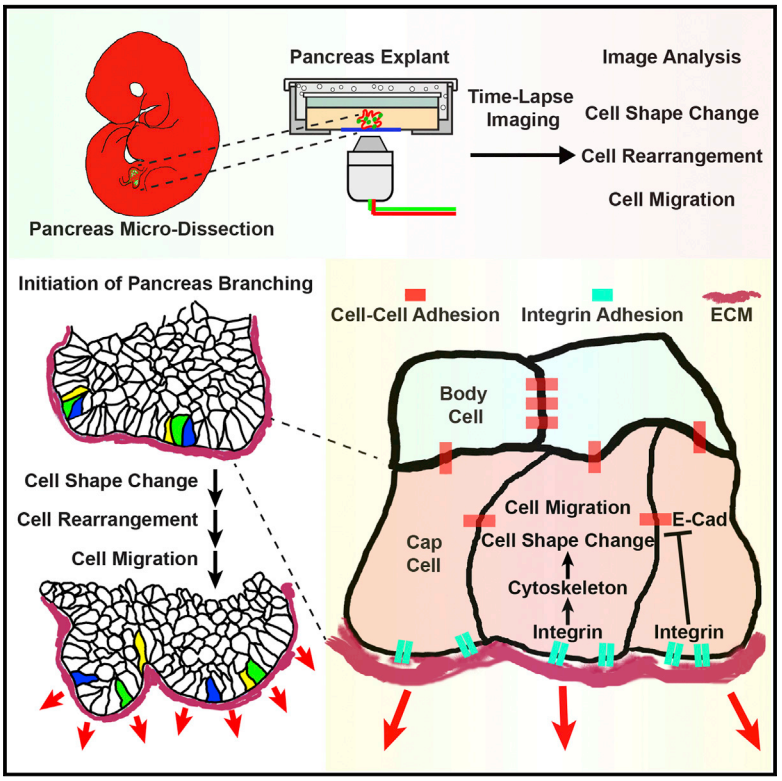
Report

Cell Reports

ECM Signaling Regulates Collective Cellular Dynamics to Control Pancreas Branching Morphogenesis

Graphical Abstract



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In Brief

Shih et al. uncover region-specific cellular behaviors in pancreatic epithelial cells during branching morphogenesis by using live imaging. Genetic and pharmacological inhibition analyses show that pancreas branching is initiated by local cues from the basement membrane through integrin-signaling-mediated control of actomyosin dynamics and cell-cell adhesion.

Highlights

- Live imaging of developing pancreata reveals region-specific cellular behaviors
- Region-specific cellular behaviors are elicited by ECM-integrin signaling
- ECM-integrin signaling controls actomyosin dynamics and pancreas branching
- ECM-integrin initiates pancreas branching in part by modulating cell adhesion

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ECM Signaling Regulates Collective Cellular Dynamics to Control Pancreas Branching Morphogenesis

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SUMMARY

During pancreas development, epithelial buds undergo branching morphogenesis to form an exocrine and endocrine gland. Proper morphogenesis is necessary for correct lineage allocation of pancreatic progenitors; however, the cellular events underlying pancreas morphogenesis are unknown. Here, we employed time-lapse microscopy and fluorescent labeling of cells to analyze cell behaviors associated with pancreas morphogenesis. We observed that outer bud cells adjacent to the basement membrane are pleomorphic and rearrange frequently; additionally, they largely remain in the outer cell compartment even after mitosis. These cell behaviors and pancreas branching depend on cell contacts with the basement membrane, which induce actomyosin cytoskeleton remodeling via integrin-mediated activation of FAK/Src signaling. We show that integrin signaling reduces E-cadherin-mediated cell-cell adhesion in outer cells and provide genetic evidence that this regulation is necessary for initiation of branching. Our study suggests that regulation of cell motility and adhesion by local niche cues initiates pancreas branching morphogenesis.

INTRODUCTION

Branch formation is a morphogenetic process to construct organs comprised of elaborate epithelial networks. Branching allows organs to maximize their surface area, which is critical for absorptive and secretory functions. Recent advances in live imaging and the advent of fluorescent reporter strategies have begun to reveal the cellular behaviors used to create the unique branching patterns of the salivary glands, mammary gland, and kidney (Chi et al., 2009; Ewald et al., 2008; Larsen et al., 2006). However, the mechanisms underlying pancreas branching morphogenesis are still unknown.

The pancreas develops as ventral and dorsal evaginations of the endodermal epithelium into the surrounding mesenchyme (Shih et al., 2013). The earliest sign of pancreas branching becomes apparent around embryonic day (E) 11.5, when the initially smooth epithelial surface begins to form stubby outgrowths that subsequently elongate into branches (Villasenor et al., 2010). Careful analysis of pancreatic sections throughout development shows that pancreas branching is associated with the formation of a multi-lumen tubular plexus, which then extends and remodels into a single-lumen ductal system (Kesavan et al., 2009; Petzold et al., 2013; Villasenor et al., 2010). Failure to organize pancreatic epithelial progenitors into tubes causes a defect in their lineage allocation, suggesting a link between morphogenesis and cell specification (Kesavan et al., 2009).

Time-lapse imaging studies have provided insight into global patterns of pancreas branching (Puri and Hebrok, 2007). However, previous imaging studies in the pancreas were not designed to follow the behavior of individual cells. Hence, the cellular mechanisms by which the pancreatic epithelium transforms into a highly branched organ remain unclear.

The cellular behaviors that drive tissue morphogenesis require the actomyosin network to change cell shape and cell contacts (Guillot and Lecuit, 2013; Munjal and Lecuit, 2014). The forces generated by such networks govern cellular behaviors through coupling to the plasma membrane by E-cadherin complexes or the basement membrane by integrins (Legate et al., 2009). Cross-regulation between E-cadherin-mediated cell-cell adhesions and integrin-mediated cell-extracellular matrix (ECM) contacts has been demonstrated at a cellular level, in particular in the context of tumor cells (Canel et al., 2013). Yet, the role of cell-cell and cell-ECM contacts in pancreatic organ morphogenesis is unknown.

Here, we used genetic strategies to mosaically label pancreatic epithelial cells with fluorescent proteins, allowing us to follow the behaviors of individual cells by time-lapse microscopy in pancreas explants.