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Pulling together: Tissue-generated forces that drive lumen morphogenesis

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ABSTRACT

Mechanical interactions are essential for bending and shaping tissues during morphogenesis. A common feature of nearly all internal organs is the formation of a tubular network consisting of an epithelium that surrounds a central lumen. Lumen formation during organogenesis requires precisely coordinated mechanical and biochemical interactions. Whereas many genetic regulators of lumen formation have been identified, relatively little is known about the mechanical cues that drive lumen morphogenesis. Lumens can be shaped by a variety of physical behaviors including wrapping a sheet of cells around a hollow core, rearranging cells to expose a lumenal cavity, or elongating a tube via cell migration, though many of the details underlying these movements remain poorly understood. It is essential to define how forces generated by individual cells cooperate to produce the tissue-level forces that drive organogenesis. Transduction of mechanical forces relies on several conserved processes including the contraction of cytoskeletal networks or expansion of lumens through increased fluid pressure. The morphogenetic events that drive lumen formation serve as a model for similar mechanical processes occurring throughout development. To understand how lumenal networks arise, it will be essential to investigate how biochemical and mechanical processes integrate to generate complex structures from comparatively simple interactions.

Contents

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ECM, extracellular matrix; FRET, Förster resonance energy transfer; JNK, c-Jun *N*-terminal kinase; PCP, planar cell polarity; ROCK, Rho-associated protein kinase; VEGF, vascular endothelial growth factor.

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1. Introduction

Many organs are characterized by the presence of a tubular architecture, usually consisting of a central lumen surrounded by epithelial cells. These can be simple straight tubes, as exemplified by the intestine or neural tube, or they may have an intricate branching pattern, observed in the lung, kidney, and many secretory organs. Lumen formation requires several morphogenetic movements and is governed by the coordinated efforts of genetic and physical mechanisms. Classically, lumens may form by any of several conserved processes. An epithelial sheet may wrap into a cylinder to enclose a lumen. Alternatively, lumens may arise from within a rod of cells, which undergo cellular rearrangements to generate a central cavity during cord hollowing. Lumens may also form by hollowing through a single cell. Once formed, hollow epithelia can undergo branching morphogenesis to extend a lumen in new directions [1–3].

Lumen formation is essential for organogenesis and can serve as a model for fundamental processes that shape development. The morphogenesis of many organs is guided by interactions between physical processes and biochemical signals. Whereas the effects of several genetic and signaling processes have been examined extensively, the mechanical forces that drive morphogenesis remain far less well characterized. Changes in cell shape and tension can have dramatic effects on the architecture and migration of the tissues in which they reside. Cells are capable of not only generating mechanical force, but also of sensing and transmitting forces. Understanding how cells generate and interpret mechanical forces will be essential for understanding morphogenesis. Here we review the physical processes that shape epithelia and how these mechanisms contribute to lumen formation and organogenesis.

2. Types of morphogenetic movements

2.1. Epithelial bending

One fundamental mechanical process that occurs during lumen morphogenesis is bending of epithelia. Epithelial bending can initiate new lumens by inducing the invagination of a sheet of cells and can extend new branches by generating deformations that extend an existing lumen in new directions. This process was initially characterized during the development of the chicken neural tube, where tissue deformations are driven by changes in the shape of the neuroepithelial cells, which were found to contract at their apical surfaces [4] (Fig. 1A, B). The link between apical constriction of individual cells and bending of epithelial tissue has been best characterized during gastrulation in several species [5–7], which has served as a model for other morphogenetic events. During gastrulation, this change in cell shape bends the embryo and drives involution necessary for differentiating cell types in the early embryo.

Apical constriction can also drive the initial stages of lumen morphogenesis. The vertebrate lung uses recursive branching events to generate a complex and nearly stereotypic airway tree. In the chicken lung, new branches are initiated by localized apical constriction of airway epithelial cells [8] (Fig. 1A). Similar changes in cell shape have been suggested to drive branching in the mouse lung [9]. Apical constriction can also generate a new lumenal organ from an epithelial sheet. For example, the *Drosophila* salivary gland arises from a pit of apically constricting epithelial cells [10], and the resulting invagination initiates the formation of a new lumen. Simple changes in cell shape can drive dramatic bends and folds in epithelia throughout organogenesis.

Interestingly, recent work suggests that apoptotic cells may generate transient pulling forces that bend the apical surfaces of epithelia. In the *Drosophila* leg disk epithelium, apoptotic cells help initiate epithelial bending [11]. This transient force precedes the onset of apical constriction, suggesting a mechanical regulation of apical constriction. Similarly, apoptotic cells have been noted at critical locations during bending of the vertebrate neural tube [12]. It will be interesting to determine whether the forces generated by apoptosis serve as a more widespread mechanism for bending epithelia and resolving lumens. Regardless, forces generated from within cells can exert dramatic effects on the surrounding tissue, capable of bending epithelia and initiating new lumen outgrowth.

2.2. Collective migration

Once initiated, lumen outgrowth requires epithelial extension, which can be driven by collective migration. As they migrate, epithelial cells maintain adhesive connections to their neighbors while being guided by a group of tip cells at the leading edge. The fruit fly has been instrumental for identifying and characterizing genetic regulators of the physical processes that underlie collective migration during lumenal morphogenesis. In the highly branched tracheal system, which transfers gases throughout the body of the fly, new branches arise by collective migration of cells that enclose a central lumen (Fig. 1C). The position of these branches is directed by fibroblast growth factor, which stimulates a group of tip cells to migrate toward the signal and elaborate the network [13–15].

Collective migration is also essential for morphogenesis of many vertebrate organs. Similar to the *Drosophila* trachea, collective migration of endothelial cells in the vertebrate vasculature generates a network that extends throughout the animal (Fig. 1C). Vascular development has been examined extensively in zebrafish, where the optical transparency of the developing larva has permitted direct observation of vascular migration in response to a variety of signals. Secretion of vascular endothelial growth factor (VEGF), in particular, plays a key role in the morphogenesis of vertebrate vasculature [16,17]. Tip cells at the leading edge of a sprout lead the collective migration of new vascular branches towards the VEGF source. Similarly, semaphorin and plexin signaling can direct the growth and movement of new vessels by guiding cellular migration [18]. Collective migration can also be influenced by mechanical cues. In the zebrafish pronephric duct, fluid flow stimulates collective migration of kidney epithelial cells [19]. Obstructing the ductal lumen, which blocks fluid flow, inhibits cell migration and disrupts kidney morphogenesis.

Collective migration has been well studied during development of the mouse mammary gland. Similar to other lumenal networks, the mouse mammary gland branches through collective migration of groups of cells away from the central lumen [20]. During migration of the mammary gland epithelium, individual cells maintain limited junctional contacts and can be observed migrating within the epithelium [21]. Normal collective migration of these cells depends on contacts with the extracellular matrix (ECM). Changes in the basement membrane or deletion of adhesion proteins can drive increased collective migration from the mammary epithelium [22]. Adhesions transmit mechanical forces during collective