SnapShot: Branching Morphogenesis

Cheng-Ming Chuong,1,3 Ramray Bhat,2 Randall B. Widelitz,1 and Mina J. Bissell2

1Department of Pathology, University of Southern California, Los Angeles, CA 90033, USA, 2Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA, 3Center of Wound Repair and Regeneration, Cheng Kung University, Tainan, Taiwan

Mammary gland
Branding by invasion

Male and female newborn

Puberty

Secondary branching

Estrogen ↑
ER-α ↑
MMP3 ↑
H2BST ↑
HGF↓
VDR ↓
MMP2↓
TIMP1↑
TGF-β↓

终端端芽（TEBs）

Regulating factors

MMP14↑
TIMP1↑
Nuclear actin↑
FGF2↑
MMP2↑
TIMP1↑
TGF-β↓

Adapted from Hennighausen and Robinson, 2005

Fat

Feather

Branching by cell death

Barb and rachis formation by periodic invagination

Barb ridge patterns form by differential cell death

Radial, bilateral symmetry, and asymmetric branching patterns form by modulating basal branching circuit

Feather follicle opens by apoptosis to form a vane

Wnt3a gradient, Sprouty

Shh, Caspase

Follicle formation
Regulating factors

β-catenin↓
Wnt↑
FGF↑
Shh↓
MMP3↑
TIMP2↑

Regulating factors

Barb forming zone

Branches form through apoptosis

Rachis zone

Patterned branches

Barb and rachis formation by a periodic invagination

Barb ridge

Marginal plate

Patterning branches

Barb ridge

Marginal plate

Patterned branches

Rachis

Patterning branches

Anlage

Fibroblastic stroma and fat

Terminal duct lobular units

Fat

Fat pad

Adapted from Hennighausen and Robinson, 2005

Barb forming zone

Barb forming zone

Barb

Marginal plate

Patterned branches

Rachis

FEEDBACK
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2Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA
3Center of Wound Repair and Regeneration, Cheng Kung University, Tainan, Taiwan

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 lush 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 metalloproteinases (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. The initial periodic patterning is triggered by apoptosis including pulp epithelia lying internal to the filament cylinder, feather sheath enclosing the filament cylinder, and barb generative zone located in the posterior follicle. Thus, feather branches open up after the branching pattern is sculpted by programmed cell deaths (Chang et al., 2004).

Feathers in different body regions serve different functions and have different branching patterns. The radially symmetric downy feathers mainly in the ventral trunk maintain the endothrophy of the animal, whereas the bilaterally symmetric vaned feathers seen in the dorsal trunk and tail are used for communication. The bilateral-asymmetric feathers in the wing allow aerodynamic flight. The developing feathers begin as a cylinder, and their complex shape forms from the distal to proximal end. Feather stem cells form a ring located above the dermal papilla, a mesenchymal signaling center at the follicle base. Epithelial progenitors are displaced upward and, after a distance (marked as m, m1, m2), will undergo branching morphogenesis. The morphology (shaft or different branching patterns) reflects the cues received from the follicular microenvironment when progenitor cells are generated. A Wnt3a gradient is responsible for the tilting of the stem cell ring and parallel barb ridges toward the anterior side, thus converting radi ally symmetric feathers to bilaterally symmetric ones (Yue et al., 2006).

ABBREVIATIONS

Ant, anterior; BGZ, barb generative zone; BM, basement membrane; BMP, bone morphogenetic protein; BMPR1A, BMP receptor 1A; ECM, extracellular matrix; ER-α, estrogen receptor α; FGF, fibroblast growth factor; FGFR2, FGF receptor 2; GATA-3, GATA-binding protein 3; HGFR, hepatocyte growth factor receptor; HS2ST, heparan sulfate 2-O-sulfotransferase; HSP90, heat-shock protein 90; MMP, matrix metalloproteinase; NCAM, neural cell adhesion molecule; NDST1, N-deacetylation/N-sulfotransferase 1; Post, posterior; PR-B, progesterone receptor-B; Ptc1, patched homolog 1; PTHrP, parathyroid hormone-related protein; Shh, Sonic hedgehog; SnoN, Ski-related novel protein N; SOCS1, suppressor of cytokine signaling 1; STAT, signal transducer and activator of transcription; TGF-β, transforming growth factor-β; TIMP1, tissue inhibitor of metalloproteinases 1; VDR, vitamin D receptor; WNT, wingless.

REFERENCES