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Generating tissue topology through remodeling of cell-cell adhesions

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ABSTRACT

During tissue morphogenesis, cellular rearrangements give rise to a large variety of three-dimensional structures. Final tissue architecture varies greatly across organs, and many develop to include combinations of folds, tubes, and branched networks. To achieve these different tissue geometries, constituent cells must follow different programs that dictate changes in shape and/or migratory behavior. One essential component of these changes is the remodeling of cell-cell adhesions. Invasive migratory behavior and separation between tissues require localized breakdown of cadherin-mediated adhesions. Conversely, tissue folding and fusion require the formation and reinforcement of cell-cell adhesions. Cell-cell adhesion plays a critical role in tissue morphogenesis; its manipulation may therefore prove to be invaluable in generating complex topologies ex vivo. Recapitulating these shapes in engineered tissues would enable a better understanding of how these processes occur in vivo, and may lead to improved design of organs for clinical applications. In this review, we discuss work investigating the formation of folds, tubes, and branched networks with an emphasis on known or possible roles for cell-cell adhesion. We then examine recently developed tools that could be adapted to manipulate cell-cell adhesion in engineered tissues.

1. Introduction

During morphogenesis, cells and tissues rearrange themselves to generate complex three-dimensional (3D) architecture, such as folds, tubes, and branched networks [1]. Cell adhesions participate in these dynamic rearrangements and maintain tissue integrity throughout adult life. During collective cell movements that drive changes in tissue shape, cell-cell adhesions must be remodeled, broken down, or reinforced depending on the cellular behaviors required. For a given morphogenetic movement, the regulation of cadherin-based adhesions may be implicated in establishing cell polarity, mechanically coupling neighboring cells, and/or directing cell migration.

A large body of recent work has shed light on the physical mechanisms underlying organ development. Improved imaging capabilities have enabled us to study morphogenesis in vivo or using organ explants, and where this is not possible researchers have turned to organoid or cell culture models. However, replicating tissue shapes observed in vivo using cell culture is challenging. Nonetheless, if we can build organs in the lab, we can better understand how their development is misregulated and potentially generate organs for transplant into human patients. Using a variety of new technologies, manipulation of cell-cell adhesion in precise spatial or temporal ways could help to generate complex architecture in engineered tissues. Here, we review recent work highlighting the role of cell-cell adhesion in generating tissue folds, tubes, and branched networks. We then explore possible ways in which experimental control of cell-cell adhesion might be used to direct tissue morphogenesis in culture models.

2. Morphogenesis of 3D tissue architecture in vivo

2.1. Folds

Many morphogenetic processes begin with a flat or curved sheet of cells that eventually gives rise to complex topologies such as folds. Folds can be generated by a monolayer of cells, by stratified cell sheets, or by multiple interacting tissues. Consequently, cell-cell adhesions must play different roles depending on the cellular behaviors required. A simple and well-studied example of tissue folding occurs during ventral furrow formation in the *Drosophila* embryo; in this case, folding is driven by pulsatile apical constriction of a row of cells within a monolayered epithelium (Fig. 1**A**). Myosin-driven reduction of apical surface area causes the tissue to bend out of plane and fold into the

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; BMP, bone morphogenetic protein; Btbd7, BTB/POZ domain containing 7; Cdc42, cell division control protein 42; ECM, extracellular matrix; MAPK, mitogen-activated protein kinase; PCP, planar cell polarity; pMLC, phospho-myosin light-chain; ROCK, Rho-associated protein kinase; Shh, sonic hedgehog; TEB, terminal end bud; VEGFR, vascular endothelial growth factor receptor

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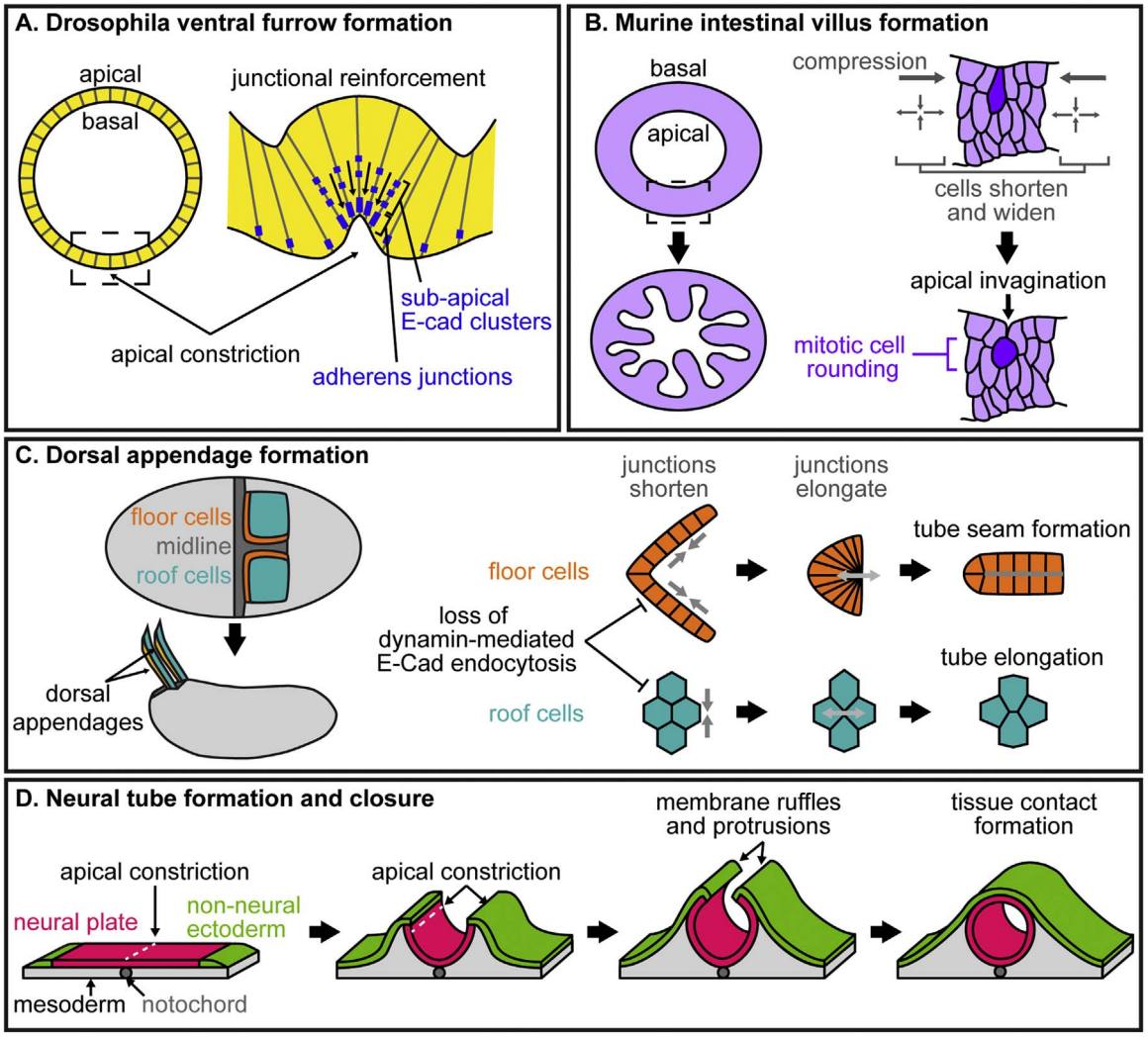

Fig. 1. Folds and tubes (A). Apical constriction leads to tissue folding during ventral furrow formation in the *Drosophila* embryo. Subapical clusters of cadherin move apically to reinforce adherens junctions between apically constricting cells. (B) The internal (apical) surface of the murine intestine starts off smooth and gives rise to folded morphology and eventually villi. In the early stages of this process, epithelial cells shorten and widen, generating compressive forces on cells between future villi. Cells in these regions undergoing mitosis become rounded and generate apical invaginations, leading to folds in the intestinal epithelium. (C) Dorsal appendage formation in the *Drosophila* egg involves junctional remodeling and cell intercalation of roof cells (to extend the tube) and floor cells (to seal the tube). Rearrangements in both cell populations require dynamin-mediated cadherin endocytosis. (D) Neural tube formation begins with apical constriction along the length of the neural plate. A second round of constriction along both sides brings the neural plate and the non-neural ectoderm into apposition. Non-neural ectodermal cells extended protrusions towards their counterparts, leading to closure of the tube.

center of the embryo [2–4]. Cell adhesion must be remodeled and reinforced to maintain tissue integrity in the presence of active, pulsatile contraction of actomyosin networks. Cycling of subapical clusters of E-cadherin is coupled to actomyosin pulses during gastrulation, allowing these clusters to join the apical junctions and reinforce intercellular adhesion [5].

More complex folds exist on the interior surface of tubular tissues, including the intestine and the oviduct. In the chicken, intestinal epithelial morphogenesis occurs concomitantly with differentiation of the surrounding mesenchyme into layers of smooth muscle. Each topological change in the lumenal epithelium coincides with the formation of a new smooth muscle layer surrounding the intestine [6]. When the first layer of smooth muscle forms circumferentially, the inner surface of the tube buckles and forms longitudinal ridges. Subsequently, the formation of a second layer of smooth muscle longitudinally causes the epithelium to buckle perpendicular to these ridges and generates a zigzag pattern. Finally, the third layer of smooth muscle is assembled longitudinally between the epithelium and the circumferential layer, causing the development of villi [6]. The resulting topology generates an uneven pattern of morphogens, including sonic hedgehog (Shh), across the intestinal epithelium. Consequently, signals from the epithelium to the surrounding mesenchyme are concentrated in the tip of the emerging villus. Signals from the mesenchyme that suppress intestinal stem cell fate are thus enhanced at the villus tip, restricting intestinal stem cells to the crypt regions between villi [7].

Intestinal villus morphogenesis in the mouse occurs by different mechanisms than in the chicken; villi emerge fairly rapidly and without the intermediate ridges and zigzag patterns [7]. In the mouse intestine, regularly sized and spaced clusters of mesenchymal cells appear beneath future villi [8]. Formation of these clusters is achieved not by mechanical influences of the surrounding smooth muscle, but by a self-organizing Turing-like field of Shh and bone morphogenetic protein (BMP) signaling [8,9]. The physical mechanisms underlying murine villus morphogenesis have recently been described by Freddo et al. After mesenchymal clusters have formed, epithelial cells directly above them shorten and widen, generating compressive forces felt by cells between clusters. Mitotic cells in these compressed regions undergo internalized cell rounding and generate apical invaginations that spread and deepen over the course of intestinal development (Fig. 1**B**) [10].

E-cadherin is required for villus formation during mouse embry-