



## Late Inductions: Hair, Teeth and Glands

### Late Inductions

- Late inductions involve Epithelial-Mesenchymal Interactions: interactions between the epithelium and the mesenchyme
- These interactions occur even in adulthood (e.g., skin transplanted to different regions takes on the nature of region it is transplanted to)
- Epithelium: Outer layer of cells; derived from any of the 3 primary germ layers (ectoderm, endoderm, mesoderm)
- Mesenchyme: Loose tissue comprised of irregular, stellate shaped cells, lies under epithelium
- Mesodermal Papillum: Tight aggregate of mesodermal cells; determines formation of teeth, nails, hair, etc.

### Inductive Interactions & Resulting Structures

Let's look at the late inductive interactions that mediate the development of the mammary glands and other structures.

<b>Epithelium</b>	<b>Mesoderm</b>	<b>Structure</b>
<b>Ectoderm</b>	<b>Dermis</b>	<b>Hair, Sweat Glands, Mammary Glands, Teeth</b>
<b>Ectoderm</b>	<b>Mesenchym e</b>	<b>Limbs</b>
<b>Endoderm</b>	<b>Mesenchym e</b>	<b>Gut Organs (Liver, Pancreas, etc.) Pharyngeal Organs (Lungs, Thyroid, etc.)</b>
<b>Mesoderm</b>	<b>Mesenchym e</b>	<b>Kidneys</b>

### Communication Mediated by the Extracellular Matrix

The extracellular matrix is a complex of proteins, glycoproteins and proteoglycans—in short a mixture of protein and sugar complexes that exists between all human cells. Cells in tissues are surrounded by different amounts and types of ECM from the fuzzy coating of the intestinal tract to basal lamina and basement membranes to skin and bone. Most of us are aware of collagen, a major ECM component.

When it was first studied, the extracellular matrix (ECM) was considered to be simply a supporting matrix for cells and tissues. It is clear now that the ECM affects the way cells behave and how they communicate with each other. The ECM also plays central roles in cell adhesion, shape, migration and proliferation.

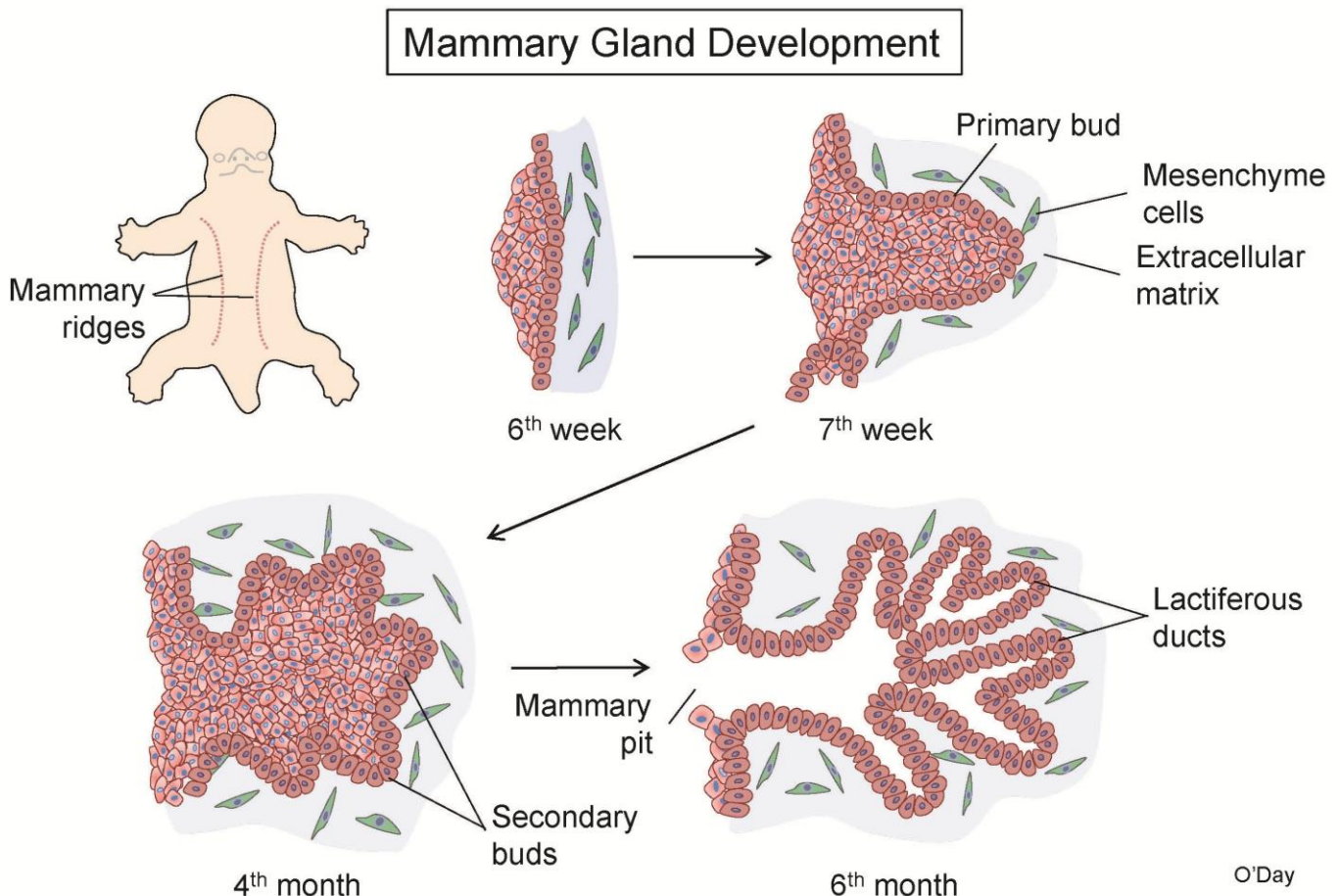
### Secretory Gland Morphogenesis

- Secretory Glands are glands made up of cells that secrete materials needed for various functions
- Some examples are: Sweat Glands, Mammary Glands, Salivary Glands, thyroid gland, etc.
- Epithelial-mesenchymal interactions mediate secretory gland morphogenesis
- In addition to the cells themselves, the mesenchyme requires ECM to function; the ECM is involved in mediating the communication between the mesenchyme and the epithelium

### Mammary Gland Development

Before we launch into a discussion of the communication events that mediate late inductions, let's look at the development of one type of gland: the mammary glands.

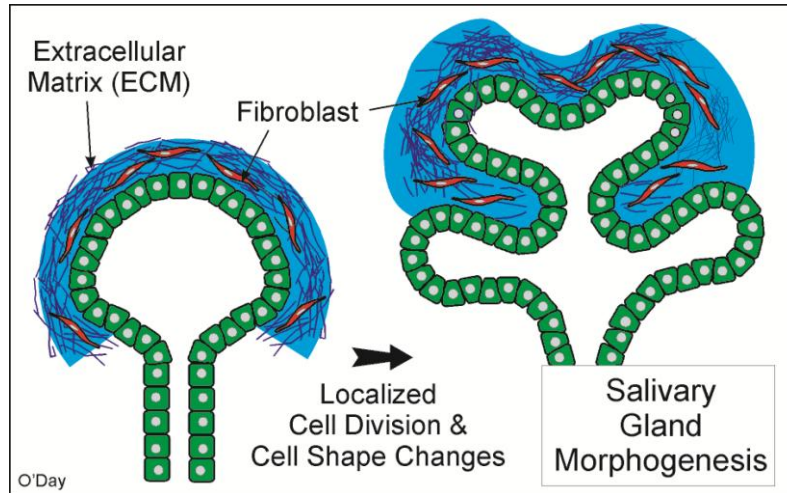
While humans typically develop only a pair of mammary glands, mammary ridges have many sites which form multiple glands in other mammals. An early thickening of the epithelial ectoderm is the first evidence a gland is developing. As detailed below, this and subsequent development is controlled by the underlying ECM and mesenchyme cells. Thickening results in the formation of the primary bud which then forms secondary branches. The lactiferous ducts form as cavities develop and extend out to the mammary pit.



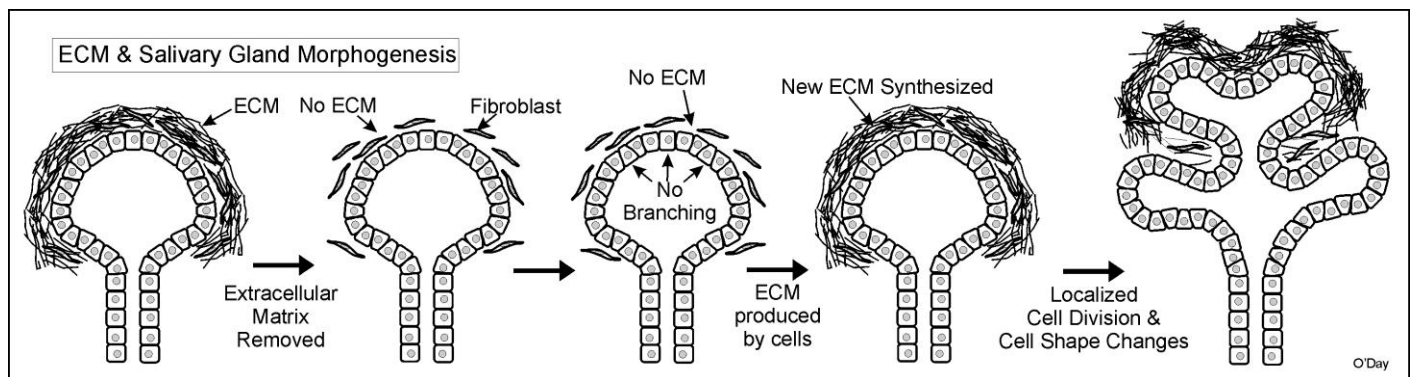
While an extensive array of lactiferous ducts exist by 8 months in the fetus, milk production will not begin until hormonal stimulation occurs typically during pregnancy.

Now, let's look at the tissue interactions that occur using salivary glands as an example.

### Following experiments demonstrate role of ECM in tissue morphogenesis



### In Vitro Experiments in Mouse



- Control: Branching Occurs
- Remove ECM--Can do this in different ways to show the resulting effect is due to the loss of the ECM not the treatment method: treat explant with proteases, carbohydrate digesting enzymes to digest away the ECM or inhibit ECM synthesis
- After treatment the Fibroblasts remain but they have no ECM surrounding them: In the absence of ECM: No Branching Occurs
- When the treatment is stopped the cells will make new ECM over time; Once the ECM has reappeared: Branching Occurs (This verifies that the cells were viable and only the presence or absence of ECM affected the branching)

Collagens, fibronectin and laminin are all critical proteins in the ECM-mediated events during salivary gland morphogenesis. Similarly the ECM is modified by MMPs during salivary gland development.

### MMPs & ECM

- Matrix metalloproteinases (MMPs): a family of enzymes that can digest all of the proteins of ECM
- Individual MMPs show specificity for the type of ECM protein that they can digest (e.g., neutrophil collagenase digests intercellular collagen)

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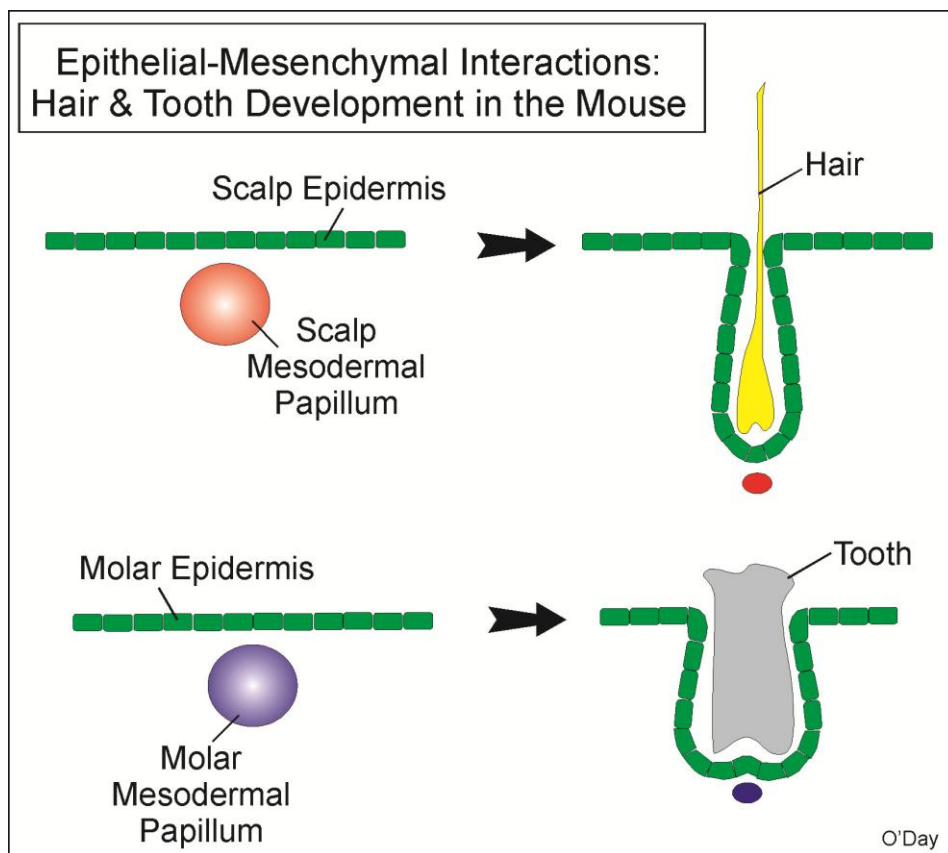
- Certain MMPs function during morphogenesis (e.g., mammary gland development) and they may be involved in ECM remodeling
- Researchers are looking at the role of MMPs & ECM in breast cancer and metastasis of cancer cells
- Growth factors often lead to activation of MMP genes
- Uncontrolled matrix MMP activity may lead to tissue damage in many diseases

### Epithelial-Mesenchymal Interactions

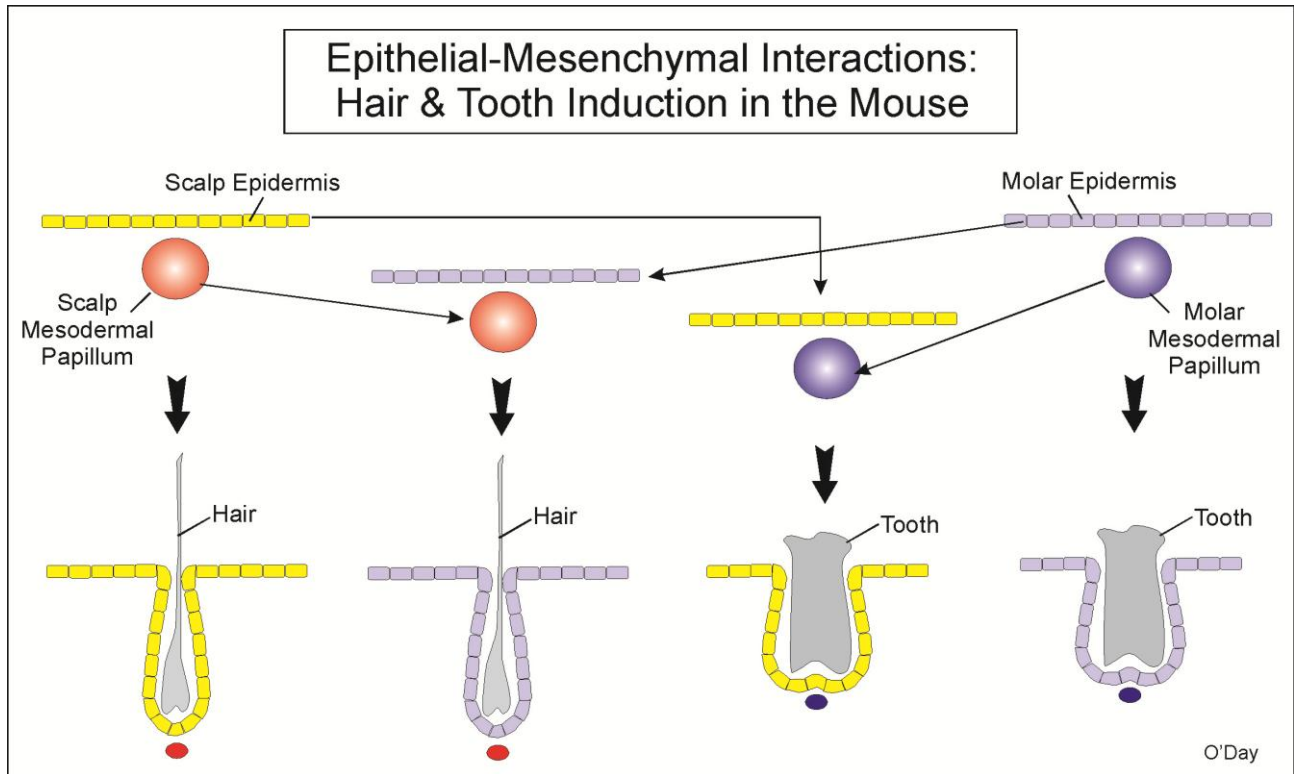
- Mesoderm induces the epithelium to form structure
- Type of structure is determined by regional differences in mesoderm not the epithelium

### Epithelial-Mesenchymal Interactions: Hair & Tooth Induction in the Mouse

- Small mesodermal papilla lie in the dermis
- The mesodermal papilla induce the morphogenesis of specific structures (E.g., teeth, feathers)



Transplantation experiments reveal that the papilla can induce foreign epithelium to form papilla specific structures:



### Final Comments

- Late inductions are typified by epithelial-mesenchymal interactions
- They occur later during embryogenesis and throughout life
- The mesoderm is the controlling (inducing) tissue in epithelial-mesenchymal interactions
- Some of the morphogenetic and differentiation factors have been discovered and their roles in development are being elucidated

### References

Patel, et al, 2006. Salivary gland branching morphogenesis. *Differentiation* 74: 349-364.

Sternlicht et al, 2006. Hormonal and local control of mammary branching morphogenesis. *Differentiation* 74: 365-381.

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