Mini Review
Volume 13:11, 2022

Journal of Cytology & Histology

ISSN: 2157-7099 Open Access

Cellmatrix-Driven *vs.* Cell-Cell Adhesion-Driven Nascent Epithelial Morphogenesis

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Abstract

Many embryonic organs undergo epithelial morphogenesis, which results in the formation of tree-like hierarchical structures. However,it is unknown what drives the budding and branching of stratified epithelia,such as those found in the embryonic salivary gland and pancreas.We used single-cell resolution live-organ imaging of mouse embryonic salivary glands to show that budding morphogenesis is driven by the expansion and folding of a distinct epithelial surface cell sheet characterised by strong cell-matrix adhesions and weak cell-cell adhesions.Profiling of this epithelium's single-cell transcriptomes revealed transcriptional spatial patterns that underpin these cell adhesion differences.We then recreated budding morphogenesis in 3D spheroid cultures of engineered cells by suppressing E-cadherin expression and inducing basement membrane formation, which required b1-integrin-mediated cell-matrix adhesion for successful budding.

Keywords: Adhesion • Embryonic • Morphogenesis • Cell

Introduction

Epithelial organs frequently use branching morphogenesis to increase their functional surface area. All branching organs have a core epithelium surrounded by mesenchymal cells that is encased by a layer of basement membrane. The mesenchyme produces growth factors that are essential for epithelial growth and morphogenesis. However, when appropriate growth factors and extracellular matrix are provided, the epithelium of many organs can branch without the mesenchyme, indicating that the epithelium's core capacity for branching is intrinsic.

Branching epithelia can be stratified or single-layered with a lumen. Buckling of the epithelial sheet occurs during branching of a single-layered epithelium. External sculpting forces from airway smooth muscle cells, among other cell types, can guide the buckling of single-layered lung epithelium. However, because of the apparent lack of a sheet-like structure in stratified epithelia, the concept of buckling cannot be easily applied. The embryonic salivary gland and pancreas are classic examples of stratified epithelia that go through branching morphogenesis that includes budding and ductal morphogenesis [1].

Description

In this study, we used volumetric live-organ imaging to track individual cells throughout the mouse embryonic salivary gland during branching morphogenesis. We discovered that surfacelocalized epithelial cells and the BM form an integral layer that expands and folds inward to drive budding morphogenesis. We use mathematical modelling and experimental perturbations to support a model in which a combination of weak cell-cell adhesion and strong cell-matrix adhesion of peripheral epithelial cells drives surface epithelial sheet expansion and folding.

Single-cell RNA sequencing and single-molecule RNA fluorescence in situ hybridization show that these surface epithelial bud cells have distinct transcriptional features. Importantly, we show that by reducing E-cadherin expression and inducing BM formation in 3D spheroid cultures of engineered epithelial cells that do not normally form buds, we can successfully reconstitute budding morphogenesis. Our findings point to a fundamental self-organizing mechanism based on preferential cellmatrix adhesion over cell-cell adhesion, which could explain how stratified epithelia undergo budding morphogenesis [2].

The origin of new epithelial surface cells was then determined. The distinct difference in expression levels between peripheral and interior epithelial cells suggested that new surface cells are formed primarily through the proliferation of pre-existing surface cells. However, no surface cells divided locally to produce two daughter cells, so the surface layer remained intact. Instead, 92.4% of division-ready surface cells moved below the surface to divide into two daughter cells in the gland interior, while the remaining 7.6% divided into one surface daughter cell and one interior daughter cell. Importantly, all surface-derived interior daughter cells eventually returned to the surface by reinserting between surface cells, resulting in delayed surface expansion [3,4].

We fixed transgenic glands immediately after live imaging and immunostained for E-cadherin to identify surface-originating interior-located cells by cell tracking and compared their E-cadherin expression with surface cells to determine whether surface-derived cells maintained low Cadherin expression when temporarily interior located after cell division. The average intensity of the two adjacent cells had a clear negative correlation with E-cadherin intensity at cell-cell junctions. We then used cell tracking to identify interior-located daughter cells after surface cell division and measured E-cadherin intensities at cell-cell junctions between these cells and their neighbours. Importantly, the intensity of E cadherin at these junctions was indistinguishable from that of randomly sampled junctions between high-RFP cells and their neighbours.We also discovered significantly accelerated catch-up branching after collagenase washout, which we believe is due to the attachment of accumulated surface-originated low-E-cadherin cells to the restored BM.After 24-h collagenase treatment, when both collagen IV and laminin were greatly reduced at the BM, the accumulation of surface-originated cells in the bud interior can be directly visualised. We conclude that BM disruption can decouple surface expansion from the accumulation of a pool of low-E-cadherin cells within the body.Due to BM anchorage of these interior low-E-cadherin cells,BM restoration allows for rapid surface expansion

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Received: 02 November, 2022, Manuscript No.jch-22-84083; **Editor Assigned:** 04 November, 2022, PreQC No. P-84083; **Reviewed:** 18 November, 2022, QC No. Q-84083; **Revised:** 23 November, 2022, Manuscript No. R-84083; **Published:** 30 November, 2022, DOI: 10.37421/2157-7099.2022.13.663

and branching. We then inquired as to how BM disruption affects surface-originating cell divisions and cell dynamics. We discovered a small proportion of in-plane divisions as well as two new types of cell divisions in which one or two daughter cells were temporarily extruded outward from the mother cell [5].

Conclusion

Buckling of the surface epithelial sheet in a stratified epithelium, on the other hand, is restricted by both the surrounding mesenchyme and the interior epithelium. The bifurcation angle of stratified terminal end buds of mammary gland epithelium is constrained by localised matrix in the surrounding mesenchyme during branching. However, in the stratified salivary gland epithelium, the interior epithelium appears to be more dominant than the surrounding mesenchyme. Budding morphologies in our mesenchyme-free cultures of primary salivary gland epithelial cells resembled intact salivary gland cultures with mesenchyme. Indeed, as demonstrated by our model, preferential expansion of a surface layer attached to an inner cell core is sufficient to drive surface layer folding.

Finally, our findings support the notion that a specific combination of strong cell-matrix adhesion and weak cell-cell adhesion of peripheral epithelial cells is critical for the expansion and buckling of a cryptic surface epithelial sheet, which drives budding morphogenesis of a stratified epithelium. We anticipate that this unifying view of branching morphogenesis as epithelial sheet buckling will aid in the development of unifying physical models of branching morphogenesis that include single-layered and stratified epithelia. Understanding branching morphogenesis will pave the way for stem cell-engineered functional branched organs.

Acknowledgement

None.

Conflict of Interest

There are no conflicts of interest by author.

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How to cite this article: Nezis, Ioannis P. "Cellmatrix-Driven *vs.* Cell-Cell Adhesion-Driven Nascent Epithelial Morphogenesis." J Cytol Histol 13 (2022): 663.