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Tissue mechanics regulates form, function, and dysfunction

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Morphogenesis encompasses the developmental processes that reorganize groups of cells into functional tissues and organs. The spatiotemporal patterning of individual cell behaviors is influenced by how cells perceive and respond to mechanical forces, and determines final tissue architecture. Here, we review recent work examining the physical mechanisms of tissue morphogenesis in vertebrate and invertebrate models, discuss how epithelial cells employ contractility to induce global changes that lead to tissue folding, and describe how tissue form itself regulates cell behavior. We then highlight novel tools to recapitulate these processes in engineered tissues.

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Introduction

Morphogenesis determines the unique shape and correct positioning of tissues and organs in the body. Just as all cells come from cells ('*omnis cellula e cellula*') [1], all tissues come from cells that contain essentially the same genetic information. Many of the signaling pathways that control organ morphogenesis are conserved across species [2], and common changes in cell adhesion, cell shape, and cell migration drive morphological changes on a tissue scale. Nonetheless, every tissue exhibits a distinct architecture and function, which indicates that cells integrate information from signaling networks and mechanical cues in a context-dependent manner to determine the physical output of gene expression [3,4].

The spatiotemporal control of morphogenetic processes accommodates and is driven by surface area and volume constraints to give rise to various tissue architectures: from arborized networks of blood vessels, neurons, and bronchial tubes to vilified epithelial sheets. In order to meet mass-transport requirements, most animals employ a network of interconnected epithelial tubes with barrier and secretory functions [5]. For instance, the human vascular network enables about five liters of blood to be delivered to tissues each minute [6], while the arborized structure of the lungs maximizes the surface area for gas exchange at the alveolar tips to enable the oxygenation of blood. How groups of epithelial cells form polarized sheets that buckle and bend in response to mechanical and biochemical cues, and thus acquire various shapes and functions, remains mostly a mystery. It is well appreciated, however, that the generation and maintenance of proper tissue architecture is required for homeostasis whereas its loss is a prerequisite for disease [3].

Studies of model organisms and cultured tissues have provided key insights into how mechanical forces generated at the cellular level are integrated with biochemical cues to convert gene expression patterns into sophisticated tissue structures in a context-dependent manner. Most of our understanding of morphogenetic processes emanates from well-defined invertebrate models because of widely available genetic and molecular tools. A well-studied example is ventral furrow formation in *Drosophila*, during which the tension generated by actomyosin contractility across the apical surface of a sheet leads to apical constriction and localized tissue folding [7–9]. This requires dynamic changes in actomyosin contractility at the molecular level to be transmitted across larger length scales through junctional domains between cells in the tissue sheet [10].

Development is choreographed such that tissue structure can be tuned in response to microenvironmental factors. The interactions between the cells that constitute a tissue and their surrounding extracellular matrix (ECM) can guide cellular behavior and changes in tissue morphology. According to the principle of dynamic reciprocity, cells communicate with the ECM through the transport of growth factors or through direct contact with membrane-associated components, and these interactions evolve over time [11]. This crosstalk has been examined extensively in the context of the mammary gland, which can undergo cycles of development, differentiation, and apoptosis in order to accommodate the temporary need to produce and deliver milk [12]. The regulation of ECM remodeling in morphogenesis has revealed that the loss of

proper tissue architecture underlies malignant transformation, while reconstitution of normal tissue architecture through the restoration of healthy cell–ECM communication overrides genetic abnormalities [3,4,13–15].

Disrupting the force-generation and transmission machinery leads to aberrant tissue morphologies that underlie many congenital diseases such as defects of neural tube closure, pulmonary hypoplasia, and abnormal alveolar structures [16]. Morphogenesis of diseased tissues relies on the same signaling pathways that guide healthy development. Thus in a way, acquired diseases such as cancers are errors of development, as Virchow asserted, since 'tumors appear by the same law which regulated embryonic development' [1].

Here, we discuss how a group of undifferentiated cells employ cytoskeletal contractility, proliferation, apoptosis, and interactions with their surrounding microenvironment to generate complex and reproducible epithelial tissue architectures. We review recent work on how long-range transmission of mechanical forces sculpts sheets of cells into their final form, and how its dysregulation leads to the disruption of healthy tissue architecture.

Cellular contractility generates tissue folds

Many morphogenetic events that remodel epithelial sheets result from dynamic changes in cell shape. A well-known example is apical constriction, in which the apical surface of a cell shrinks due to the purse-string effect produced by actomyosin contractility [17]. This local change in cell geometry impacts global tissue morphology when contractile forces are transmitted across a sheet through cell–cell junctions, and its role has been implicated in cell ingression, cell extrusion, delamination, and wound healing [17,18].

Actomyosin contractility has been shown to underlie the initiation of epithelial buds during branching morphogenesis of the chicken lung. Localization of phosphorylated myosin light chain (pMLC) and filamentous actin (f-actin) to the apical surface of the epithelium was demonstrated to induce cellular shape changes as a result of apical constriction that precedes domain branching, and induces branch initiation (Figure 1a1). Inhibiting actomyosin contractility prevented both apical constriction and domain branching, whereas blocking proliferation had no effect on branch initiation [19].

Ventral furrow formation in *Drosophila* is driven by dynamic pulsatile actomyosin contractions [7], and the coordination of these pulses leads to collective apical constriction [20] that drives individual cell shape changes. The transmission of contractile forces relies on the coupling of cell–cell junctions to actomyosin networks [21]; recently, the use of optogenetic tools to manipulate cytoskeletal contractility with spatial specificity demonstrated for the first time that depleting actin from the cortex arrested invagination of the ventral furrow [22]. Guglielmi *et al.* used light to modulate the levels of plasma membrane phosphoinositides, or phosphatidylinositol-4,5-biphosphates, which regulate cortical actin polymerization, achieving spatiotemporal control over cellular contractility. These experiments demonstrated that apical constriction is necessary to both initiate and sustain invagination [22]. Since this optogenetic approach provides spatial and temporal control over apical constriction, it could be used in other developmental systems to assess the extent of force transmission required to induce tissue folding.

Actomyosin contractility also has an important role in providing the mechanical forces necessary to drive cytokinesis during cell division [23], and causes local tissue deformation by inducing cell-shape changes in apoptotic cells [24]. Recently, it was found that actomyosin contractility drives epithelial folding in the *Drosophila* leg by creating an apico-basally directed force in apoptotic cells. Following the initiation of apoptosis, it was observed that a cable-like myosin II structure in apoptotic cells deforms the apical surface of the epithelium through myosin II-dependent pulling (Figure 1b). This force then propagates throughout the fold domain via adherens junctions, and finally, the distribution of apoptotic events within the fold domain leads to a global redistribution of myosin II to induce epithelial folding [25•].

Cellular contractility drives the initiation of unique tissue patterns, and it is in turn modulated by predefined spatial constraints. During gastrulation in *Drosophila*, mechanical constraints imposed by the ellipsoid shape of the embryo lead to anisotropic tension along its long axis, causing the actomyosin meshwork to be aligned in anterior–posterior direction, and leads to ventral furrow formation [26•]. These findings point to the reciprocal nature of mechanosensing, since actomyosin contractility can drive tissue folding but results as a consequence of mechanical constraints imposed by the microenvironment.

Reciprocal interactions between cells and their surrounding microenvironment determine final tissue architecture

Crosstalk between cells and their surrounding microenvironment dictates the various patterns of cell shape changes, proliferation, apoptosis, and rearrangement of cells within an epithelial sheet. The basement membrane (BM), a specialized type of ECM comprised mainly of laminin, collagen IV, and several large glycoproteins, separates the epithelium from its surrounding mesenchyme [27]. During branching morphogenesis of organs such as the lung, salivary gland, and mammary gland, the epithelium expands rapidly while still being enveloped within a BM [19,28,29].