



BIO380HF

Mammary Gland Morphogenesis & Branching: On-Line Self-Study

Goals of this exercise

- To review the cellular and ECM interactions that mediate secretory gland development
- To learn more about morphogenesis
- To learn about mammary gland development as an example of tissue morphogenesis
- To understand some of the molecules involved in regulating the branching process

Morphogenesis

The organs of the body are typically complex multilayered structures. The events of morphogenesis (literally, generation of form) convert simpler sheets and collections of cells into complex three-dimensional tissues and organs. The morphogenetic movements during embryogenesis bring different cell groups together so that they can interact in new ways to build complex structures such as the eyes and limbs. The final form of a developing embryo requires the coordination of the driving forces of morphogenesis coupled with cell growth and differentiation, cell proliferation and death.

Clearly some of the fundamental events of morphogenesis are common to many different events. This includes the segmentation of cell groups, the folding of epithelial sheets and the outgrowth of buds. Each of these events involves changes in cell adhesion and motility, alterations in cellular interactions with and adhesions to the extracellular matrix and internal changes in the cytoskeletons of the participating cells. The more complex issue to be understood is how these events are coordinated in each tissue- and organ-specific process.

Epithelial Trees and Branching Morphogenesis

Many human physiological events require the exchange of large amounts of materials between the outside and inside of the body:

Breasts: release of large quantities of milk for infant nutrition

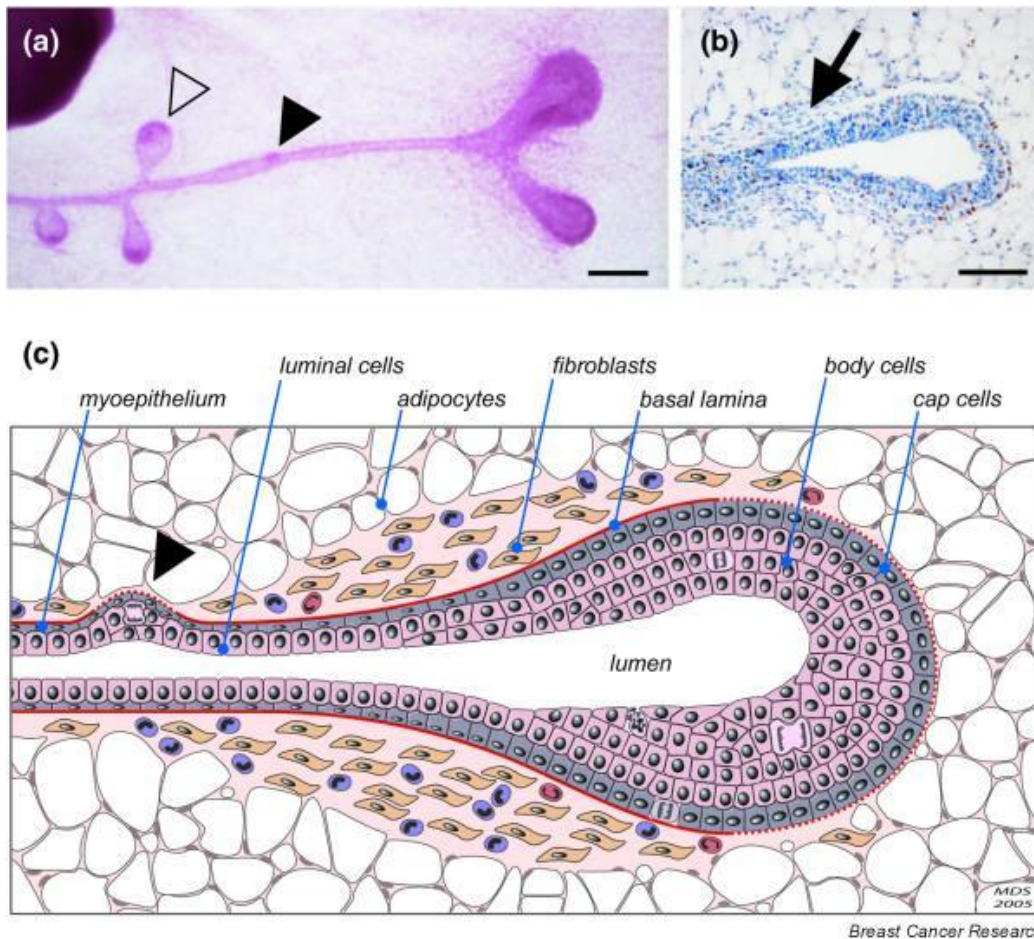
Lungs: exchange of oxygen and carbon dioxide

Kidneys: release of fluid containing potentially toxic materials

Each requires a large amount of surface area for exchange of materials (i.e., milk alveoli, air alveoli, salivary alveoli, urinary nephrons) to be concentrated in a relatively small region (i.e., mammary glands, lungs, salivary glands, kidneys) with access to the outside environment via a large number of tree like system of branched epithelial tubes (i.e., milk ducts, trachea, salivary ducts, urinary collecting ducts). This is achieved by epithelial branching during embryogenesis. We will use the salivary gland to demonstrate this process.

Morphogenesis: Mammary Gland Branching

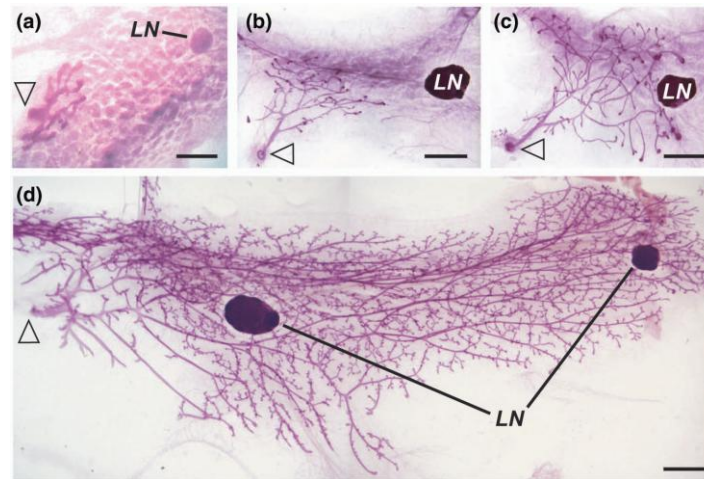
Milk Duct Structure and Branching



“Terminal end bud (TEB) and duct morphology. (a) High-magnification carmine alum-stained wholemount of a primary duct that has recently passed the central lymph node (upper left corner). The bifurcating TEB is in the final stages of forming two new primary ducts with independent TEBs. Three newly formed lateral (secondary) side-branches are also present along the trailing duct (open arrowhead), as is an area of increased cellularity that may represent a nascent lateral bud (filled arrowhead). Increased stromal cellularity is also apparent about the bifurcating TEB. Scale bar, 200 μm . (b) Immunophotomicrograph of a TEB illustrating its considerable proliferative activity, as indicated by the large number of cells that have undergone DNA replication and have thus incorporated bromodeoxyuridine (brown diaminobenzidine-stained nuclei) during a 2-hour chase period. Rather than pulling themselves forward, TEBs seem to be pushed through the adipose-rich stroma by virtue of this high proliferative activity [6]. Hematoxylin counterstaining also reveals the stromal collar, rich in fibroblasts and collagen, that characteristically surrounds the TEB neck (arrow) and its conspicuous absence beyond the invading distal cap. Scale bar, 100 μm . (c) Schematic diagram depicting the salient architectural features of TEBs and their subtending ducts, including their fibroblast-rich stromal collar and high mitotic index. Though there is no evidence that normal ductal cells ever cross the basal lamina, thinning of the basement membrane (dotted lines) does seem to occur at the tips of invading ducts as a result of their partial enzymatic degradation and/or incomplete *de novo* synthesis. Stromal macrophages and eosinophils are also depicted.” Fig. 2 from Sternlicht, 2006

Morphogenesis: Mammary Gland Branching

Milk Duct Branching in Mouse



“Nuclear-stained wholemounts illustrating ductal branching morphogenesis of the abdominal (no. 4) mammary gland. (a) Embryonic day 18.5; (b) age 3 weeks; (c) age 4.5 weeks; (d) age 11 weeks. Ductal penetration into the mammary fat pad can be judged with respect to the nipple and/or main lactiferous duct (arrowhead), central lymph node (LN), distal LN (as seen in (d)) and fat pad margins. Terminal end buds are readily apparent in the growing 4.5-week gland, and short tertiary branches are apparent in the mature 11-week gland. Scale bars, 0.5 mm (a) and 1 mm (b–d).” Fig. 1 from Sternlicht, 2006

The Regulation of Branching

Branching, which began during embryogenesis, stops at birth and then is re-initiated by estrogen at the onset of puberty. As seen earlier in the course, it involves localized tissue interactions which lead to the controlled localized regulation of cell division and changes in shape. The extracellular matrix also needs to be modified to allow the branching to occur.

Various molecules come into play to regulate the branching process:

- EGF (epidermal growth factor) and HGF (heptocyte growth factor) stimulate branching
- TGF β is an inhibitor of epithelial branching in kidneys, lungs and mammary glands
- ADAM, a disintegrin and metalloproteinase, and MMPs, matrix metalloproteinases, are important for remodeling the ECM to allow the branching to occur.

References

- Hogan (1999) Morphogenesis. Cell 96: 225–233.
Lee and Davies, 2007. Epithelial branching: the power of self-loathing. BioEssays 29: 205-207.
Sternlicht, 2006. The cues that regulate ductal branching morphogenesis. Breast Cancer Research 8: 201-212.



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