Skin embryology and development

Structure and Function of the Skin
AAD Meeting 2019

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Outline

- Why study embryology and development of the skin?
- Skin: Key structures
- Key stages of human embryology
- Molecular principles of development
- Development of the epidermis
- Development of the dermis
- Development of skin appendages
- Clinical scenarios and correlations
Why study embryology and development of the skin?

Better understanding of skin diseases

NF-κB pathway

Incontinentia Pigmenti
Why study embryology and development of the skin?

Tissue engineering of functional skin

Why study embryology and development of the skin?

Stem cell biology and personalized medicine
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Structure of the skin
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Key stages of human embryology

9 months
Key stages of human embryology
Key stages of human embryology

Carlson, Human Embryology (2012)
Key stages of human embryology

Carlson, Human Embryology (2012)
Formation of neural tissue
**Major tissue embryological derivatives**

<table>
<thead>
<tr>
<th>Ectoderm</th>
<th>Mesoderm</th>
<th>Endoderm</th>
</tr>
</thead>
<tbody>
<tr>
<td>All nervous tissue</td>
<td>Skeletal, smooth, and cardiac muscle</td>
<td>Epithelium of digestive tract (except that of oral and anal cavities)</td>
</tr>
<tr>
<td>Epidermis of skin and epidermal derivatives (hairs, hair follicles, sebaceous and sweat glands, nails)</td>
<td>Cartilage, bone, and other connective tissues</td>
<td>Glandular derivatives of digestive tract (liver, pancreas)</td>
</tr>
<tr>
<td>Cornea and lens of eye</td>
<td>Blood, bone marrow, and lymphoid tissues</td>
<td>Epithelium of respiratory tract, auditory tube, and tonsils</td>
</tr>
<tr>
<td>Epithelium of oral and nasal cavities, of paranasal sinuses, and of anal canal</td>
<td>Endothelium of blood vessels and lymphatics</td>
<td>Thyroid, parathyroid, and thymus glands</td>
</tr>
<tr>
<td>Tooth enamel</td>
<td>Serosae of ventral body cavity</td>
<td>Epithelium of reproductive ducts and glands</td>
</tr>
<tr>
<td>Epithelium of pineal and pituitary glands and adrenal medulla</td>
<td>Fibrous and vascular tunics of eyes</td>
<td>Epithelium of urethra and bladder</td>
</tr>
<tr>
<td>Melanocytes</td>
<td>Synovial membranes of joint cavities</td>
<td></td>
</tr>
<tr>
<td>Some cranial bones and branchial cartilages (derived from neural crest)</td>
<td>Organs of urogenital system (ureters, kidneys, gonads, and reproductive ducts)</td>
<td></td>
</tr>
</tbody>
</table>
Embryonic origin of key skin derivatives

<table>
<thead>
<tr>
<th>Skin component</th>
<th>Derivation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidermis:</strong></td>
<td></td>
</tr>
<tr>
<td>Keratinocytes</td>
<td>Ectoderm</td>
</tr>
<tr>
<td>Melanocytes</td>
<td>Ectoderm (neural crest)</td>
</tr>
<tr>
<td><strong>Dermis:</strong></td>
<td></td>
</tr>
<tr>
<td>Fibroblasts (trunk/limbs)</td>
<td>Mesoderm</td>
</tr>
<tr>
<td>Fibroblasts (scalp/face)</td>
<td>Ectoderm (neural crest)</td>
</tr>
</tbody>
</table>
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Principle: TFs and signaling molecules direct cell fates

**Transcription Factor:**
Protein that binds specific DNA sequence to activate transcription of a region of DNA to RNA

**Signaling molecule:**
Protein that transmits information to a cell either by binding to a receptor on the surface or the inside of a cell

**Signal transduction**
A cascade of chemical signals that leads to a specific molecule or target reaction

Principle: Signal transduction pathways

Signal transduction pathways are often denoted by key ligands and transduction molecules in the canonical pathway

Principle: Organs and tissues form by restriction and differentiation

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Specification of the epidermis

Wnt/β-catenin

Fibroblast growth factors (FGFs)

Bone morphogenic proteins (BMPs)

Fuchs, Nature (2007)
Development of the epidermis

• By the end of the first month of development, single layer (simple) epithelium proliferates to form a outer covering. This is the periderm.
Development of the epidermis

- In 2nd-3rd month of development, proliferation of an new underlying basal layer begins to “push” these pericytes upwards.
Development of the epidermis

- In 4th-5th month of development, basal layer cells proliferate to form intermediate layers and sloughs off the periderm into the amniotic fluid.
The fully stratified epidermis
Epidermal stratification

**Key pathways required for stratification**

- Notch
- Nuclear factor-kB (NF-kB)
- Mitogen-activated protein kinase (MAPK)

**Key transcription factors/regulators**

- p63
- KLF4
- miR-203
- C/EBP
- GRHL3
p63 is an essential TF for epidermal development
Notch and miR-203 demarcate epidermal differentiation compartments

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Two lineages of dermal fibroblasts

Papillary Dermis
• Structural interaction with epidermis via dermal papillae (rete ridges)
• Looser and finer connective tissue

Reticular Dermis
• Extends from superficial plexus to hypodermis
• Denser connective tissue

Two lineages of dermal fibroblasts

- Multipotent Fibroblasts
  - Wnt/β-catenin
  - TGF-β

- Transforming growth factor

  - Papillary fibroblasts
    - Hair follicle formation
    - Piloerection

  - Reticular fibroblasts
    - Adipocyte formation
    - Wound healing

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Patterns of appendage development

Sequential and reciprocal crosstalk between overlying epithelium and underlying mesenchyme

Placodes in different appendages

Tissue interactions form the skin
Reciprocal signaling forms hair follicles

Wnt/β-catenin

↓

Edar (NF-kB)

Sonic hedgehog  Fgfs

↓

Cyclin D
Other epidermal appendages: Sweat glands

EDA/EDAR/NF-kB
Wnt-βcatenin
Sonic hedgehog
BMP

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Clinical correlations

- In 4<sup>th</sup>-5<sup>th</sup> month of development, epidermal basal layer cells proliferate to form intermediate layers and sloughs off the periderm into the amniotic fluid. What happens if the periderm does not slough off <i>in utero</i>?
Clinical correlations

- In **epidermal and sebaceous nevi**, there is epidermal acanthosis. What signaling pathway is commonly mutated to cause these lesions?
Epidermal stratification

Pathways required for stratification
- Notch
- Nuclear factor-kB (NF-kB)
- Mitogen-activated protein kinase (MAPK)

Key transcriptional regulators
- p63
- KLF4
- GRHL3
- miR-203
- C/EBP
Clinical correlations

- Mutations in the EDAR gene cause loss-of-function of this protein and its related pathway. What is the associated disease and what skin components are affected?
Similarities between appendage development
Summary: Take Home Messages

• Studying skin embryology and development helps us understand skin diseases and provides a basis for tissue engineering and regeneration.

• Transcription factors, signaling molecules, and receptors help determine cell/tissue restriction and differentiation.

• Reciprocal epithelial-mesenchymal signaling forms the basis for appendage development.

• There is still much about development of the skin that is unknown.
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