Cutaneous Structure and Function

Skin Biology Lecture Series
The skin includes three primary compartments:

**Epidermis**
- Stratum corneum
- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum basalis
- Proteins and glycolipids
- Dermo-epidermal junction

**Dermis**
- Fibroblasts
- Extracellular matrix
- Blood and lymphatic vessels
- Nerves
- Pilosebaceous units
- Eccrine and Apocrine glands

**Subcutaneous fat**
- Adipocytes
• The epidermis is a **stratified, cornified epithelium**.
• At the deepest layer are **basal cells** (BL) that rest on the basement membrane of the dermal-epidermal junction (DEJ).
• Basal cells differentiate into cells of the **spinous layer** (SL) with abundant desmosomal spines.
• Spinous cells become **granular layer cells** (GL), that make many of the components of the cornified envelope.
• Finally, terminally differentiated keratinocytes shed their nuclei and become the **stratum corneum** (SC), a cross-linked network of **proteins** and **glycolipids**.
There are anatomic variations in epidermal thickness.

- Acral skin
- Eyelid

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Stem cells:
- slow-cycling
- long-lived
- Undifferentiated
- progenitor cells
- Make up a small percentage of the total epithelial cell population
- Stem cell division produces transit amplifying or committed progenitor cells
- These cycle rapidly and produce a clonal expansion of the offspring
- Eventually the daughter cells become the mature, terminally differentiated cells that make up the bulk of the epithelium.

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The interfollicular epidermis forms columns called EPUs:

An EPU has about 10 basal cells, including a single stem cell (yellow), its transit-amplifying cell progeny (blue), and early-differentiating cells.

More differentiated keratinocytes (green) followed by mature enucleated squamous cells sit directly above.

This forms an ordered column rising above the basal layer.

Each EPU is a self-renewing column of interfollicular epidermis.

Epidermal cells

- Keratinocytes
- Langerhans cells
- Merkel cells
- Melanocytes
Keratinocytes

- Ectodermally derived
- 80% of total epidermal cells
- Differentiate into corneocytes

Keratinocyte Proteins: Keratin

- A family of intermediate filaments (IF) (~10nm)
  - IF are cytoplasmic fibers averaging 10 nm in diameter
  - Are "intermediate" in size between actin filaments (8 nm) and microtubules (25 nm)

- The hallmark of all epithelial cells and the major IF

Keratins

2 families:

- **acidic** (type I, K9–19)
- **basic-to-neutral** (type II, K1–8)

All keratins assemble into filaments
Forming obligate hetero-polymers
Polymers contain a member of each family (acidic and basic)

- Type I keratin genes: long arms of chromosome 17
- Type II keratin genes: long arms of chromosome 12

Keratin typing is used to identify cancer type and differentiation status (prognosis), amongst other uses.
Keratin tripartite structure:
Central $\alpha$-helical rod flanked by non-helical head and tail

- Regions of highest conservation between the various keratin types are located on the helix boundary motifs.
- Helical regions near the ends of the central rod are important in filament elongation.
- Non-helical domains may be important in forming lateral associations.
- Head and tail domains can interact with other filaments and/or proteins.

Keratin IF form a network that spans the entire cytoplasm

At the periphery they are attached to desmosomes

Keratin function

Mechanical functions:

- Enhance the cell’s ability to withstand trauma by interacting with adhesion complexes (desmosome, hemidesmosomes), actin and microtubules

- Keratin mutations lead to fragile keratinocytes that are weak under mechanical stress

Non mechanical functions:

- Participate in melanosome and organelle distribution in keratinocytes

- Participate in control of keratinocyte proliferation (K10)
## Keratin Types

### Table 7-2 Expression Patterns of Keratin Genes and Keratin-Associated Diseases

<table>
<thead>
<tr>
<th>Basic</th>
<th>Acidic</th>
<th>Tissue Expression</th>
<th>Disease Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Suprabasal keratinocytes</td>
<td>Bullous congenital ichthyosiform erythroderma; diffuse nonepidermolytic PPK (keratin 1)</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>Suprabasal keratinocytes (palmoplantar skin)</td>
<td>Epidermolytic PPK (epidermolytic hyperkeratosis)</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Upper spinous and granular layers</td>
<td>Ichthyosis bullosa of Siemens</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>Cornea</td>
<td>Meesmann's corneal dystrophy</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>Mucosal epithelium</td>
<td>White sponge nevus</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>Basal keratinocytes</td>
<td>Epidermolysis bullosa simplex</td>
</tr>
<tr>
<td>6a</td>
<td>16</td>
<td>Outer root sheath, hyperproliferative keratinocytes, palmoplantar keratinocytes</td>
<td>Pachyonychia congenita type I; focal nonepidermolytic PPK</td>
</tr>
<tr>
<td>6b</td>
<td>17</td>
<td>Nail bed, epidermal appendages</td>
<td>Pachyonychia congenita type II; steatocystoma multiplex</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>Simple epithelium</td>
<td>Cryptogenic cirrhosis</td>
</tr>
</tbody>
</table>

PPK = palmoplantar keratoderma.

Source: Fitzpatrick’s Dermatology in General Medicine, 7th Edition. Copyright The McGraw-Hill Companies. All rights reserved.
Question:
In which disease do K5 or K14 mutations result in keratinocytes that are unable to sustain mechanical stress?
Epidermolysis bullosa simplex

- EBS is a group of diseases characterized by intra-epidermal bulla formation.
- Phenotypes range from mild to severe.
- The three most common EBS types have dominant inheritance and include:
  - generalized (Koebner)
  - localized (Weber-Cockayne)
  - herpetiform (Dowling-Meara) - which is the most severe, and has oral mucosa involvement (seen in photograph at last slide).
- Mutations in the most conserved regions of K5 and K14, the helix boundary domains, correlate with the most severe EBS forms.
- Milder forms of EBS are associated with mutations in less conserved regions.

Question:
In which disease do K5 or K14 mutations result in keratinocytes that are unable to sustain mechanical stress?

Epidermolysis bullosa simplex
Question:
In which inherited disease are there mutations in K1 or K10?
Question:
In which inherited disease are there mutations in K1 or K10?

Epidermolytic hyperkeratosis
(Bullous congenital ichthyosiform erythroderma)

- Mutations: Keratins 1 and 10
- Blistering, redness and peeling at birth
- Later there are verrucous hyperkeratotic plaques with or without erythroderma
Question:
When there is a palmar/plantar involvement in epidermolytic hyperkeratosis which keratin do you expect to be mutated?
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</table>
Question:
In which disease are there mutations in keratins 4 and/or 13?

Question:
In which disease are there mutations in keratins 4 and/or 13?

Answer:
White sponge nevus

- Presents during childhood with bilateral white keratotic macules and plaques on the buccal mucosa
- Thick, white, often corrugated plaques
- Usually asymptomatic
- Benign, no malignant potential
- No treatment is required
Question:
Which inherited condition has mutations in keratins 6a or 16?
Question:
Which inherited condition has mutations in keratins 6a or 16?

Pachyonychia congenita type I
Question: Which inherited condition has mutations in keratins 6b or 17?
Question:
Which inherited condition has mutations in keratins 6b or 17?

Pachyonychia congenita type II
Pachyonychia congenita

- Autosomal dominant disorders
- Severe nail thickening due to massive nail hyperkeratosis
- Type 1 PC: mutations of K6a and K16
- Type 2 PC: mutations of K6b and K17

Features common to both:
- Thickened nails, subungual hyperkeratosis
- Focal palmo-plantar keratoderma may be present
- Many patients have oral leukokeratosis

Type 2 specific
- Steatocystoma multiplex, vellus hair cysts,
- Coarse or twisted hair
- Early primary teeth loss and natal teeth
- Reflecting expression of K6b and K17 in adnexal structures.
Integrins

- Integrin receptors mediate attachment between a cell and its surrounding tissues.
- Integrins always have two transmembrane glycoprotein subunits:
  - $\alpha$ subunit
  - $\beta$ subunit

Question:

Which integrin constitutes a marker of epidermal stem and basal cells?
Question: Which integrin constitutes a marker of epidermal stem and basal cells? 

Answer: β1 integrin

40% of interfollicular basal cells are “β1 integrin bright”

Stem cells: Low levels of transferrin receptor (CD71)
Transit-amplifying cells: High levels of transferrin receptor

Follicular stem cells are located in the bulge region

- We have discussed interfollicular epidermal stem cells in the EPU
- The hair follicle bulge area contains a separate and distinct stem cell population
- Bulge stem cells do not contribute to interfollicular epidermis during homeostasis, but do during wounding

Langerhans cells

- **Antigen processing and presenting cells (APCs)**
- Present antigen to T-cells
- 2%-8% of the epidermal population
- Contain rod- or racket-shaped structures: Birbeck granules

Reduced in:
- Psoriasis
- Sarcoidosis
- Contact dermatitis

Are impaired by UV(B) irradiation

Langerhans cells

Bone marrow–derived leukocytes

Antigen presenting migrating cells

Birbeck granule function only partially known, likely involved in uptake of mannose containing antigens

Contain Langerin, a transmembrane lectin

Lectin = a protein that binds specific oligosaccharides

Merkel cells

Slowly adapting type I mechanoreceptors

Present in hair-bearing and glabrous (non-hairy) skin of digits, lips, oral cavity.

Stain for keratins 8, 18, 19 and 20

Keratin 20 found only in Merkel cells

Contain membrane bound granules, similar to neurosecretory granules, containing:

- metenkephalin (opioid peptide)
- vasoactive intestinal peptide
- neuron specific enolase
- synaptophysin

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Dermo-Epidermal Junction and Basement Membrane

Hypothetical relationships of molecules within the dermal-epidermal junction basement membrane

- Hemidesmosome
- Focal contact
- Keratin 5/14
- BPAG1
- Actin
- Kindlin
- CD 151
- $a_6b_4$ integrin
- Collagen XVII
- Laminin 332
- Laminin 311
- Nidogen
- Perlecan
- Collagen XIII
- Dermal fibril
- Talin
- Vinculin
- $a_3b_1$ integrin
- Collagen VII
- Anchoring fibrils

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Desmosomes

✓ Mediate keratinocyte adhesion
✓ Anchor intermediate filaments

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Desmosome ultrastructure

Symmetric structure:
- 2 apposing dense plaques inside the membrane
- Dense area inside the desmoglea
- Inner dense plaques

\( dg = \text{desmoglea (30nm)} \) (Gk: desmosome glue) ; \( dm = \text{dense midline} \)
\( odp = \text{outer dense plaque} \) ; \( kf: \text{keratin filaments} \) ; \( idp = \text{inner dense plaque} \)

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Biochemical characterization of desmosomes

3 major gene families encode desmosomal proteins

- Plakins (desmoplakin) (dp)
- Armadillo proteins (plakoglobin, plakophilins) (pg, pkp)
- Desmosomal cadherins (desmogleins, desmocolins) (dsg, dsc)

- Plakins are in the inner dense plaque
- Armadillo proteins are in the outer dense plaque.
- Desmosomal cadherins are transmembrane. Their extracellular amino terminus comprises the desmogleins.

Desmoplakin:
Linking keratin filaments and desmosomonal plaque

- a modular protein
- carboxy terminus binds to keratin
- amino terminus binds to plakoglobin/plakophilin
- central part of one molecule coils around the central part of another molecule to form rod-like structure

Question:
In which syndrome are there desmoplakin mutations?

Question: In which syndrome are there desmoplakin mutations?

Carvajal syndrome

- Epidermolytic striate palmoplantar keratoderma
- Particularly at sites of pressure
- Left ventricular cardiomyopathy
- Woolly hair
- Enamel dysplasia

Plakoglobin:
Linking desmoplakin and desmosomal plaque

- a modular protein
- binds to desmoplakin, desmoglein (DSG), desmocolins (Dsc) & plakophilins (PP)

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Desmogleins and Desmocollins:
Linking extracellular desmogleiia and intracellular plaque

- Desmogleins and Desmocollins are in the cadherin supergene family.
- Cadherins are calcium-dependent transmembrane adhesion proteins.
- Desmogleins are encoded by 4 genes: 1, 2, 3, 4.
- Desmoglein 1 & 3 are predominant in the epidermis and mucous membranes.
- Desmocollins are encoded by 4 genes: I, II, III, IV.

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Desmogleins and Desmocollins

- Abnormalities in calcium transport will lead to decrements in desmoglein and desmocollin function
- Result is epidermal discohesion

Desmosomal cadherins (dsg & dsc) bind plakoglobin (pg) and other armadillo proteins

The extracellular tail provides adhesion with desmosomal cadherins expressed on apposing cells

Desmogleins in mucosal and epidermal disease

Anti Dsg1 in PF causes acantholysis only in the superficial epidermis

In early PV, antibodies are present only against Dsg3 causing mucous membrane blistering

Later in PV, antibodies are Present against Dsg3 and Dsg1 causing mucous membrane & epidermal blistering

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Desmosomal proteins in dermatologic disease

Question:
In which disease is there a mutation in the gene SERCA2 (sarco/endoplasmic reticulum Ca\(^{2+}\)-ATPase type 2 isoform) that regulates calcium transport?
Question:
In which disease is there a mutation in the gene SERCA2 that regulates calcium transport?

Darier Disease

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Question:
In which disease is there a mutation in the gene ATP2C1 (ATPase Ca^{2+} transporting type 2C, member 1) a regulator of cytoplasmic calcium concentration?

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Question:
In which disease is there a mutation in the gene ATP2C1 (ATPase Ca^{2+} transporting type 2C, member 1) a regulator of cytoplasmic calcium concentration?

Hailey-Hailey disease
Intercellular junctions

Seal neighboring cells and control the passage of molecules

Separate the apical from the basolateral parts of a cell

Tight Junction- more apical

Adherens junctions-
- Usually more basal
- linked to the actin cytoskeleton

Claudin is a tight junction protein

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Question:
In which disease are there mutations in claudin-1?

Question:
In which disease are there mutations in claudin-1?

Neonatal ichthyosis with sclerosing cholangitis (NISH)

- Ichthyosis
- fine white scales
- hypotrichosis
- scarring alopecia
- Hypodontia
- sclerosing cholangitis
Gap junctions: formed by connexin proteins

- Connexins are transmembrane proteins
- Connexins homo- or heteromerize on the plasma membrane to form a connexon
- Allow the passage of ions and small molecules between cells and form gap junctions

Gap Junctions: Connexin Disorders

Question:
In which syndrome are there mutations in \textit{GJB2}, encoding connexin-26?

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Question:
In which syndrome are there mutations in \textit{GJB2}, the gene encoding connexin-26?

Vohwinkel's Syndrome
Keratoderma Hereditarium Mutilans

- Honeycombed keratoderma involving the palmoplantar surfaces
- Flexion contractures and constricting bands of digits, particularly of the fifth digit, result in auto-amputation
Question:
What is another syndrome with mutations in GJB2, encoding connexin-26?
Question:
What is another syndrome with mutations in *GJB2*, encoding connexin-26?

**KID syndrome**

- keratitis (with progressive corneal opacification)
- ichthyosis
- deafness (neurosensorry)
- Discrete erythematous plaques, with mild, generalized hyperkeratosis.
- Furrowing about the mouth
- Follicular hyperkeratosis, which can result in a scarring alopecia
- "Leather-like" palmoplantar keratoderma
Question:
What is a third syndrome with mutations in GJB2, encoding Connexin-26?

Question:
What is a third syndrome with mutations in *GJB2*, encoding Connexin-26?

**Bart-Pumphrey syndrome**

- Hereditary deafness
- Palmoplantar hyperkeratosis
- Knuckle pads
- Leukonychia
Question:
In which syndrome are there mutations in \textit{GJB6}, the gene encoding connexin-30?

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Question:
In which syndrome are there mutations in \textit{GJB6}, the gene encoding connexin-30?

\textbf{Clouston Syndrome}
\textbf{Hidrotic Ectodermal Dysplasia}

- Wiry brittle pale scalp hair
- Patchy to total alopecia
- Nails thickened and dystrophic
- Palmar/plantar hyperkeratosis
- Sweating is normal
- Teeth are normal
Stratum corneum

SC is composed of:
Cells embedded in an intercellular matrix containing non-polar lipids Organized as lamellar lipid layers

At stratum granulosum (SG)- stratum corneum (SC) interface there are lamellar bodies (LB)

LB content is extruded forming continuous lipid bilayers (LBL).

Desmosomes become corneosomes in the process of cornification.

Corneocyte is lipid depleted

Has an inner protein envelope and an outer lipid envelope

Ceramides are covalently bound to cornified envelope proteins, particularly to involucrin.

Junction of stratum corneum and granulosum

Lamellar granules
- form in spinous layer
- deliver precursors of SC lipids into the intercellular space
- contain
  - Glycoproteins
  - Glycolipids
  - Phospholipids
  - Glycosylceramides
  - Free sterols
  - Acid hydrolases: lipases, proteases, acid phosphatases, glycosidases, steroid sulfatase

Steroid and lipid metabolism is important for normal epidermal sloughing of cornified cells

Formation of lamellar granules

• **ABCA12 lipid transporter** transfers lipids from cytosol into lamellar granules
• **lipid-processing enzymes, proteases, and protease inhibitors** act on lipids
• At the granular–corneum interface, lamellar granules fuse with cell membrane
• LG release content into the intercellular lamellae.
• Enzymatic reactions modify lipid composition of intercellular space (cholesterol, ceramides, free fatty acids)
• Provide effective water-permeability barrier
• Corneocytes detach from each other in superficial layers of stratum corneum as a result of cleavage of corneo-desmosomes.

Question:
In which disease are there mutations of the enzyme steroid sulfatase?
Question:
In which disease are there mutations of the enzyme steroid sulfatase?

Recessive X-linked ichthyosis

- Scaling most prominent on extensors, although also significant flexural involvement
- More severe involvement than ichthyosis vulgaris
- Larger scales
- Comma-shaped corneal opacities do not affect vision
- Affected males have increased risk of cryptorchidism and, independently increased risk of testicular cancer
Question:
In which disease are there mutations in the lipid transporter ABCA12?

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Question: In which disease are there mutations in the lipid transporter ABCA12?

**Harlequin ichthyosis**

An absence of ABCA12 prevents lipid transfer into lamellar granules
LG are abnormally shaped, reduced in number, or absent
Exocytosis of lamellar granule content is reduced and intercellular lipid lamellae are absent
Abnormal lipid-containing vacuoles form in the cytoplasm of the corneocytes
The stratum corneum is remarkably thickened and does not desquamate.
Keratohyalin granules (KHG) are composed of:

- Pro-filaggrin
- Keratin
- Loricrin

Profilaggrin is released from keratohyalin granules. It undergoes calcium dependent cleavage. Filaggrin monomers associate with keratin to form macrofilaments.

Loricrin

- Cystein rich protein
- The major component of the cornified envelope
- After its release from KHG, loricrin binds to desmosomal structures
- Becomes cross-linked with other cornified envelope proteins and lipids
- Transglutaminase cross links the complex to the membrane forming the cornified envelope

Involucrin

- Is present early in cornified envelope formation
- Forms a scaffold for incorporation of other cornified envelope proteins
- Involucrin expression is initiated in the early spinous layer
- Transglutaminases cross link involucrin, loricrin and other cornified envelope proteins

Question: Which disease has mutations in the gene encoding filaggrin?

Question:
Which disease has mutations in the gene encoding filaggrin?

Ichthyosis vulgaris

- Scale most prominent on the extensor surfaces of the extremities
- Lower extremities most severely involved
- Hyperlinear palms
- Keratosis pilaris
Question:
Loricrin mutations are found in which syndrome?

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Question: Loricrin mutations are found in which syndrome?

Vohwinkel syndrome with ichthyosis

- Honeycombed palmoplantar keratoderma
- Flexion contractures and constricting bands of digits, particularly of the fifth digit, resulting in autoamputation
- Diffuse, generalized ichthyosiform dermatosis
- NO HEARING LOSS
Question:
Mutations in transglutaminase 1 gene have been found in which disease?

Question:
Mutations in transglutaminase 1 gene have been found in which disease?

Lamellar ichthyosis

• Newborn in collodion membrane
• Later develops large, plate-like scales, which may appear mosaic
• Lips and mucous membranes spared
• Adnexal structures may be compromised by the adherent, firm scale leading to a scarring alopecia
Question:
What is this syndrome and which gene is mutated?

Question:
What is this syndrome and which gene is mutated?

Acral peeling skin syndrome
TGM-5 mutation

✓ Autosomal recessive
✓ Painless sloughing of the stratum corneum from an intact stratum granulosum
✓ Missense mutations in the transglutaminase-5 gene
The end