SnapShot: Branching Morphogenesis

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Mammary gland

Branching by invasion

- Male and female newborn
  - Anlage
  - Fibroblastic stroma and fat
- Puberty
  - Invasion of epithelia into stromal fat pad
  - Ductal tree formation by iterative branching
- Adult
  - Budding and proliferation of alveoli (Progesterone, GATA3, STAT6, NODST1, Caveolin-1)
  - Alveolar maturation and milk production (Prolactin, Oxytocin, SnoN, STAT5, Caveolin-1 SOCS1)
  - Cell death, ECM remodeling, restored branching (serotonin, lactoferrin, STAT3, SMAD3)
- Lactation
  - Proliferation
- Pregnancy
  - Tertiary branching
  - Progesterone, GATA3, STAT6, NDST1, Caveolin-1
  - Alveolar maturation and milk production (Prolactin, Oxytocin, SnoN, STAT5, Caveolin-1 SOCS1)
  - Cell death, ECM remodeling, restored branching (serotonin, lactoferrin, STAT3, SMAD3)
- Involution
  - Ductal tree formation by iterative branching

End bud

- Terminal end buds (TEBs)
  - MMP14
  - TIMP1
  - Nuclear actin
  - FGFR2
  - MMP2
  - HSP90

Regulating factors

- Estrogen
- ER-
- ER-α
- MMP3
- HS2ST
- HGF
- FR
- VDR
- MMP2
- TIMP1
- TGF-β
- MMP11

Lymph node

- Bud outgrowth
  - PTHrP
  - BMP4
  - BMPR1A
  - FGFR1

Regulating factors

- Mammary bud

Tertiary branching

- Regulating factors

- Pregestosterone
- PR-B
- Wnt4
- MMP3
- HS2ST
- HGF
- MMP2
- TIMP1
- TGF-β

End bud

- Duct

Regulating factors

- Laminin-1/βM
- MMP1
- MMP7
- nuclear actin
- Leukocytes
- TGF-β
- Mechanical stress

Feather

Branching by cell death

- Barb and rachis formation by a periodic invagination
  - BMP, Noggin, Sprouty, FGF
- Basal branch patterns form by differential cell death
  - NCAM, Shh, caspase
- Radial, bilateral symmetric, and asymmetric branching patterns form by modulating basal branching circuit
  - Wnt3a gradient, Sprouty
- Feather follicle opens by apoptosis to form a vane
  - Shh, Caspase

Regulating factors

- β-catenin
- Wnt
- FGF
- BMP
- Shh
- TGF-β
- MMP2

Mammillary formation

- Follicle formation
- Dermal papilla

Bilateral symmetry

- Anterior
  - Wnt3α
- Shh
- BMP
- Posterior
  - Wnt3α
- β-catenin

Regulating factors

- BMP10
- Sprouty
- Noggin

Marginal plate

- Shh
- Apoptosis
- MMP2

Barb plate

- Ptc1
- Proliferation
- TIMP2
- Keratinization

Regulating factors

- Proliferation
- BMP2
- Sprouty
- FGF
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Ectodermal appendages such as feathers, hair, mammary glands, salivary glands, and sweat glands form branches allowing a much-increased surface for functional differentiation and secretion. There are similarities among these branching organs, not only in their embryonic origin and their architecture, but also in repetitive deployment of some central signaling molecules such as BMPs, TGF-β, FGF, and MMPs, which are used in all branching organs. Details of the molecular and architectural pathways of branching, however, are context dependent. The difference in branching morphogenesis in vivo is based on chemical, mechanical, and geometric cues in the mesenchymal stroma that "sculpt" epithelial progenitors (see, for example, Nelson et al., 2006). Here, we choose the mammary gland and feathers to demonstrate these principles (Widelitz et al., 2007).

Once a branched appendage develops, its structure needs to be retained through the life of the individual. In ectodermal branching organs, much of the lurch morphogenesis happens after birth. By undergoing cyclic involution and growth, mammary glands and feathers renew their branching phenotypes coupled to body hormone status and seasonal changes for the best possible functional performance (Chuong et al., 2012). Some of the molecules mediating organ specificity remain similar to those involved in organ development, yet they differ in that the former now must prevent the organs from losing their structural and functional identities, ensuring that the mammary gland and the feather, while both branching, remain distinct from each other (Bhat and Bissell, 2014).

Mammary Gland: Branching by Invasion

Male and female mammals are born with a rudimentary mammary gland referred to as an “anlage.” During puberty, under the action of ovarian hormones, the embryonic anlage undergoes extensive branching by invading into the mammary fat pad in the female and ceases after expanding to the outer limits of the mesenchymal fat pad. The tree-like epithelial network is made of a bilayer of luminal duct or luminal milk-secreting cells, surrounded by myoepithelial cells and basement membrane. Myoepithelial cells provide structural and functional support for their luminal counterparts and, along with the stroma, are responsible for synthesis and organization of the basement membrane. During pregnancy, the alveolar compartment proliferates and expands to prepare for lactation, during which alveolar luminal cells synthesize milk proteins. Milk is ejected by systematic contraction of myoepithelial cells in response to suckling-mediated release of oxytocin. After weaning, the mammary gland involutes.

During branching, epithelial cells have to mobilize the necessary machinery for invasion of the growing ducts into the fat pad and the formation of secondary and tertiary branches to complete the eventual adult mammary architecture. This relies on the activities of a number of matrix metalloproteases (MMPs) (Fata et al., 2004). Although MMPs’ proteolytic activity is central to all branching structures, recent findings show that the signaling function of a number of them is through domains other than their catalytic domains (e.g., Correia et al., 2013; Mori et al., 2013).

Whereas the epithelial compartment of human breast is separated from fat tissue by interstitial stroma, mammary epithelial structures in mouse are embedded directly in fat tissue, which distinguishes formation of mammary cancers in mice and humans.

Feathers: Branching by Differential Cell Death

The basal layer of the cylindrical epithelia of feather filament forms periodic invaginations and segregates into alternating zones of cells destined for proliferation and death. Each valley becomes a marginal plate that will undergo programmed cell death, creating space between barbs. Each becomes a barb ridge with bilaterally positioned barbule plates and centrally positioned axial plates. Axial plate cells will eventually disappear to give space to opening barbules. Each ridge undergoes extensive branching by invading into the mammary fat pad and forming secondary and tertiary branches.

Cellular and Molecular Events in Mammary Gland and Feathers

The epithelial-stromal network in both feathers and the mammary gland is under the influence of signal transduction pathways that modulate cell proliferation, apoptosis, and differentiation. In the mammary gland, the role of hormone receptor signaling is evident. However, the role of other molecules and pathways varies between structures. The epithelial-stromal interface is an active participant in determining organ function, and in many cases, environmental signals can elicit changes in cell behavior that can influence the development of diseases. In the mammary gland, this interface is critical for the development of mammary cancer in mice and humans.

REFERENCES