EXPERIMENTAL CELL RESEARCH 321 (2014) 64–70

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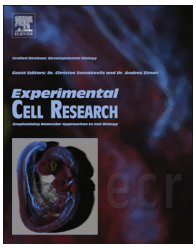

Review Article

Luminal matrices: An inside view on organ morphogenesis

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ARTICLE INFORMATION

Article Chronology:
Received 31 July 2013
Received in revised form
14 September 2013
Accepted 17 September 2013
Available online 25 September 2013

Keywords:
Apical extracellular matrix
Organogenesis
Tubulogenesis
Lumen
Chitin
Mechanical forces
Luminal pressure

ABSTRACT

Tubular epithelia come in various shapes and sizes to accommodate the specific needs for transport, excretion and absorption in multicellular organisms. The intestinal tract, glandular organs and conduits for liquids and gases are all lined by a continuous layer of epithelial cells, which form the boundary of the luminal space. Defects in epithelial architecture and lumen dimensions will impair transport and can lead to serious organ malfunctions. Not surprisingly, multiple cellular and molecular mechanisms contribute to the shape of tubular epithelial structures. One intriguing aspect of epithelial organ formation is the highly coordinate behavior of individual cells as they mold the mature lumen. Here, we focus on recent findings, primarily from *Drosophila*, demonstrating that informative cues can emanate from the developing organ lumen in the form of solid luminal material. The luminal material is produced by the surrounding epithelium and helps to coordinate changes in shape and arrangement of the very same cells, resulting in correct lumen dimensions.

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http://dx.doi.org/10.1016/j.yexcr.2013.09.010

Introduction

Many developing epithelial organs start out as small tubular primordia that will expand to give rise to mature functional organs. The cells constituting these organ primordia are polarized along the apical-basal axis and connect to each other via junctional complexes that maintain polarity and provide adhesive functions. While the apical plasma membrane generally faces the lumen and exhibits specialized secretory functions, the basal membrane rests on a surrounding basal lamina. Additional cell layers, often of mesodermal origin, may encircle the tubular epithelium to provide support and contractile forces to the organ. The subsequent size-maturation of primordial organ lumina involves distinct and preprogramed phases of growth, both in length and diameter, to accommodate functional dimensions. Such tube growth is mediated by highly coordinated changes in cell shape and cell rearrangements, and it can be accompanied by cell proliferation as the entire organ grows.

Key cellular processes involved in epithelial lumen morphogenesis include membrane and protein trafficking, cytoskeletal changes, junction rearrangement, growth and cell division. For instance, the addition of apical membrane to accommodate rapid lumen diameter expansion can be driven by exocytosis, as in the *Drosophila* tracheae [1,2], or by reshuffling of intracellular membrane to the apical surface, as in the excretory organ in *Caenorhabditis elegans* [3]. Oriented cell intercalation, cell division and cell elongation also participate in regulating lumen dimensions during size-maturation of the organ. In the developing *Drosophila* tracheae, axial tube elongation relies on polarized cell shape changes along the tube axis [4,5], while in *Xenopus* embryos, the pronephric tubules elongate through rosette-based cell intercalation [6]. The latter is similar to the highly stereotyped cell intercalation events observed during germband elongation in *Drosophila* [7], and both processes depend on planar cell polarity (PCP) signaling. PCP appears to control the spatially oriented cell rearrangements and the orientation of cell divisions along the renal tube axis, and defects in this process have been proposed to cause cyst formation in polycystic kidney disease (PKD) [8]. The stability and proper dimensions of lumina in epithelial tubes are further supported by subapical actin and the intermediate filament-based terminal web [9,10].

An interesting problem is how the diverse cellular events are coordinated across the epithelium to produce a correctly shaped lumen. Part of the answer may rely on the transmission of forces within the tissue to produce coordinate global changes in shape. Over the past years, much progress has been made in describing tissue and organ morphogenesis as biomechanical processes [11]. The self-organizing features of actin networks, the dynamics of actomyosin contractility, and the dynamic remodeling of cell–cell junctions and ECM all contribute to the mechanical properties of epithelial tissues. Tubular epithelia present a special case with regard to tissue mechanics, as they form lumina that can provide an additional source for force generation and integration to steer cellular behavior in the surrounding epithelium. Luminal hydrostatic pressure, for example, generated by liquid secretion or osmosis, will exert a uniform force on the enclosing cells (Fig. 1A and B). Indeed, such hydrostatic pressure was proposed to play important roles in lumen formation and expansion in the gut [12], in Kupffer's vesicle [13] and in brain ventricles [14] in zebrafish, and in the excretory cell [15] and vulva [16] in *C. elegans*. Moreover, the cylindrical geometry of tubular structures brings along physical constraints that are distinct from those experienced by cells in planar epithelial sheets. Laplace's law states that circumferential surface tension on a pressurized cylinder is larger than axial surface tension. This force anisotropy can be exemplified by an over-boiled sausage, which always bursts along its length (Fig. 1A). Thus, although the distribution and scale of forces in tubular epithelia have not been well documented, luminal pressure can in principle also generate planar asymmetry along the tube axis. Aside from hydrostatic pressure, flow of the luminal content can generate shear stress that acts on cells lining the

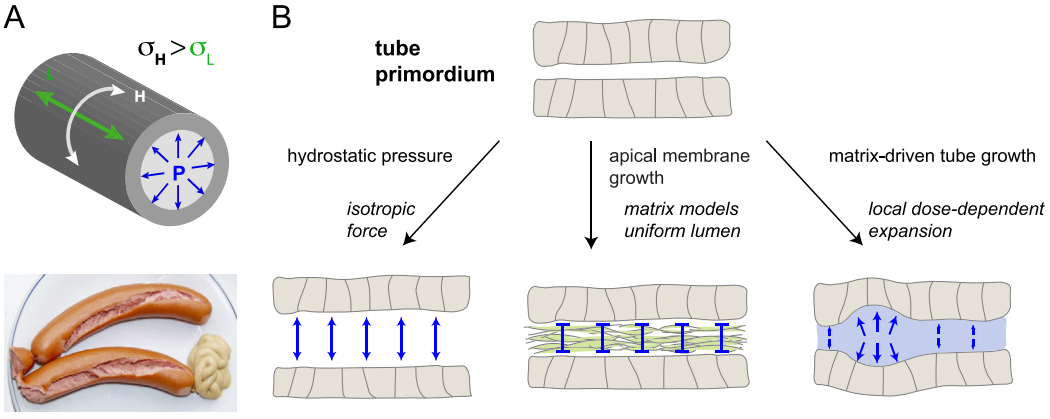

Fig. 1 – Physical cues in epithelial tube expansion. (A) Internal isotropic pressure in a cylinder will produce hoop stress (σ_H) and longitudinal stress (σ_L). The hoop stress is larger than the longitudinal stress, as illustrated by the longitudinally ruptured skin of an over-boiled sausage. (B) Three ways that physical luminal cues can act during diameter expansion of a tubular primordium. Left: hydrostatic pressure generates equal force normal to the lumen surface. Depending on the magnitude and duration of force and on the mechanical properties of the tissue, the resulting deformation can lead to expansion of the entire tube diameter. Middle: apical membrane growth results in lumen dilation. A rigid luminal matrix serves as a scaffold that holds on to the lumen surface and supports uniform lumen diameter growth. Right: a luminal matrix generates an internal pressure. The low mobility of the matrix inside the lumen facilitates differential lumen dilation along the tube axis, depending on the local amount of matrix deposition.