolic growth or osmotic swelling. Cell shape changes can range from large-scale changes, such as cell elongation, to local modulations in cell shape, such as the formation of specialized cell protrusions. Finally, changes in cell position are brought about by either cell migration or cellular rearrangements, such as cell intercalations and/or neighbor exchanges. Important for all these cellular processes to trigger tissue shape change is some form of force transmission between individual cells, commonly mediated by cell-cell adhesion. This will allow individual cell changes to be translated into more global changes in tissue morphology. An example for coordinated changes in the shape of individual cells giving rise to global alterations in tissue morphology is the constriction of epithelial cells at their apical side, leading to local bending of epithelial cell sheets (reviewed in Pilot and Lecuit, 2005). Likewise, coordinated changes in the position of individual cells trigger tissue rotation (Aigouy et al., 2010; Suzanne et al., 2010) or simultaneous tissue narrowing and elongation due to cell intercalations (for review, see Keller, 2006). Finally, spatially controlled cell proliferation, cell division orientation, and cell death within multicellular tissues can give rise to global changes in tissue shape (reviewed in Hopyan et al., 2011). Thus, understanding tissue morphogenesis requires deciphering how forces are being generated on an individual cell basis, how those forces are being transmitted to neighboring cells, and how they are integrated within the tissue to trigger global changes in tissue shape.

Although cells can generate forces via actin or microtubule polymerization and osmotic pressure, cellular force generation typically relies on the activities of motor proteins, such as myosins (reviewed in Howard, 2001). These proteins interact with cytoskeletal structures such as actin fibers to change their organization (reviewed in Salbreux et al., 2012). Cytoskeletal changes are transmitted to neighboring cells and the extracellular environment by connecting the cytoskeleton to cell-cell and cell-matrix adhesion molecules such as cadherins and integrins,

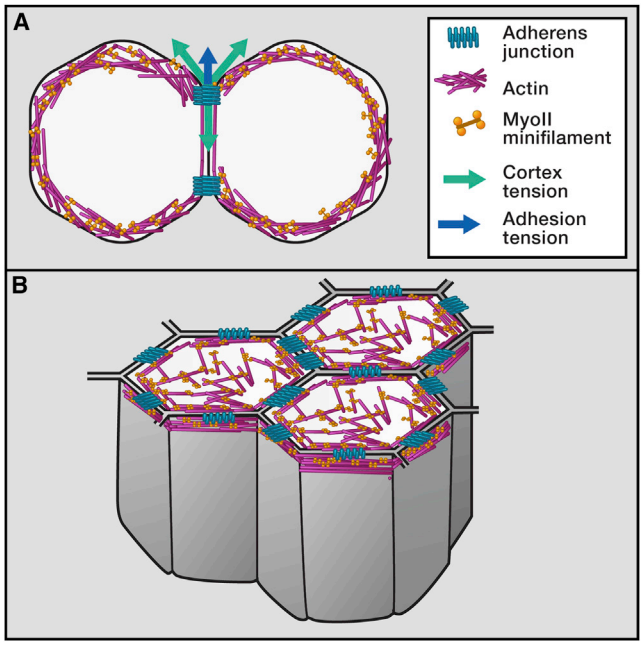

Figure 1. Self-Organization of Cells at Steady State Determined by Actin-Myosin Contractility and Cell Adhesion

(A) Upon cell-cell contact, the contacting cells change their shape in response to mechanical forces associated with actin-myosin contractility (green arrow) and adhesion (blue arrow).

(B) In epithelial tissues, adhesive contacts and the actin-myosin network are organized in belt-like structures at the apical domain of the cell. At steady state, the arrangement of epithelial cells at their apex is determined by actin-myosin contractility and cell-cell adhesion.

respectively. It is now well established that cell cortical tension due to actin-myosin contraction and cadherin-mediated cell-cell adhesion represent two fundamental and evolutionarily highly conserved force-generating and transmitting cell properties driving tissue self-organization (Dickinson et al., 2011). To conceptualize how those properties drive tissue self-organization, various models have been developed. In most models, it is assumed that the tissue evolves via a succession of equilibrium states and that, therefore, the sum of the mechanical forces is in balance. Mechanical equations can be written and solved either analytically or by using finite element methods to characterize tissue dynamics (Brodland et al., 2007; Ranft et al., 2010; Hannezo et al., 2012). Furthermore, assuming that adhesion and cortical tension are dominant determinants of cell/tissue shape and that cells/tissues have an inherent tendency to minimize their surface free energy, cell and tissue shapes can be described by their state of lowest energy (Steinberg, 1963; Foty et al., 1996). The nature of this energy relies on the binding of adhesion molecules causing cells to expand their cell-cell contacts and the contractile activity of the actin-myosin cell cortex inhibiting contact expansion at the contact and promoting it outside of the contact (reviewed in Amack and Manning, 2012; Figure 1A). A mathematical formulation of the concept of energy minimization to describe the organization of multicellular structures based on the combined activities of cortical tension and adhesion has been provided by the Cellular Potts Model

(CPM), which has successfully been used to explain the outcome of various morphogenetic processes, such as cell positioning in the *Drosophila* ommatidium and in germ-layer progenitor cell segregation during vertebrate gastrulation (Graner and Glazier, 1992; Käfer et al., 2007; Krieg et al., 2008). Although those studies show that using the CPM is, in principle, sufficient to accurately describe how the combined activities of cortical tension and adhesion determine tissue organization, experimental tools to measure the input parameters, such as cell adhesion and cortex tension, are still sparse. One approach in this direction has been studies in zebrafish, in which experimentally determined values of cell adhesion (derived from the deadhesion forces of cell-cell contacts) and cortex tension have been used to show that cortical tension, rather than adhesion energy, drives progenitor cell-cell contact formation and segregation during zebrafish gastrulation (Krieg et al., 2008; Maître et al., 2012).

The principle of energy minimization has also been applied to various forms of epithelial morphogenesis in vertebrates and invertebrates. In *Drosophila*, the configuration of cell-cell junctions is thought to be driven by the interplay between the elasticity of the cell and cortical contractility and adhesion at the junctions (reviewed in Lecuit et al., 2011; Figure 1B). The mathematical formulation of this concept in the form of a two-dimensional ''vertex-model'' and related models has been successfully applied to describe various types of morphogenetic processes in the *Drosophila* wing disc and germ-band epithelium (Farhadifar et al., 2007; Rauzi et al., 2008; Landsberg et al., 2009; Aegerter-Wilmsen et al., 2010; Aigouy et al., 2010; Schilling et al., 2011; Aliee et al., 2012). Examples for this are the formation of tissue compartment boundaries in *Drosophila*, in which anisotropic accumulation of myosin II (MyoII) at cell-cell junctions facing the boundary leads to enhanced contractility of the boundary, which, in turn, straightens the boundary and prevents cell mixing over it (Landsberg et al., 2009; Monier et al., 2010; Aliee et al., 2012). Furthermore, anisotropic MyoII accumulation at cell-cell junctions has been proposed to drive shortening of those junctions, which give rise to the cellular rearrangements underlying *Drosophila* germ-band extension and vertebrate neural tube folding (Rauzi et al., 2008; Nishimura et al., 2012). Finally, in ascidian gastrulation, reverse modeling to determine cell properties based on the morphogenetic process itself showed that increased cortical tension at the cell apex and along the lateral junctions promotes apical cell constriction and apical-basal cell shortening (Sherrard et al., 2010).

Taken together, various types of tissue self-organization can be explained by models based on the concept of energy minimization given by the combined activities of cell cortical tension and adhesion. However, the molecular and cellular mechanisms by which cortical tension and adhesion function together in these processes and the potential contribution of other fundamental cell properties, such as cell motility and directed migration, still need to be investigated.

Force Generation and Transmission at Cell Scale

The concept of energy minimization based on the activities of adhesion and cortical contractility provides valuable insights into how the distribution of molecules determining the adhesive and contractile cell properties dictate cell and tissue shape at equilibrium. To account for the inherent dynamics in cell and tissue morphogenesis, several studies have begun to analyze how dynamic changes in the subcellular distribution of cytoskeletal and adhesive components drive tissue morphogenesis. Most prominently, intracellular flows of actin and/or myosin have been involved in various key morphogenetic processes in embryogenesis. Flows of actin and myosin have been extensively studied on a single-cell level in processes such as cell migration, cytokinesis, and zygote polarization (Bray and White, 1988; Munro et al., 2004; Mayer et al., 2010). In order to understand how those single-cell flows give rise to changes in tissue morphogenesis, several important aspects related to force generation by actin-myosin flows need to be taken into account. First, the role of actin-myosin flow dynamics (pulsatile versus continuous) and direction (centripetal or anisotropic) for spatiotemporal variations in force generation have to be considered. Second, for actin-myosin flows to result in cell/tissue shape changes, the flows need to be effectively coupled to adhesion complexes at the cell surface that transmit the forces resulting from those flows to other parts of the tissue. Third, for processes in which cell/tissue deformations are transient due to pulsatile actin-myosin flows, for example, these deformations need to be stabilized in order to result in persistent cell shape changes. In the following, we will describe examples of developmental processes in which the above-mentioned aspects have been involved at varying degrees for describing the underlying dynamic changes in cell/tissue morphogenesis.

Gastrulation

In *Drosophila* gastrulation, mesoderm invagination is driven by the coordinated apical constriction of mesodermal cells (reviewed in Leptin, 1995; Movie S2). Apical constriction of invaginating mesodermal cells again is triggered by the formation of MyoII spots and fibers at their apical cortex (Martin et al., 2010). These apical MyoII structures are dynamic, repeatedly increase in intensity, and move toward the center of the cell apex, resulting in pulsatile centripetal actin-myosin flows. Pulsatile flows translate into periodic apical constrictions of mesodermal cells due to the inward movement of the apical cell-cell junctions to which the actin-myosin network is coupled (Martin et al., 2009; Roh-Johnson et al., 2012; Figure 2A and Movie S2). Apical constrictions are eventually stabilized by the maintenance of higher levels of MyoII at the apex of the cell. Actin-myosin network coupling to apical junctions also leads to apical MyoII organizing into a supracellular network that connects each cell to transmit forces across the tissue (Martin et al., 2010).

Similar to the situation in *Drosophila* gastrulation, ingression of endodermal precursors in *C. elegans* gastrulation is triggered by pulsatile, isotropic, and centripetal actin-myosin flows at the apex of these cells (Roh-Johnson et al., 2012; Movie S3). Interestingly, these pulsatile apical actin-myosin flows do not initially produce significant apical cell constrictions, suggesting that the actin-myosin network is not yet efficiently coupled to the apical junctions of the endodermal cells. Eventually, the pulsatile actin-myosin flows are translated into apical cell constrictions due to junctional coupling of the actin-myosin network, which stepwise reduces the size of the cell apex.

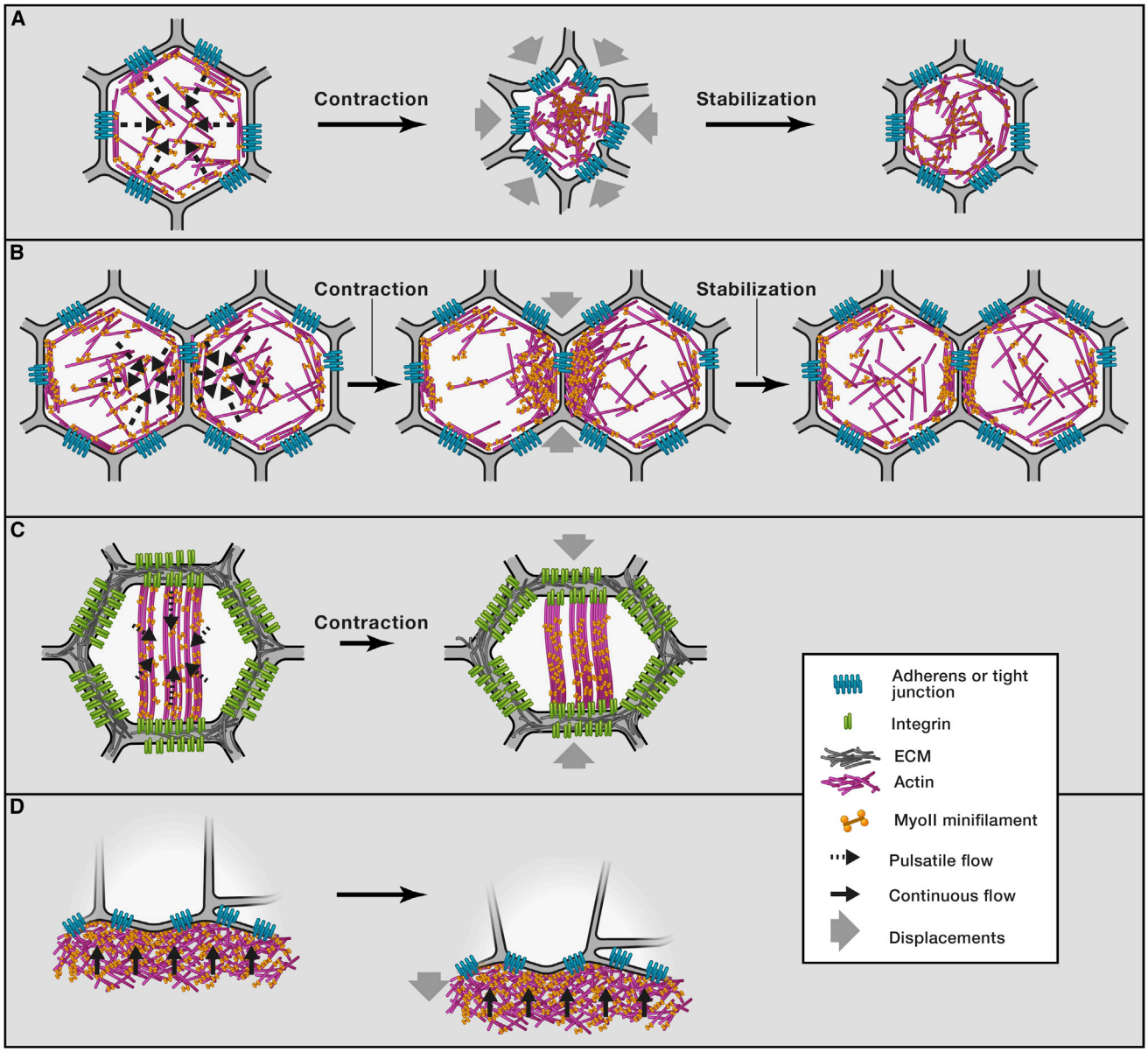

Figure 2. Actin-Myosin Network Dynamics and Force Generation

(A) Once coupled to adhesive contacts, pulsatile and centripetal flow of the apical actin-myosin network promotes apical cell constriction. In *Drosophila* mesodermal cells, the accumulation of apical actin-myosin is thought to stabilize cell shape changes between each pulse, leading to incremental reductions of the cell apex area.

(B) Pulsatile anisotropic flow induces junction shortening during cell intercalation. Resultant enrichment of actin-myosin at the junction stabilizes junction length reduction.

(C) Basal myosin flow on a static-oriented actin network produces anisotropic deformation of the base of the *Drosophila* follicular cells.

(D) Continuous actin-myosin flow in the zebrafish yolk cell produces the mechanical force necessary for EVL spreading over the yolk cell during early zebrafish development.

Coordinated Cell Intercalation

Actin-myosin flows have also been observed during epithelial tissue elongation driven by coordinated cell intercalations (Skoglund et al., 2008; Rauzi et al., 2010; Sawyer et al., 2011). Examples for this are the pulsatile actin-myosin flows found at the apex of epithelial cells during cell intercalation along the dorsal-ventral (DV) axis of the *Drosophila* germ band, leading to germ-band elongation along its anterior-posterior (AP) axis (Rauzi et al., 2010; Sawyer et al., 2011; Figure 2B and Movie S4). These flows are both centripetal, leading to the formation of local actin-myosin accumulations, and are anisotropically oriented toward the DV junctions of the cells, leading to MyoII accumulation there. Anisotropic flow of MyoII toward the DV junctions causes shortening of these junctions, which is an

important step in cell intercalation during germ-band elongation. Accumulation of MyoII at the DV junction coincides with the shortening of DV junctions and is thought to be required for stabilization of the shortened junction. The coupling and/or orientation of the actin-myosin flow to the DV junction require the activity of α-catenin, E-cadherin, and Canoe/Afadin (Rauzi et al., 2010; Sawyer et al., 2011). Notably, the concentrations of catenins and E-Cadherin are lower at DV junctions compared to AP junctions (Simões et al., 2010; Rauzi et al., 2010; Tamada et al., 2012). The E-Cadherin concentration is regulated by the Frizzled planar cell polarity pathway via RhoGEF2 (Warrington et al., 2013). Such lower concentration is hypothesized to more loosely anchor the actin-myosin network between the two DV junctions of the cell and thus allow the actin-myosin network to more freely move between these two junctions (Rauzi et al., 2010).

During cell intercalation, junction shortening is followed by the formation and extension of new junctions oriented perpendicular to the shortened junctions. In the *Drosophila* pupal wing, elongation and stabilization of these newly formed junctions is dependent on the activity of the PTEN tumor suppressor, which reduces MyoII level at the newly formed junction. This illustrates that junction lengthening can also be an active process and explains how MyoII homogenous cortical distribution can be restored upon intercalation to control tissue organization (Bardet et al., 2013).

Oogenesis

Myosin flows that lead to anisotropic force generation have also been observed at the basal side of epithelial cells in *Drosophila* oogenesis. These basal flows are centripetal and have been associated with elongation of the egg chamber (He et al., 2010). The *Drosophila* egg chamber, which consists of the oocyte and nurse cells that are surrounded by a monolayered epithelial follicular tissue, undergoes drastic AP elongation during its growth. This elongation is promoted by a global follicular epithelial tissue rotation around the AP axis of the egg chamber and then by cyclic contractions of follicular cells along the DV axis of the chamber (He et al., 2010; Haigo and Bilder, 2011). Myosin flows at the basal side of the follicular cells are pulsatile and take place on a more static DV-oriented actin network, translating the flow into a contractile force that is preferentially oriented around the circumference of the oocyte, thereby promoting global egg-chamber AP elongation (Figure 2C). The period of basal myosin pulsations is much longer than the one observed for apical flows during mesodermal cell invagination, for example, and is regulated by both E-Cadherin-dependent cell-cell adhesion and integrin-dependent ECM-cell adhesion (He et al., 2010).

Tissue Spreading

Actin-myosin flows in tissue morphogenesis have also been associated with the formation of large actin-myosin cable/ring-like structures during tissue spreading. In *Drosophila* dorsal closure, the lateral epidermis moves dorsally over the amnioserosa (AS) cells to close the dorsal hole of the embryo epidermis (for review, see Harden, 2002; Movie S5). Dorsal closure requires both c-Jun N-terminal kinase (JNK) and Decapentaplegic (DPP) expression within the leading edge of the epidermis, which specifies the leading edge cells and is associated with the formation of a large supracellular actin-myosin cable at the leading edge (Harden, 2002). Both contraction by this supracellular actin-myosin cable and apical constriction of AS cells are thought to drive closure, whereas forces from the bulk of the lateral epidermis oppose it (Hutson et al., 2003; Gorfinkiel et al., 2009; Solon et al., 2009; Almeida et al., 2011). Apical constriction of AS cells is pulsatile and mediated by pulsatile actin-myosin flows at their apex. Contraction of the supracellular actin-myosin ring within the leading edge of the epidermis has been proposed to transform the initially transient pulsatile apical constrictions of AS cells into a stable apical constriction of the AS that is required for effective dorsal closure (Solon et al., 2009).

Nonpulsatile Actin-Myosin Flows

Actin-myosin flows can also be nonpulsatile, as observed in the yolk cell of the gastrulating zebrafish embryo, in which they have been implicated in pulling the enveloping cell layer (EVL)—a squamous epithelial cell layer at the surface of the embryo—over the yolk cell (Behrndt et al., 2012; Movie S6). These flows occur at the surface of the yolk cell, which is not yet covered by the EVL, and are oriented toward the margin of the EVL, which is connected to the yolk cell by tight junctions (Figure 2D). Flow orientation is opposite to the direction of EVL spreading and is associated with the formation of a large actin-myosin cable-like structure located within the yolk cell at the margin of the EVL. The combined activities of the actin-myosin flows toward the margin, generating a pulling force on the EVL margin when resisted by friction within the yolk cell and circumferential contraction of the actin-myosin cable, are thought to drive EVL spreading over the yolk cell.

Regulation of Actin Flow and Force Transmission

Collectively, these studies show that actin-myosin network flows play a critical role in force generation and transmission triggering morphogenesis of epithelial tissues. In the majority of these processes, actin-myosin flows are pulsatile, although the effect of those pulsatile flows on cell/tissue morphogenesis can substantially vary between the individual processes. Generally, changes in cell shape resulting from those pulsatile flows depend on several critical parameters: (1) the frequency and amplitude of the actin-myosin network contractions and direction of actin-myosin flows, generating the force necessary to change the cell shape; (2) the coupling strength of the contractile actin-myosin network to junctional complexes, functioning as a molecular clutch transmitting the force from the actin-myosin network to the junction and via the junctions to neighboring cells; and (3) the stabilization of periodic shape changes due to pulsatile actin-myosin contractions, functioning as a molecular ratchet resisting cell shape changes due to relaxation of actin-myosin network. Elucidating how these parameters are controlled and coupled will be essential to understanding how pulsatile actin-myosin flows function in cell/tissue morphogenesis. As of yet, there is little known about the molecular and cellular mechanisms by which the frequency and amplitude of actin-myosin contractions are controlled within the organism. In *Drosophila* AS cells, Par3 and Par6 polarity proteins have been shown to regulate the frequency of the apical actin-myosin network contractions through a still-unknown mechanism (David et al., 2010). Although specific upstream regulators of the amplitude of actin-myosin network contractions have not yet been identified, it can

generally be assumed that the amplitude depends on the mechanical properties of the network and its coupling/friction to the cadherin or integrin cytoplasmic linkers. The mechanical properties of the actin-myosin network, in turn, are determined by its specific molecular composition of actin, myosin, and crosslinkers and also the turnover and (un)binding rates of its molecular components (Bendix et al., 2008; Koenderink et al., 2009). The direction of actin-myosin flows can be regulated by anisotropic tension (Mayer et al., 2010; Behrndt et al., 2012). Coupling of the actin-myosin network to cadherin and integrin adhesion sites, and thus the molecular clutch function, depends on the k_{on} and k_{off} of their interaction. Theoretical formulation and experimental data show that such coupling can lead to the emergence of oscillatory traction force (Chan and Odde, 2008). Furthermore, adhesion complexes undergo endocytosis and/or recycling, determining their dynamic turnover at the plasma membrane, and different components of the adhesion complex exhibit distinct binding and unbinding rates controlling the mechanical force-transducing properties of those complexes. The stabilization of periodic cell shape changes due to pulsatile network contractions, and thus the ratchet function, is even more enigmatic. As possible mechanisms underlying the ratchet function in *Drosophila* cells, the formation of large apical accumulations of MyoII associated with each centripetal flow in the mesoderm and/or an increase in cortical tension at apical junctions in the germ-band epithelium have been proposed (Martin et al., 2009, 2010; Rauzi et al., 2010). In vertebrates, the force generation and ratchet functions might depend upon distinct MyoII isoforms, which have distinct roles in epithelial tissue due to their different ATPase activity and actin-binding properties (Smutny et al., 2010).

Questions also remain as to the use of periodic versus continuous actin-myosin contractions in tissue morphogenesis. The main difference between periodic and continuous contractions lies within the dynamics of the process, with pulsatile contractions giving rise to more frequent shape changes than continuous contractions will do. This increased dynamics might simply represent an inherent feature of any idle-running actin-myosin motor that, in order to be productive, still needs to be stably coupled to its effector structures. Alternatively, pulsatile contractions might help in screening for cellular arrangements that correspond to minimal and thus preferred energy states, which, with continuous contractions alone, might be difficult to reach. Other differences between pulsatile and continuous contractions might be that pulsatile contractions differently activate mechanosensitive feedback loops in molecular ''clutches'' or ''ratchets'' that couple the actin-myosin network with junctions, thereby adapting the activity of the clutches and or ratchets to the mechanical constraints of the tissue.

Force Integration and Coordination at Tissue Scale

The analysis of actin-myosin dynamics in individual cells provides insights into how mechanical forces are locally generated and transmitted via cell-cell junctions to neighboring cells. However, only the integration of these local forces into a global tissue force pattern determines the resulting changes in cell and tissue shape. During *Drosophila* mesoderm invagination, isotropic centripetal actin flow at the apex of mesodermal cells induces apical constriction of these cells. Yet the global stress of the tissue is anisotropic with higher stress along the AP axis, and thus, each isotropic centripetal actin-myosin flow is not associated with an isotropic apical constriction but is instead associated with a preferential constriction along the DV axis (Figure 3A; Martin et al., 2010). Likewise, during *Drosophila* oogenesis, pulsatile MyoII contraction at the basal side of follicular cells generates an anisotropic circumferential contraction, which compresses and thus elongates the oocyte along its AP axis (He et al., 2010). Finally, during *Drosophila* germ-band elongation, extrinsic forces associated with mesoderm invagination promote cell elongation along the AP axis, thereby contributing to global germ-band elongation (Butler et al., 2009). Besides the role of extrinsic forces in changing the force pattern within tissues, emerging collective effects due to the combinatorial activities of small tissue deformations resulting from changes in the shape, position, and/or division of individual cells decisively influence global tissue-scale deformations. Therefore, understanding tissue morphogenesis requires not only ascertaining how actin-myosin dynamics generates mechanical forces but also how collective cell behavior is controlled and coordinated at the scale of the tissue. Recent advances in the field of planar cell polarization and mechanotransduction have provided insight in the molecular and cellular mechanisms by which individual cell dynamics are coordinated to generate large tissue-scale deformation (Figures 3B–3D).

Planar Cell Polarity

Substantial progress has been made in the dissection of the signaling mechanisms of two main pathways determining PCP in tissues: the Wnt/Frizzled (Fz) and Fat/Dachsous (Ds) pathways (for review, see Goodrich and Strutt, 2011; Gray et al., 2011). In *Drosophila*, the Wnt/Fz-PCP pathway is predominantly required to determine hair, bristle, and ommatidia polarity but has little direct function in tissue morphogenesis. In contrast, Wnt/Fz-PCP signaling in vertebrates plays a major role for cell intercalations driving germ-layer morphogenesis during gastrulation and neurulation (reviewed in Roszko et al., 2009). In particular, recent studies on the function of Wnt/Fz-PCP signaling in neural tube morphogenesis provide insights into how this pathway simultaneously controls neural plate folding and convergent extension movements (Nishimura et al., 2012). Neural tube closure involves (1) neuroepithelial cell intercalations associated with convergent extension movement of the neural plate and (2) bending of the neural plate along its AP axis (Movie S7). Neural plate bending is driven by the coordinated apical constriction of neural plate cell close to the neural plate midline, which depends on the activity Shroom3, recruiting Rho-kinase (ROCK), and thereby activating of MyoII at the apex of these cells (Hildebrand and Soriano, 1999; Haigo et al., 2003; Hildebrand, 2005; Nishimura and Takeichi, 2008). Notably, apical constriction of neural plate cells is anisotropic, and this anisotropic constriction is, in principle, sufficient to explain both oriented cell intercalation driving convergent extension movements and polarized bending of the neural plate. Polarized localization of the Wnt/Fz-PCP component Celsr1, a vertebrate homolog of *Drosophila* Flamingo, at apical junctions along the DV axis of the neural plate is required for ROCK accumulation at these junctions

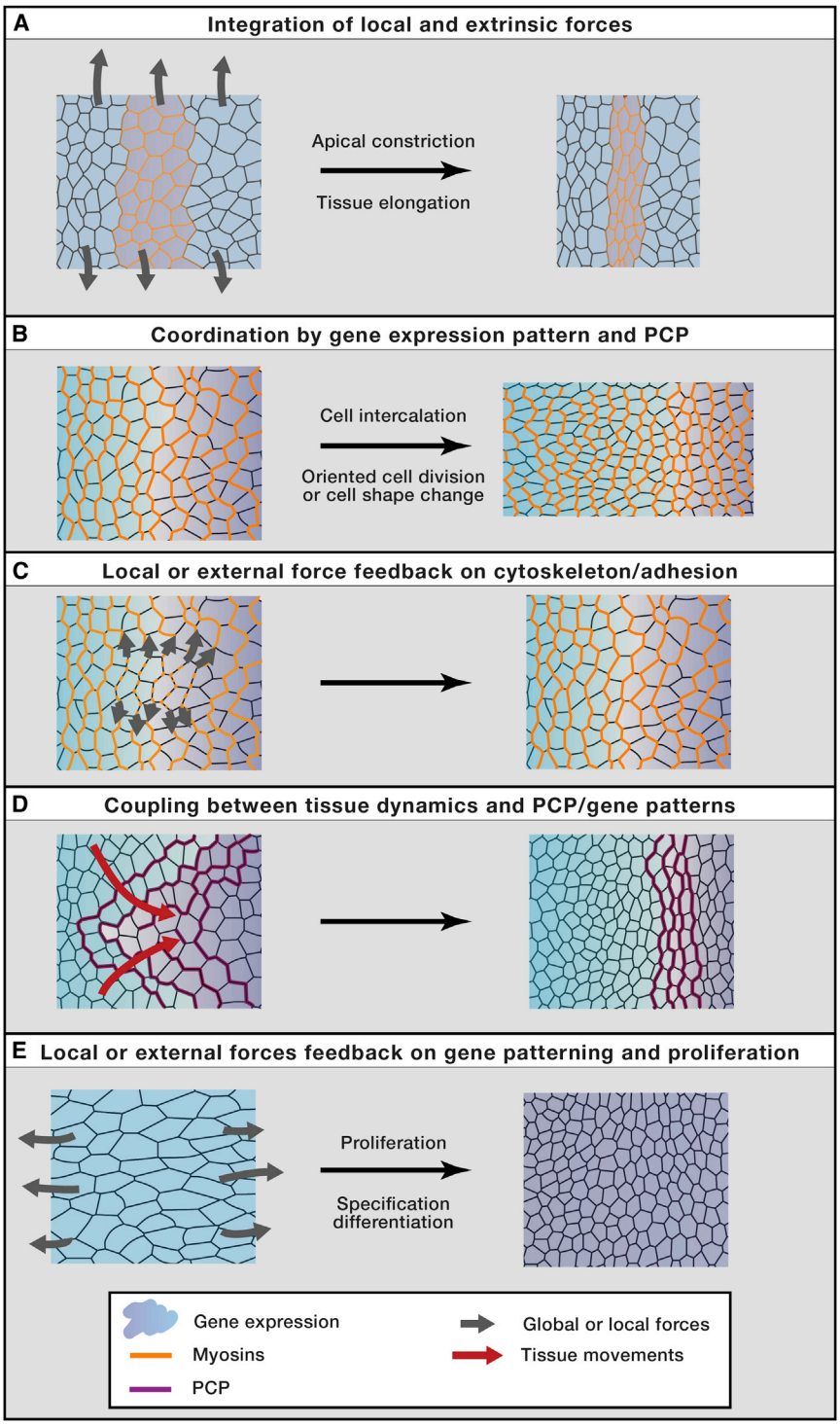

Figure 3. Principles Determining Tissue Morphogenesis and Patterning

(A) The integration of local and global mechanical forces determines cell/tissue shapes changes. Here, apical isotropic actin-myosin contractility and external pulling force lead to anisotropic apical cell constriction.

(B) Gene expression patterns coordinate local cell mechanical properties (anisotropic cell contraction via PCP in [B] or apical cell constriction in [A]) to generate collective cell dynamics (cell shape changes, oriented cell divisions, oriented cell rearrangements) associated with large-scale tissue deformations.

(C) Tissue morphogenetic movements deform gene expression and planar cell polarity patterns.

(D and E) Mechanotransduction functions in cell/tissue morphogenesis by modulating cell mechanical properties, cell proliferation/death, and gene expression.

(Nishimura et al., 2012). ROCK, in turn, leads to phosphomyosin light-chain accumulation and preferential constriction of DV junctions, driving AP-oriented cell intercalation and neural plate bending (Nishimura et al., 2012). Although the mechanisms by which Celsr1 localizes to DV junctions in the first place remain to be uncovered, the observation of Celsr1 simultaneously regulating neural tube convergent extension and bending provides novel insight into Wnt/Fz-PCP function in integrating different morphogenetic movements.

The *Drosophila* Fat/Ds-PCP pathway plays fundamental roles for the regulation of *Drosophila* epithelial tissue morphogenesis (Baena-López et al., 2005; Mao et al., 2006; Saburi et al., 2008; Aigouy et al., 2010; Mao et al., 2011; Bosveld et al., 2012). *fat* and *ds* encode protocadherins, whose heterophilic binding is modulated by the four-jointed (Fj) Golgi resident kinase (Ishikawa et al., 2008; Brittle et al., 2010; Simon et al., 2010). In many *Drosophila* epithelial tissues, *ds* and *fj* are expressed in tissue-wide opposing gradients (Yang et al., 2002; Ma et al., 2003). Fat and Ds are found planar polarized in specific domains of the *fj* and *ds* tissue-wide expression gradients and are necessary to polarize the distribution of the Myosin Dachs (Bosveld et al., 2012; Brittle et al., 2012; Ambegaonkar et al., 2012). Whereas Fat excludes the Dachs from the cell cortex to regulate Hippo signaling (Mao et al., 2006; Rauskolb et al., 2011), Ds intracellular domain interacts with the Dachs to polarize Dachs distribution and to define lines of Dachs planar polarization (Bosveld et al., 2012). Once polarized, Dachs locally increases cortical tension along the lines of its polarized localization, leading to oriented cell rearrangements that shape the *Drosophila* dorsal thorax epithelium (Bosveld et al., 2012). Together, the studies on Wnt/Fz-PCP and Fat/Ds-PCP point at a conserved role of these pathways in regulating cell intercalation by polarizing the subcellular distribution of Myosins (Figure 3B).

Mechanotransduction

In addition to tissue polarization via signaling, mechanotransduction between neighboring cells or across different tissues has been shown to be critical for the coordination of cell contractility and dynamics. During mesoderm invagination, coordination of apical contraction of mesodermal cells is necessary to trigger tissue invagination. This coordination is thought to be achieved by MyoII-dependent apical constriction of mesodermal cells inhibiting the endocytosis and thus inactivation of the secreted protein Folded-gastrulation, which again represents a key signal promoting apical constriction in mesodermal cells (Pouille et al., 2009). Coordination of cell intercalation through mechanosensation has been described in *Drosophila* germ-band elongation, in which embryo patterning along the AP axis is necessary to enrich MyoII at AP cell junctions (Zallen and Wieschaus, 2004). In turn, MyoII-mediated cortical tension induces further MyoII recruitment on AP junctions of adjacent cells, leading to the formation of supracellular MyoII cables that trigger simultaneous intercalations of multiple cells contributing to germ-band elongation (Blankenship et al., 2006; Fernandez-Gonzalez et al., 2009). The formation of supracellular cables is also critical for compartment boundary formation preventing cell mixing due to cell divisions close to the boundary (Landsberg et al., 2009; Monier et al., 2010; Schilling et al., 2011; Aliee et al., 2012). Although Hedgehog and Wingless signaling have been implicated in supracellular cable formation at the boundary (Butler et al., 2009; Landsberg et al., 2009; Schilling et al., 2011), it is conceivable that a mechanical feedback, in which cable contraction promotes cable formation, might also be involved. Several putative mechanisms may exist by which myosin-mediated contraction enhances myosin accumulation within epithelial tissues. Myosin-mediated mechanical tension could trigger further myosin accumulation by modulating the activity of myosins themselves through the stabilization of their association with actin, for example (Cremo and Geeves, 1998; Kovács et al., 2007; Kee and Robinson, 2008). Alternatively, the E-Cad/catenin complex could act as a mechanical stress sensor to locally increase actin-myosin accumulation and contractility (Ladoux et al., 2010; Liu et al., 2010; le Duc et al., 2010; Yonemura et al., 2010; Taguchi et al., 2011; Borghi et al., 2012). Finally, polarized myosin-mediated mechanical tension might deform/align the actin-myosin network along the axis of tension, which then further enhances the contractile activity of myosin along this axis.

In *C. elegans*, mechanical coupling between the epidermis and the muscle is necessary for embryo elongation (Zhang et al., 2011). The body-wall muscles are connected to the basal side of the epidermis via hemidesmosome. Hemidesmosomes also connect the apical side of the epidermis to the exoskeleton. Intermediate filaments (IFs) spanning the epidermis cells are ''anchored'' at the apical and basal hemidesmosomes (Zhang and Labouesse, 2010). Muscle contractions promote the association of the G-protein-receptor kinase interactor (GIT-1) with hemidesmosomes. GIT-1 in turn simulates the kinase activity of the p21-activated kinase (PAK-1), which phosphorylates IFs, thereby modifying IF organization and promoting the stability of hemidesmosomes (Zhang et al., 2011).

Tissue Morphogenesis and Signaling

Signaling pathways not only coordinate individual cell dynamics to generate large tissue-scale deformations, but tissue-scale deformations also feed back on the organization of signaling centers, thereby modulating tissue patterning (Figure 3D). Studies in both animal and plant tissues have provided compelling evidence for a critical function in force-mediated cellular rearrangement within tissues to affect global tissue PCP and patterning. In the developing *Drosophila* wing blade, cells show planar polarization along their proximal-distal (PD) axis. This polarization is mediated by the localization of proteins of the Fz-PCP pathway to the distal and/or proximal sides of these wing blade cells (for review, see Goodrich and Strutt, 2011). Recent work has shown that the PD localization of these proteins is the result of an initial planar polarization of the wing cells toward the wing margin and subsequent rearrangement of the wing cells through anisotropic tension along the PD axis of the tissue (Aigouy et al., 2010; Sagner et al., 2012). The anisotropic tension rearranging the wing cells originates from contraction of the wing hinge attached to the blade. Critical cellular processes underlying the cellular rearrangements by anisotropic tissue tension are cell neighbor exchanges and cell division orientation. Both processes are also dependent on the Ft/Ds pathway, and consequently, defects in Ft/Ds signaling result in severely impaired cellular rearrangements by anisotropic tissue tension. The function of the Ft/Ds might be mediated in part by the myosin Dachs shown to control both cell rearrangement and cell division orientation (Mao et al., 2011; Bosveld et al., 2012) or by MyoII that might become polarized in response to the anisotropic tension generated by the contraction of the hinge.

Interestingly, similar observations of force-mediated cellular rearrangements and cytoskeleton reorganization affecting tissue shape and/or patterning have been made in plants (Hamant et al., 2008; Kuchen et al., 2012). Signaling centers determining leaf growth are thought to be initially positioned perpendicular to each other, determining PD and medial-lateral leaf outgrowth. These initially orthogonally arranged signaling centers have been proposed to subsequently trigger changes in leaf shape that again feed back to modulate the spatial arrangement of the signaling centers themselves. Such mutual feedback between signaling centers determining cellular growth rate and direction within the tissue and resultant cellular rearrangements altering the organization of those signaling centers has been shown to be sufficient to explain variations in leaf shapes observed in different species (Kennaway et al., 2011; Kuchen et al., 2012).

Taken together, the mechanisms by which collective effects from the cumulative and combinatorial activities of local tissue deformations influence global tissue-scale deformations begin to be unraveled. Both exogenous global force application from adjacent tissues and mechanosensation within tissues appear to play decisive roles, although the precise molecular and cellular mechanisms underlying force integration and mechanosensation within tissues are still not entirely clear.

Force Regulation of Cell Differentiation and Proliferation

The ability of cells to perceive extrinsic mechanical forces influences tissue size and architecture not only by changing their adhesive and cytoskeletal organization on short timescales but also by influencing their fate specification and differentiation on longer timescales (Figure 3E). Extrinsic mechanical forces can

originate from microscopic fluid flow and from interaction with the extracellular matrix (ECM) and global tissue stresses.

Extracellular Matrix Interactions

The role of static force in cell proliferation, fate specification, and lineage commitment is best understood in the context of cell-ECM interactions mediated by integrin receptors (for review, see Eyckmans et al., 2011). The molecular mechanisms by which cells attach to the ECM via integrins have been extensively investigated (for review, see Parsons et al., 2010). In recent years, the development of microfabricated devices to control the chemical and mechanical cell environment independently from each other has revolutionized the study of mechanotransduction and its role in stem cell differentiation and tissue development (Kobel and Lutolf, 2011). In particular, it has permitted the separation of the respective contributions of ECM attachment, cell rounding, cell-cell interactions, cell tension, and cell compaction on stem cell maintenance and differentiation. It is now clearly established that cell shape changes and variations of ECM stiffness transduced by integrins can have a drastic impact on diverse cell types, such as mesenchymal stem cells (MSCs), muscle stem cells, and endothelial cells (for review, see Discher et al., 2009). In particular, MSCs differentiate into osteoblasts on stiff ECM that mimics the natural bone environment, whereas MSCs differentiate in other lineages, such as adipocytes, on soft ECM (Discher et al., 2009).

Transducing Mechanical Forces

The MAL/SRF and YAP/TAZ transcriptional regulators have emerged as key molecules transducing the effect of mechanical forces on cell proliferation, stem cell differentiation, and lineage commitment (Connelly et al., 2010; Dupont et al., 2011; Wada et al., 2011). Mechanically induced changes in G-actin levels require MAL (megakaryocytic acute leukemia, also known as MRTF-A and MKL1) interacting with the serum response factor (SRF) transcription factor (for review, see Olson and Nordheim, 2010). The MAL/SRF complex also participates in the perception of mechanical cues from the ECM influencing epidermal stem cell fate decisions (Connelly et al., 2010) and border cell migration in *Drosophila* (Somogyi and Rørth, 2004). Yorkie-homolog YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif), which associate with TEA domain transcription factors, are emerging as key mechanosensors and mechanotransducers controlling lineage commitment and cell proliferation in many cell types, such as MSCs (Dupont et al., 2011). YAP/TAP nuclear localization is determined by ECM stiffness—high ECM stiffness and cell spreading increase cortical tension and promote stress fiber formation, which, via an yet unknown mechanism, lead to YAP/TAZ translocation to the nucleus, whereas low stiffness and cell rounding promote cytoplasmic localization (Dupont et al., 2011; Wada et al., 2011). Loss of YAP/TAZ function in MSCs induces their differentiation into adipocytes independently of ECM rigidity. Conversely, activation of YAP/TAZ function in MSCs is sufficient to promote their differentiation in osteoblasts on soft substrates in a Rho-independent manner. In response to stress fiber formation, YAP/TAZ also participate in the regulation of cell proliferation (Dupont et al., 2011; Wada et al., 2011). Supporting a role of F-actin accumulation in mediating the effect of mechanical force on YAP/TAZ activities are findings in *Drosophila*, which show that increasing F-actin levels promote cell growth/proliferation via Yorkie, the *Drosophila* YAP homolog (Sansores-Garcia et al., 2011; Fernández et al., 2011). How F-actin regulates YAP/TAZ activities and whether the ultimate signal that regulates YAP/TAZ-mediated cell behavior in response to mechanical cues is the contractile machinery of the cell remain to be characterized.

Tissue Compression

Generally, tissue compression and stresses are thought to play critical roles in tissue size regulation and cell fate specification. During *Drosophila* imaginal disc growth, models have been put forward in which the integration of signaling triggered by the TGFβ-homolog Decapentaplegic (Dpp) and mechanical stress produces a homogenous proliferation rate across the tissue, thereby controlling tissue size (Hufnagel et al., 2007; Aegerter-Wilmsen et al., 2012). Likewise, mechanical compression of the stomadeal primordium in the *Drosophila* embryo due to germ-band elongation is sufficient to upregulate primordial *twist* expression (Desprat et al., 2008). Upregulation of *twist* expression depends on compression-induced β-catenin release from the cell junctions in a Src-dependent manner (Desprat et al., 2008). Similarly in mice, muscle contraction is required for maintaining joint progenitors committed to their fate through activation of β-catenin in the progenitor cells (Kahn et al., 2009).

Condensation

In vertebrates, the condensation of MSCs during tooth formation provides an example of how cell condensation, and thus the associated mechanical compression, affects cell fate specification and differentiation (Mammoto et al., 2011). During embryonic tooth organ formation, fibroblast growth factor (FGF) produced by the dental epithelium (DE) promotes mesenchymal cell migration and thus attracts increasing numbers of mesenchymal cells beneath the dental epithelium. However, the DE epithelium also secretes a short-range repulsive signal, Sema3f, which locally repulses mesenchymal cells. Mesenchymal cells therefore condense and are compacted beneath the DE. The resulting mechanical compression induces cell rounding and loss of stress fibers and decreases RhoA activity. Reduced RhoA activity, in turn, leads to odontogenetic cell fate induction in these cells by upregulating the expression of odontogenetic genes, such as Pax9 (Mammoto et al., 2011). In *Drosophila* and zebrafish, compression force associated with overcrowding is proposed to lead to extrusion of live cells from epithelia (Eisenhoffer et al., 2012; Marinari et al., 2012).

Fluid Flows

Not only static forces but also forces resulting from microscopic fluid flows have been shown to affect cell differentiation and global patterning of tissues and embryos (Freund et al., 2012). Most prominently, fluid flow within the organ of laterality has been shown to control embryo patterning along its left-right (LR) axis in various species (Nonaka et al., 1998; McGrath et al., 2003; Tanaka et al., 2005). Here, cilia positioned in a cavity on the ventral surface of the node in chicken and mice—and in the inner surface of Kuppfer's vesicle in zebrafish—are tilted along the AP axis of the embryo (Okada et al., 2005; Hirokawa et al., 2006; Okabe et al., 2008). This unidirectional cilia tilt requires planar polarization of cilia-forming cells by the Wnt/Fz-PCP pathway and enables the cilia to induce a directional fluid

flow adjacent to the surface by effectively stroking in one direction only (Song et al., 2010; Borovina et al., 2010). The unidirectional flow above the surface is thought to asymmetrically distribute not-yet-identified signaling molecules (Tabin and Vogan, 2003) along the LR axis of the organ that subsequently polarizes the embryo along this axis (Nonaka et al., 2002; Okada et al., 2005). In addition, or alternatively, unidirectional flow due to polarized cilia beating at the surface of the organ of laterality has been proposed to trigger a mechanosensitive response in the cilia located on the left side of the cavity, which in turn polarizes the embryo along its LR axis (Tabin and Vogan, 2003).

Mechanosensitivity of cells to fluid flows has also been described for endothelial cells forming the blood and lymphatic vascular system (reviewed in Jones et al., 2006; Swartz and Fleury, 2007). In the blood vascular system, endothelial cell mechanosensing of fluid shear stress due to blood flow has been shown to modulate the shape, identity (vein versus artery; le Noble et al., 2005; Buschmann et al., 2010; Corti et al., 2011), and function of blood vessels (reviewed in Jones et al., 2006; Swartz and Fleury, 2007). Several mechanotransducers have been proposed to mediate the response of endothelial cells to fluid shear stress. In particular, primary cilia might represent one such mechanosensing structure, as defective ciliogenesis in endothelial cells is accompanied by severe impairment of heart development (Slough et al., 2008). In the lymphatic vascular system, shear flow cooperates with the transcription factors PROX1 and FOXC2 in controlling the assembly and delimitation of the lymphatic valve territory (Sabine et al., 2012). Mechanosensing of fluid shear stress is also involved in the specification of hematopoietic stem cells (HSCs), which are formed in close association with the endothelial cells of blood vessels (North et al., 2009; Adamo et al., 2009). Fluid shear stress elicits a mechanosensitive response in HSCs that leads to pronounced changes in their cell fate specification and differentiation potential.

Taken together, there is growing evidence for extrinsic mechanical forces functioning in tissue and embryo morphogenesis by modulating cell fate specification and differentiation. While the molecular and cellular mechanisms by which extrinsic forces influence cell differentiation are being elucidated, it remains to be investigated how cell fate differentiation feeds back on the ability of cells to generate and receive those forces.

Conclusions

The central role mechanical forces play in tissue morphogenesis and patterning has become increasingly clear. Although the mechanisms by which forces function in these processes have been extensively studied ex vivo, comparably little is known about the function of forces under physiological conditions within the developing embryo. It is still not entirely clear what the magnitude and distribution of forces are within embryos and how such forces elicit mechanosensitive responses in embryo cells that can decisively influence their development. The advancement of techniques to precisely measure and manipulate forces within the developing embryo will be essential to address this question. Important steps in this direction are the recent applications of computational methods to infer force from tissue deformation or segmented images (Brodland et al., 2010; Ishihara and Sugimura, 2012; Chiou et al., 2012) as well as experimental methods, such as molecular force sensors and optical tweezers, with the help of which forces can be measured and applied on a subcellular level within cells and tissues in vivo. Also, recent advances in optogenetic approaches, in which the function of specific molecules can be locally activated or inactivated using light (for review, see Toettcher et al., 2011), suggest that these will be valuable tools to manipulate force-generating and -receiving processes in a spatiotemporally highly controlled manner within the embryo. Furthermore, in order to elucidate the interplay between the function of mechanical forces in morphogenesis and cell fate specification, it will be essential to simultaneously monitor forces and the expression of genes associated with the acquisition and maintenance of specific cell fates within the embryo. Finally, although many studies have been performed on two-dimensional epithelial cell sheets, an important challenge will be to further extend recent segmentation methods, cinematic measurements, and mechanical models to three dimensions (Olivier et al., 2010; Kennaway et al., 2011; Gelbart et al., 2012; Osterfield et al., 2013).

Another important challenge ahead will be to analyze morphogenesis in tissues in which cell proliferation plays a major role. As of yet, tissue morphogenesis is best understood in nonproliferative tissues in which cell shape changes and cell rearrangements are the predominant processes driving morphogenesis. For quantifying the specific contributions of cell shape changes and cell rearrangements to global morphogenesis of those tissues, the application of various mathematical frameworks has been decisive. In contrast, although there has been important progress in analyzing morphogenesis of some proliferative tissues (Boehm et al., 2010), the contribution of the rate and orientation of cell divisions and their interplay with cell shape changes and cell rearrangements is still not entirely clear. Moreover, recent findings have provided insight into the role of mitotic cell rounding in tissue invagination (Kondo and Hayashi, 2013) and the interaction of dividing cells with their neighboring cells regulating cytokinesis and epithelial tissue organization (Founounou et al., 2013; Guillot and Lecuit, 2013; Herszterg et al., 2013). The analysis of morphogenesis in proliferative tissues is, in part, impeded by the lack of a rigorous quantitative framework, with the help of which specific contributions of cell divisions and apoptosis in addition to cell shape change and cell rearrangements to tissue morphogenesis can be determined.

Irrespective of the proliferative nature of tissues, it will be critical to understand how diverse and elaborated tissue shapes can be generated by the combinatorial activities of different signaling pathways in controlling cell shape, rearrangements, and division. Combinatorial activities of signaling pathways have been shown to be important for the regulation of diverse flower shapes in plants (Cui et al., 2010). To dissect the specific contributions of different signaling pathways in embryo morphogenesis, the development of subtractive approaches of deformation field rates and cell dynamics in embryos with defects in certain signaling pathways have turned out to be instrumental in assigning specific functions to specific signaling pathways in morphogenesis (Bosveld et al., 2012).

Although our understanding of the processes by which tissues take shape has tremendously advanced during the last years, we

are still far from understanding how the interplay between embryo patterning and tissue morphogenesis drives embryogenesis. To tackle this question, new experimental and theoretical approaches need to be developed that allow integrating cell and tissue mechanics with gene expression network dynamics during embryogenesis.

SUPPLEMENTAL INFORMATION

Supplemental Information includes seven movies and can be found with this article online at http://dx.doi.org/10.1016/j.cell.2013.05.008.

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