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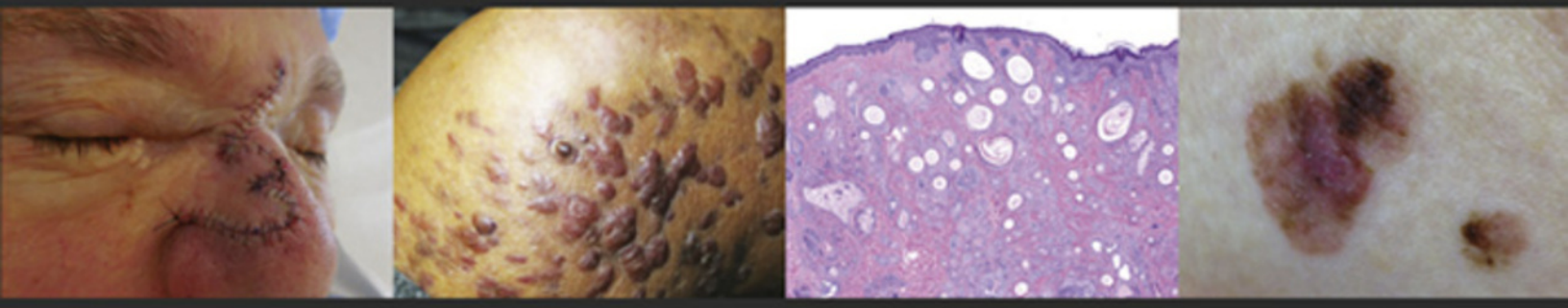
Review of Dermatology



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Review of Dermatology

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Contents

Preface

Purpose of this book

We envision this book serving as a comprehensive review for dermatology residents and practicing dermatologists. We hope that the book is used not only in the United States, but all over the world.

How the book should be used

The book can be used in many ways:

- As a resource for practicing dermatologists preparing for recertification examinations or simply as a quick reference
- As a resource for dermatology residents preparing for board examinations, in-service examinations, or simply as a quick reference (it could even be used throughout residency as a place to compile notes and facts learned from reading textbooks and journal articles, much the way First Aid© was used during medical school)

How the book should NOT be used

There is NO substitution for reading textbooks and journal articles during residency. This book should serve as a review or a syllabus of dermatology, but should not take the place of textbooks and original literature. Many great resources to truly learn dermatology exist – our favorites are *Dermatology* (commonly referred to as Bolognia), *Andrews' Diseases of the Skin*, *Comprehensive Dermatologic Drug Therapy* (commonly referred to as Wolverton), The *Requisites in Dermatology Series* (particularly dermatopathology and dermatologic surgery), *Practical Dermatopathology* (commonly referred to as Rapini), and *Hurwitz Clinical Pediatric Dermatology*.

Other information

Please remember that space was limited for this book, as it is for all books – we had to make important choices to leave certain information out of the book.

We are extremely grateful to the authors and editors of the textbooks listed above, as well as those of *McKee's Pathology of the Skin* and *Weedon's Skin Pathology*, as nearly all of the figures came from these resources.

Despite reading and re-reading this text many times, we imagine that some errors may have snuck by (particularly as this is our first edition). We encourage you to email us at **reviewofdermatology@gmail.com** with any errors or suggestions so we can correct these for our second edition. Please also email us if you have ideas to improve the book or would like to contribute to future editions.

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2.6 Antimicrobial agents
2.7 Phototherapy
2.8 Miscellaneous agents
2.9 Drug interactions and the cytochrome P-450 system

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3.2 Eczematous dermatoses
3.7 Monoclonal gammopathies of dermatologic interest
3.8 Xanthomas
3.9 Urticaria and angioedema
3.10 Neutrophilic dermatoses
3.11 Eosinophilic disorders
3.12 Figurate erythemas
3.14 Drug reactions
3.15 Photodermatoses and other physical dermatoses
3.16 Amyloidoses
3.17 Neurodermatology and psychodermatology
3.18 Palmoplantar keratodermas
3.19 Nutritional disorders in dermatology
3.20 Depositional and calcification disorders
3.21 Ulcers
3.22 Vasculitides, vasculopathies, and other vascular disorders
3.23 Panniculitides and lipodystrophies
3.24 Dermatoses of pregnancy
3.25 Hair, nail, and mucosal disorders

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1.3 Wound healing
1.4 Genetics
1.5 Laboratory techniques and molecular biology
1.6 Ultraviolet light
1.7 Immunology
1.7.1 Innate vs adaptive immunity
1.7.2 Immunologic mediators
1.7.3 Complement pathways
1.7.4 Cells of significance
1.7.5 Major histocompatibility complex

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6.2 Cysts
6.3 Melanocytic neoplasms
6.4 Adnexal neoplasms and hamartomas
6.5 Hair follicle neoplasms/hamartomas
6.6 Sebaceous proliferations
6.7 Neural neoplasms
6.8 Smooth muscle neoplasms
6.9 Hematolymphoid neoplasms
6.10 Fibrohistiocytic neoplasms
6.11 Vascular proliferations
6.12 Neoplasms of adipocytic lineage
7.1 Essential concepts in dermatopathology
7.2 Dermatopathology diagnoses at a glance

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8.1 Surgical anatomy
8.2 Surgical instruments and needles
8.3 Suture techniques
8.4 Wound closure materials
8.6 Antisepsis – garbs and preps
8.8 Cryosurgery
8.9 Excisions
8.15 Nail surgery

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10 Cutaneous manifestations of internal disease and metastases
10.1 Cardiovascular/cardiopulmonary
10.2 Endocrine
10.3 Gastroenterology
10.4 Neurology
10.5 Renal
10.6 Paraneoplastic syndromes

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6.5 Hair follicle neoplasms/hamartomas
6.6 Sebaceous proliferations
6.8 Smooth muscle neoplasms
6.9 Hematolymphoid neoplasms
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3.3 Interface dermatitis
3.4 Blistering diseases
3.6 Granulomatous/histiocytic disorders
3.8 Xanthomas
3.10 Neutrophilic dermatoses
3.11 Eosinophilic disorders
3.12 Figurate erythemas
3.14 Drug reactions
3.16 Amyloidoses
3.18 Palmoplantar keratodermas
3.19 Nutritional disorders in dermatology
3.20 Depositional and calcification disorders
3.21 Ulcers
3.24 Dermatoses of pregnancy

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5.3 Bacterial infections
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5.5 Parasites and other creatures

Section editor for section
11 Epidemiology, Statistics, Study Design, and Public Health Principles
11.1 Statistical definitions
11.2 Epidemiological principles
11.3 Types of studies and their limitations
11.4 Types of bias
11.5 Maintenance of certification for the American Board of Dermatology
11.6 Billing

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1.2 Embryology
1.3 Wound healing
1.4 Genetics
1.5 Laboratory techniques and molecular biology
1.6 Ultraviolet light
1.7 Immunology
1.7.1 Innate vs adaptive immunity
1.7.2 Immunologic mediators
1.7.3 Complement pathways
1.7.4 Cells of significance
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9.3 Dermal fillers
9.4 Liposuction and fat reduction
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3.3 Interface dermatitis
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To my wife, for her unwavering and unconditional love and support

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To my parents, who always encouraged me to follow my dreams

To my sister, whose daily conversations keep me laughing

Thomas Hocker

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1

Basic Science

Adnan Mir and Rahul Chavan

CONTENTS LIST

1.1 STRUCTURE AND FUNCTION OF THE SKIN

- Functions: interfaces with environment, collects sensory data, protects against infection and chemical penetration, temperature regulation, water retention, and excretion of drugs/waste
- Comprised of three layers: epidermis, dermis, and subcutis
  - Epidermis
    - Squamous epithelium comprised of keratinocytes connected by desmosomes, adherens junctions, tight junctions, and gap junctions (see Table 1-1)
      - Intercellular junctions
        - ➔ **Desmosomes**: primary keratinocyte intercellular junction
          - Provide structure and integrity to the epidermis by anchoring/attaching to **keratins**
          - Consist of desmoplakin (cytoplasmic), plakophilin (cytoplasmic), plakoglobin (cytoplasmic), desmocollin 1/2/3 (transmembrane), and desmoglein 1/3 (transmembrane)
          - Desmocollin, desmoglein, and other cadherins are **calcium-dependent**
        - ➔ **Adherens junctions**: also mediate tight intercellular binding (Fig. 1-1)
          - Anchor/attach to **actin** filaments
          - Consist of α-catenin (cytoplasmic), β-catenin (cytoplasmic), plakoglobin (cytoplasmic), and classic cadherins (E and P; transmembrane)
        - ➔ **Tight junctions**: composed of claudins and occludins; form tight seal against water loss in granular layer
        - ➔ **Gap junctions**: facilitate intercellular communication; composed of **connexons** (tubular channels composed of **six connexins**)
    - Cells originate in the cuboidal basal layer and flatten out as they ascend to the surface – four to five layers/strata (deep to superficial): **stratum basale, s. spinosum, s. granulosum, s. lucidum** (only on palmoplantar surfaces), and **s. corneum**
    - **Stratum basale**: mitotically active cuboidal cells from which the upper layers of the epidermis are derived
      - Attached to dermis by hemidesmosomes
      - **Keratins 5 and 14 produced here**
      - Cellular proliferation stimulated by various factors, including trauma and UV (↑**ornithine decarboxylase** expression is associated with (a/w) proliferative states)
        - ➔ Ornithine decarboxylase is inhibited by corticosteroids, retinoids, and vitamin D3
      - 10% of cells in the basal layer are stem cells, which give rise to other **stem cells** and **transient amplifying cells** that can still replicate, but only for a few cycles, until they reach a

Table 1-1. Intercellular Junction Proteins

Protein	Protein Family	Junction Type	Disease State
Desmoglein 1	Cadherin	Desmosome	Autoimmune: pemphigus foliaceus, PNP, PV (mucocutaneous form), IgA pemphigus (intraepidermal neutrophilic type) Inherited: **striate PPK** Infectious: bullous impetigo and SSSS
Desmoglein 3	Cadherin	Desmosome	Pemphigus vulgaris (mucosal-predominant and mucocutaneous forms), PNP, IgA pemphigus (intraepidermal neutrophilic type)
Desmoglein 4	Cadherin	Desmosome	**Monilethrix** (autosomal recessive form), autosomal recessive hypotrichosis
Desmocollin 1	Cadherin	Desmosome	**IgA pemphigus (SPD type)**
Desmocollin 2	Cadherin	Desmosome	Carvajal-like phenotype in one family
Desmocollin 3	Cadherin	Desmosome	Hypotrichosis
Plakoglobin	Armadillo (catenin)	**Desmosome and Adherens**	**Naxos syndrome**
Plakophilin	Armadillo	Desmosome	Ectodermal dysplasia with skin fragility
Desmoplakin	Plakin	Desmosome	**Carvajal syndrome**
E-Cadherin	Cadherin	Adherens	Somatic mutations in many neoplasms
β-Catenin	Armadillo	Adherens	Somatic mutations in many neoplasms, including **pilomatricomas;** also may be seen in **myotonic dystrophy and Rubenstein-Taybi**
Connexin 26 (GJB2)	Connexin	Gap	**Vohwinkel** syndrome, **KID** syndrome, **Bart-Pumphrey** syndrome, **PPK with deafness**; also common in nonsyndromic deafness!
Connexin 30 (GJB6)	Connexin	Gap	**Hidrotic ectodermal dysplasia**
Connexin 30.3 (GJB 4)	Connexin	Gap	**Erythrokeratoderma variabilis**
Connexin 31 (GJB 3)	Connexin	Gap	**Erythrokeratoderma variabilis**

terminal differentiation phase, where they move upwards and eventually desquamate
- ◆ Transit time from basal layer to stratum corneum = **14 days**; transit through the stratum corneum/desquamation = **14 days (total = 28 days** from basal layer to desquamation)

- ○ **Stratum spinosum**: named for the "spiny" appearance of intercellular desmosomal connections on microscopy
  - ◆ Contain multiple types of intercellular junctions
  - ◆ Keratins 1 and 10 made here
  - ◆ Terminal keratinocyte differentiation 2° to ↑**intracellular calcium** in suprabasal epidermis
  - ◆ Odland bodies (lamellar granules) are produced by Golgi bodies in spinous layer
    - ➔ Primarily contain **ceramide (most important lipid** involved in epidermal barrier function; the most prevalent/important lipid in the stratum spinosum), along with glycoproteins, glycolipids, and phospholipids
    - ➔ Are specialized lysosomes that exert most of their action in the stratum corneum, by discharging ceramides and other lipids to the extracellular space of the junction between the stratum granulosum and stratum corneum ➔ **ceramides help form the cornified cell envelope** (see below), and eventually replace the cell membrane
    - ➔ Flegel's disease and Harlequin ichthyosis are 2° to ↓lamellar granules
    - ➔ **X-linked ichthyosis** occurs due to absent steroid sulfatase in lamellar granules
- ○ **Stratum granulosum**: flattened cells with prominent basophilic **keratohyaline granules**, which contain **profilaggrin** (converted to filaggrin at junction of stratum granulosum and stratum corneum), **loricrin**, keratin intermediate filaments, and involucrin
  - ◆ Cells begin to lose nuclei, but keep overall structure
  - ◆ **Cornified cell envelope** production primarily takes place in the granular layer (Fig. 1-2)
    - ➔ Cross-linked protein and lipid structure encased in extracellular lipids forming a strong polymer that eventually replaces the plasma membrane
      - ◈ Process starts with envoplakin, periplakin, and involucrin scaffolding along the inner cell membrane (which is eventually replaced by ceramides from lamellar granules)
      - ◈ Further reinforcement by cross-linking **loricrin (#1 component of cornified envelope**, first appears in granular layer; mutated in Vohwinkel syndrome variant lacking deafness**)**, small proline-rich proteins, keratin, and filaggrin
      - ◈ **Cross-linking occurs via transglutaminase I** ➔ γ-glutamyl lysine isopeptide bonds (**Boards factoids:** TG-1 is mutated in lamellar ichthyosis; TG-3 is antigenic target in dermatitis herpetiformis)
      - ◈ Other components include envoplakin (helps connect desmosomes to cornified envelope), periplakin, elafin, and others
      - ◈ Outer surface of the cornified envelope is ultimately surrounded by lipids (primarily ceramide) = **cornified lipid envelope**

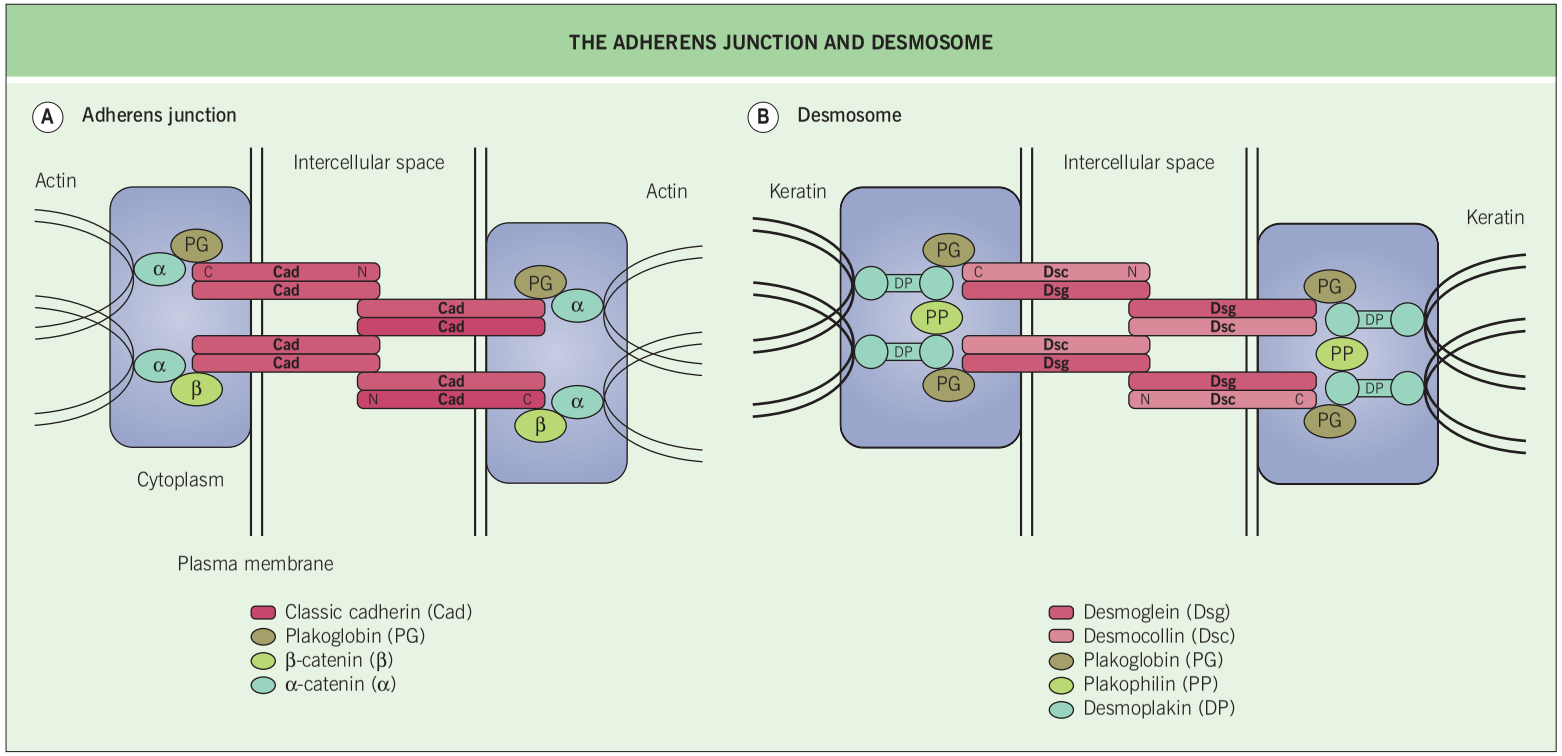

Figure 1-1. The adherens junction and desmosome. (A) The adherens junction complex contains classic cadherins as transmembrane constituents, and α-catenins, β-catenins, and plakoglobin as cytoplasmic constituents. A classic cadherin is directly coupled through its cytoplasmic tail to β-catenin or plakoglobin, which in turn is linked to α-catenin, which binds to actin. (B) The desmosome complex includes desmogleins and desmocollins as transmembrane constituents, and plakoglobin, plakophilin, and desmoplakin as cytoplasmic constituents. Desmogleins and desmocollins associate with plakoglobin, which in turn binds to desmoplakin and links keratin to the membrane. N = amino-terminus; C = carboxy-terminus. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

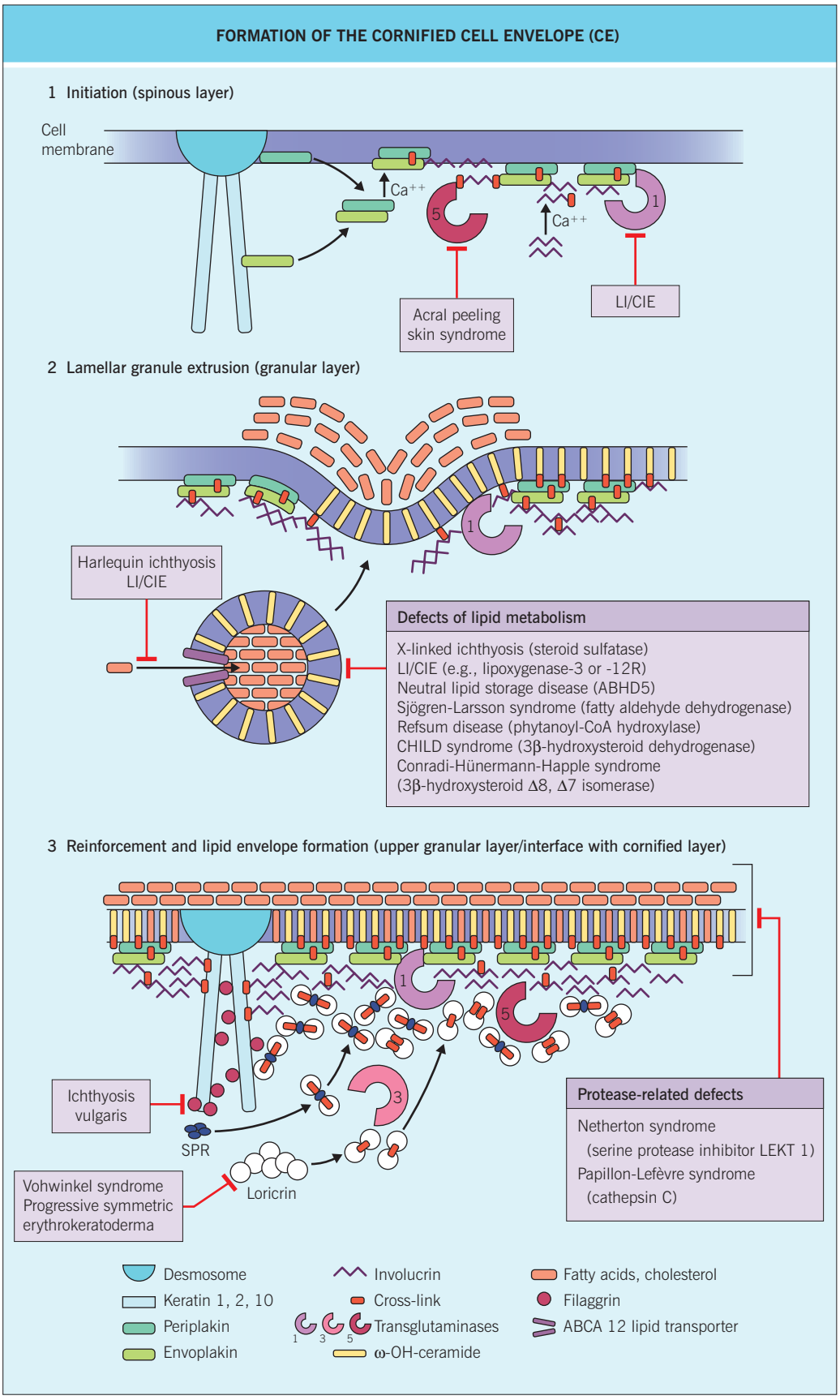

Figure 1-2. Formation of the cornified cell envelope (CE). Terminal differentiation of keratinocytes is triggered by an increase in the intracellular Ca^{2+} concentration of the suprabasal epidermis. CE assembly is initiated in the upper spinous layer via formation of a cross-linked scaffold composed of envoplakin, periplakin, and involucrin along the inner surface of the cell membrane (1). This is followed by (or perhaps coincident with) extrusion of lamellar granules into the extracellular space (2). Specialized ω-hydroxyceramides are delivered to, and eventually replace, the cell membrane, where they become linked to scaffold proteins. Reinforcement occurs via cross-linking and translocation to the cell periphery of loricrin (accounts for >80% of the mass of the CE) and small proline-rich proteins (SPRs) (3). Complexes of keratin and filaggrin also become cross-linked to the CE. In addition, proteases play important roles in processing of CE proteins and the proteolysis of corneodesmosomes that is required for desquamation. A mature and terminally differentiated cornified cell thus consists of keratin filaments covalently attached to the CE, which is composed of protein and lipid envelope components and is imbedded in the extracellular lipid lamellae. Defects in transglutaminases, lipid metabolism, CE structural proteins, and proteases leads to a variety of diseases characterized by ichthyosis and/or keratoderma (1–3). CHILD, *c*ongenital *h*emidysplasia with *i*chthyosiform erythroderma and *l*imb *d*efects; LI, lamellar ichthyosis; CIE, congenital ichthyosiform erythroderma. (Courtesy, Julie V Schaffer, MD) (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

- ◈ **Ultimately provides strong water-impermeable outer barrier**

- **Stratum corneum**: outermost layer, which serves as a mechanical barrier between the epidermis and the environment
  - Composed primarily of protein-rich corneocytes ("bricks"; **contain NO nuclei**; keratin filaments attached to cornified envelope) embedded in a lipid matrix ("mortar," cornified lipid envelope)
  - Serves as a barrier to water loss (conditions that perturb the skin ➔ ↑transepidermal water loss) and toxins/infectious agents
- Epidermal cells of importance
  - <u>Keratinocytes</u> are the primary cells of the epidermis and produce proteins (e.g., keratin filaments) and lipids important for barrier function
    - ➔ Keratins: intermediate filaments that comprise the primary cytoskeleton of the epidermis (see Table 1-3)
      - ◈ Type I keratins: **low-MW**; **acidic**; **K9-28**, K31-40 (hair keratins); **chromosome 17**
      - ◈ Type II keratins: **high-MW; basic**; **K1-8**, K81-86 (hair keratins); **chromosome 12**
      - ◈ Basic structure is an α-helical rod domain (consisting of heptad amino acid repeats) divided into four segments (1A, 1B, 2A, and 2B) that are interrupted by three nonhelical segments ("linkers")
      - ◈ Functional unit consists of **heterodimers of type I and type II** filaments that form tetramers and ultimately filaments
      - ◈ Anchored to plasma membrane by desmosomes
      - ◈ 40–70 kD
    - ➔ Keratinocytes produce IL-1, IL-6, IL-8, IL-10, IL-12, and **TNF-α**, among others
    - ➔ Keratinocytes respond to IL-2, IL-4, IL-13, IL-22, and TNF-α, among others
  - <u>Melanocytes</u>
    - ➔ **Neural crest-derived** melanin-producing dendritic cells found in the stratum basale (≈1 : 10 ratio with keratinocytes, when viewed in 2-dimensional plane)
      - ◈ **c-kit** activation is needed for melanocyte development/migration; **piebaldism** occurs as a result of c-kit loss ➔ impaired melanocyte migration and proliferation; **c-kit mutations** are a/w mucosal and acral melanoma
    - ➔ Each melanocyte interfaces with **36 keratinocytes** when analyzed three-dimensionally **(epidermal melanin unit)**
    - ➔ Melanin is produced in melanosomes (lysosome-type organelles) from its precursor, tyrosine, through a multistep enzymatic process involving **tyrosinase (copper-dependent enzyme)**
      - ◈ Tyrosine ➔ $^{\text{(tyrosinase-dependent step)}}$ DOPA ➔ $^{\text{(tyrosinase-dependent step)}}$ DOPAquinone ➔ **pheomelanin** (yellow/red; made by round melanosomes) or **eumelanin** (black/brown; made by elliptical melanosomes)
      - ◈ Melanosomes are transported along dendritic processes and transferred to keratinocytes through phagocytosis of dendrite tips
      - ◈ Racial variation in pigmentation: identical melanocyte density in dark and light skinned individuals; **melanosomes in darker skinned individuals are larger, darker (↑melanin), more stable, and are transferred individually** (vs smaller, lighter, less stable, and **clustered** melanosomes in lighter skin)
      - ◈ Melanin production is stimulated by melanocyte-stimulating hormone **(MSH)** and **ACTH** activity on **MC1-R** on melanocytes; also stimulated through various pathways induced by UV radiation
      - ◈ **MC1-R loss** of function mutations ➔ **↑pheomelanin:eumelanin** ratio (phenotype = **red hair**/fair skin, **↑risk of melanoma**)
      - ◈ Melanin absorbs UV ➔ protects against UV-induced mutations
      - ◈ UV exposure ➔ immediate tanning (from oxidation of existing melanin) and delayed tanning (requires new melanin synthesis)
    - ➔ Other high-yield examination facts:
      - ◈ Defects in enzymes required to convert tyrosine to melanin ➔ **oculocutaneous albinism**; OCA1 (*Tyrosinase*), OCA2 (*P gene*), OCA3 (*TRP-1*)
      - ◈ Defects in packaging of melanosome-specific proteins ➔ **Hermansky-Pudlak** syndrome (HPS1 > HPS3 > other gene mutations)
      - ◈ Defects in lysosome and melanosome trafficking to dendrites ➔ **Griscelli** (*MYO5A, RAB27A,* and *MLPH* mutations) and **Chédiak-Higashi syndrome** (*LYST* mutations)
  - <u>Langerhans cells (LCs)</u>: major antigen presenting cells (APC) of the skin
    - ➔ Dendritic histiocytes characterized by **reniform** (kidney shaped) nuclei, and tennis racket-shaped **Birbeck granules** seen on electron microscopy
    - ➔ Interact with keratinocytes via E-cadherin
    - ➔ Positive immunostains: **CD207 (langerin**; most sensitive IHC stain; specific for Birbeck granules), **CD1a**, **S100**, CD34, vimentin, and actin
    - ➔ Originate from CD34+ progenitor cells in bone marrow like other monocytes/macrophages
    - ➔ Found mainly in stratum spinosum, where it first encounters and processes antigens, and **subsequently migrates to the lymph nodes** to activate T-cells
    - ➔ **Downregulated in skin after UV exposure** ➔ ↓immune surveillance
    - ➔ See p. 24 for further discussion of function

- ◆ **Merkel cells**: slow-adapting mechanoreceptors found in fingertips, lips, oral cavity, and hair follicle ORS
  - ➔ Found in stratum basale; communicate with neurons
  - ➔ **$CK20^+$ in perinuclear dot pattern** sensitive/specific for Merkel cells; also (+) for neurofilaments, S100, synaptophysin, chromogranin A, vasoactive intestinal peptide, neuron-specific enolase, and calcitonin gene-related peptide

■ **Basement membrane zone (BMZ)** (Fig. 1-3 and see Table 1-2)

- ○ Semipermeable barrier between epidermis and dermis that also serves to adhere basal keratinocytes to the underlying dermis
- ○ Key steps within each location:
  - ◆ Basal keratinocyte/hemidesmosome: intracellular keratin filaments (**K5** and **K14**) attach to electron-dense hemidesmosomal plaques (**plectin** and **BPAG1 [BP230]**) on the basal plasma membrane ➔ hemidesmosomal plaque proteins bind to intracellular portions of the anchoring filaments (BPAG2 and α6β4 integrin)
  - ◆ Lamina lucida: extracellular portion of **anchoring filaments** (**BPAG2, α6β4 integrin**, and **laminin 332**) extend from the hemidesmosome down to the lamina densa; the thin filaments result in an electron-lucent region; is the weakest portion of BMZ ➔ is zone of separation in **salt-split skin** and also in **suction blisters**
  - ◆ Lamina densa: anchoring filaments attach to **type IV collagen** (#1 component) and other proteins (laminin 332, laminin 331, and nidogen) in the lamina densa ➔ results in attachment between basal keratinocyte and lamina densa
  - ◆ Sublamina densa: loops of **type VII collagen (anchoring fibrils)** arise from the underside of lamina densa, extend down into the dermis, hooking around dermal **type I and III collagen fibers**, and then loop back up to reattach to lamina densa (or anchoring plaques in dermis) ➔ firmly anchors the lamina densa (and all aforementioned structures) to the papillary dermis
- ○ BMZ also functions as a permeability barrier: **heparan sulfate** proteoglycan (**negatively charged**) in lamina densa is a major contributor

■ Dermis

- ○ Located below the epidermis, derived from mesoderm, and divided into papillary dermis (superficial) and reticular dermis (deep)
- ○ Cells of significance
  - ◆ Fibroblasts-create extracellular matrix and are involved in wound healing

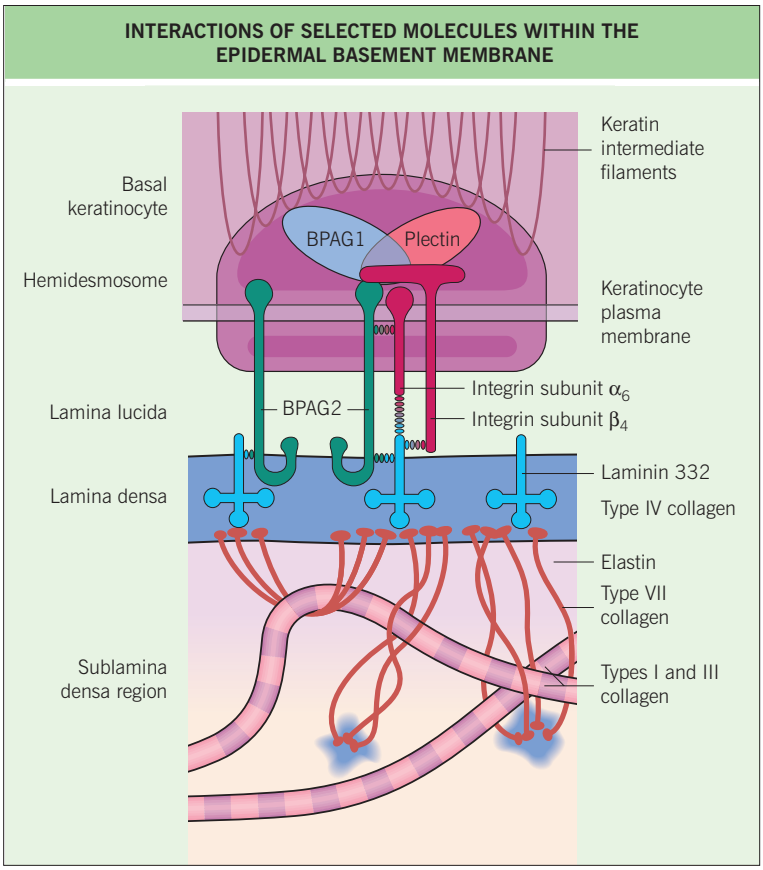

Figure 1-3. Interactions of selected molecules within the epidermal basement membrane. These interactions promote epidermal adhesion and also play a key role in a number of dermatologic diseases. Important molecular interactions include those between: (1) plakin family members, BPAG1 and plectin, with keratin intermediate filaments; (2) the former with BPAG2 and integrin $\alpha_6\beta_4$ (specifically the large cytoplasmic domain of integrin subunit β_4); (3) the cytoplasmic domains of BPAG2 and integrin subunit β_4; (4) the extracellular domains of BPAG2 and integrin subunit α_6 as well as laminin 332 (formerly laminin 5); (5) integrin $\alpha_6\beta_4$ in hemidesmosomes and laminin 332 in the lamina densa; (6) laminin 332 and type VII collagen; (7) type VII collagen with type IV collagen, fibronectin, and type I collagen in the sublamina densa region. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

Table 1-2. Basement Membrane Zone Proteins

Protein	Site	Source	Family	Function	Disease State
BPAg1 (230 kD)	Hemidesmosome/ keratinocyte	Keratinocyte	Plakin	Binds keratins and integrins; intracellular/ part of attachment plaque	BP, EB simplex
BPAg2 (180 kD)	Hemidesmosome/ keratinocyte ➔ lamina lucida Amino terminus is intracellular and carboxy terminus is extracellular –NC16A domain is closer to amino terminus but is extracellular	Keratinocyte	Collagen (XVII)	Transmembrane protein and one of the anchoring filaments; interacts with BPAg1, laminin 5, β4 integrin, and plectin	N16A Terminus: BP, pemphigoid gestationis, linear IgA bullous disease Carboxy Terminus: Cicatricial pemphigoid
α6β4 Integrin	Hemidesmosome/ keratinocyte ➔ lamina lucida	Keratinocyte	Integrin	Interacts with keratins, laminin 5, plectin, BPAg1, BPAg2; part of the anchoring filaments	**Ocular** cicatricial pemphigoid (antibodies to **β4**), **EB with pyloric atresia** (85%)
Laminin 332 (laminin 5, epiligrin)	Lamina lucida ➔ Lamina densa	Keratinocyte	Laminin	Connects other anchoring filaments (BPAg2 and α6β4 integrin) to collagen VII; part of the anchoring filaments	**Antiepiligrin pemphigoid** (a/w malignancy), **JEB-Herlitz**
Plectin	Hemidesmosome	Keratinocyte	Plakin	Binds keratins and integrins; intracellular/ part of attachment plaque	**EB with muscular dystrophy**, EB with pyloric atresia (15%)
Nidogen (entactin)	Lamina densa	Unclear	Nidogen	Adaptor between laminin 1 and collagen IV in lamina densa; stabilizes proteins of lamina densa	
Collagen IV	Lamina densa	Unclear	Collagen	Anchors laminins in lamina densa ➔ structural support; also a component of **anchoring plaques** in dermis, which attach collagen VII to collagen I and III	Goodpasture disease, Alport syndrome
Collagen VII	Sublamina densa	Fibroblasts	Collagen	Major component of anchoring fibrils	**Dystrophic EB**, **bullous lupus, EB acquisita**
Heparan sulfate proteoglycan	Lamina densa	Fibroblasts	Proteoglycans	Contribute to matrix of and give an overall **negative charge** (**creating a permeability barrier**) to the basement membrane	

- ◆ Mononuclear phagocytes – discussed on p. 23
- ◆ Mast cells – discussed on p. 23
- ◆ Glomus cells – specialized smooth muscle cells derived from **Sucquet-Hoyer canals**, which allow for blood **shunting** from arterioles to venules (bypassing capillaries); found mainly in the **palms/soles**
  - ➔ Overproduction ➔ glomus tumor (favors acral sites because of ↑glomus cell density)
- ◆ Dermal dendritic cells – bone marrow-derived APC that resides within dermis; **highly phagocytic**

- ○ Extracellular matrix (ECM)
  - ◆ Provides structure and support to the dermis; essential for water retention and for signal transduction
  - ◆ Synthesized by dermal fibroblasts
  - ◆ Composed of collagens, elastin, fibrillins, fibulins, integrins, laminins, glycoproteins, and proteoglycans
    - ➔ Collagens are **triple helices** formed by amino acid chains where every third residue is **glycine (Gly-X-Y),** with a high likelihood of **proline** and **hydroxyproline**/ **hydroxylysine** in the X and Y positions, respectively
      - ◈ Accounts for **75%** of dry weight of the skin; #1 component of the dermis
      - ◈ **Collagen I is the primary collagen** (85%) of the ECM; type III (10%; important and prevalent in **blood vessels**, fetal skin, GI tract, new scars, and keloids) and V are also present
      - ◈ **Lysyl hydroxylase** and proline hydroxylase catalyze crosslinking of collagen; **vitamin C-dependent process** (deficiency ➔ scurvy)
      - ◈ Defects in collagen and/or collagen cross-linking result in most forms of Ehlers-Danlos syndrome: ***COL1A1/2*** (EDS arthrochalasia type, and osteogenesis imperfecta); ***COL3A1*** (EDS vascular type); ***COL5A1/2*** (classical EDS); Lysyl hydroxylase/***PLOD1*** gene (EDS kyphoscoliosis type)
      - ◈ Matrix metalloproteinases degrade collagen
      - ◈ Retinoids ➔ ↑collagen production
      - ◈ Corticosteroids and UV ➔ ↓collagen production
    - ➔ Elastic fibers provide resilience from stretching and modulate TGF-β and BMP signaling

Table 1-3. Protein Components of the Epidermis (Including Nonepidermal Keratins)

Protein	Site of Synthesis	Function	Disease State
Keratin 1	Suprabasal keratinocytes (produced in spinous layer)	Primary keratinocyte cytoskeleton	Epidermolytic ichthyosis (preferred new name for EHK), epidermolytic and nonepidermolytic (Unna-Thost) PPK, ichthyosis hystrix of Curth-Macklin*
Keratin 2	Granular layer		Superficial epidermolytic ichthyosis (Siemens)
Keratin 3	Cornea		Meesmann's corneal dystrophy
Keratin 4	Mucosal epithelium		White sponge nevus
Keratin 5	Basal keratinocytes		EBS, Dowling-Degos disease*
Keratin 6a	Outer root sheath of hair		Pachyonychia congenita I*
Keratin 6b	Nail bed epithelium		Pachyonychia congenita II
Keratin 9	Palmoplantar suprabasal keratinocytes		Vorner (epidermolytic) PPK
Keratin 10	Suprabasal keratinocytes (produced in spinous layer)		Epidermolytic ichthyosis*
Keratin 11	Granular layer		
Keratin 12	Cornea		Meesmann's corneal dystrophy
Keratin 13	Mucosal epithelium		White sponge nevus
Keratin 14	Basal keratinocytes		EBS, Naegeli-Franceschetti-Jadassohn syndrome, dermatopathia pigmentosa reticularis
Keratin 16	Outer root sheath of hair		Pachyonychia congenita I*
Keratin 17	Nail bed epithelium		Pachyonychia congenita II, steatocystoma multiplex
Keratin 19	Stem cells of basal layer		
Keratin 71, 73, 74	Hair inner root sheath		Wooly hair
Keratin 32, 35, 82, 85	Hair cuticle		
Keratin 17, 33, 34, 36, 37, 75, 81	Hair medulla		Pseudofolliculitis barbae
Keratins 31–38, 81, 83, 85, 86	Hair cortex		Monilethrix (*KRT81, KRT83, KRT86* most commonly; also *DSG4*)
Filaggrin/profilaggrin	Granular layer	Aggregates keratin, flattening granular layer cells. Degraded in the stratum corneum into **urocanic acid** and pyrrolidone carboxylic acid, which **help block/absorb UV radiation**. Urocanic acid is also a component of **natural moisturization factor** – helps keep stratum corneum hydrated/moist	Ichthyosis vulgaris, atopic dermatitis
Loricrin	Granular layer	**Most abundant component of cornified cell envelope**. Cross-linked to involucrin by transglutaminase 1**.	Vohwinkel syndrome with ichthyosis (NO deafness) Decreased in psoriasis
Involucrin	Granular layer	Component of cornified cell envelope. Proteins are cross-linked together by transglutaminase 1 ➔ strong border	Increased in psoriasis

**In psoriasis and other hyperproliferative states, keratin 6 and 16 are upregulated and keratin 1 and 10 are downregulated*
***Transglutaminase 1 mutations ➔ lamellar ichthyosis and NBCIE*

- Account for 4% of dry skin weight
- **90% elastin** (core) and **10% fibrillin** (surrounds elastin); elastin contains high levels of **desmosine** and **isodesmosine ➔** these crosslink with fibrillin via **lysyl oxidase (copper necessary for function)**
- Notable defects in elastic tissue: ***Fibrillin 1*** mutation (Marfan's syndrome); ***Fibrillin 2*** mutation (Congenital contractural arachnodactyly); ***Fibulin 5*** (Cutis laxa; gene defect results in decreased desmosine); ***LEMD3*** mutation (Buschke-Ollendorf syndrome; defect results in increased desmosine); ***ABCC6*** mutation (Pseudoxanthoma elasticum; mutation results in fragmentation and calcification of elastic fibers)
- **Elaunin** fibers run horizontal/parallel in reticular dermis and **oxytalan** fibers run vertical/perpendicular to DEJ in papillary dermis; **mnemonic: "stand** (= vertical) **up**-high (= high in dermis) with **OXY**gen (= OXYtalan)"
- UV radiation ➔ damage of elastic fibers

- All aforementioned fibers are set in a matrix of proteoglycans and glycosaminoglycans (**GAGs**) that **retain large quantities of water** (up to 1000× their volume!) = ground substance
  - ➔ Most important GAGs = **hyaluronic acid**, chondroitin sulfate, dermatan sulfate, and heparan sulfate
  - ➔ GAGs are broken down by lysosomal hydrolases
- Cutaneous vasculature
  - Cutaneous vasculature important for metabolic support of the skin and maintenance of body temperature
  - Two vascular plexuses: superficial (➔ vessels of the reticular dermis) and deep (➔ follicles, glands)
  - **VEGF** is the primary mediator of **vasculogenesis**
    - ➔ ↑VEGF: most cancers, psoriasis, POEMS syndrome, and other diseases with increased vasculature
  - Lymphatic vessels collect fluid and proteins from interstitium and direct it into the lymph circulation
  - **Prox1**, **Podoplanin (D2-40)**, **LYVE-1**, and VEGFR-3 are lymphatic vessel markers
- Cutaneous neurology
  - Nerves of the skin are responsible for detecting touch/pressure, pain, itch, and other sensations
  - Cutaneous sensory nerves are divided into free nerve endings and corpuscular nerve endings (round/globular collection of neural and other cells)
    - ➔ Free nerve endings
      - **Itch and pain: A-δ** (larger; myelinated) and **C-polymodal nociceptor** afferent fibers (smaller; unmyelinated)
      - End in the epidermis/superficial dermis
    - ➔ Specialized nerve receptors (corpuscular nerve endings)
      - Krause end bulbs: **genitalia**, perianal region, and vermillion lips; mnemonic "Krazy **Krause ends** on erotic areas"
      - Meissner's corpuscle: superficial (dermal papillae) mechanoreceptor of **digits**; fast adapting; suited for pressure/**light touch**
      - Pacinian corpuscle: deep (deep dermis/fat) mechanoreceptor of palmoplantar skin, nipples, and genital region; fast adapting; suited for **vibration** and deeper pressure
      - Merkel nerve ending: superficial (basal epidermis) mechanoreceptor most concentrated in fingertips, lips, and external genitalia; slow adapting; suited for pressure/touch
      - Ruffini corpuscle: deep (fat) mechanoreceptor most concentrated around fingernails; slow adapting; suited for **sustained pressure**
  - Innervation of cutaneous appendages:
    - ➔ Adrenergic control: **vascular smooth muscle**, **apocrine** glands, and arrector pili contraction
    - ➔ Cholinergic control: **eccrine** glands
- Adnexal structures
  - Eccrine glands
    - Secretory exocrine gland primarily responsible for **thermoregulation** and waste excretion
    - Found on all cutaneous surfaces except: external auditory canal, lips, glans penis, clitoris, and labia minora
    - Highest concentration = palms and soles
    - Controlled by hypothalamus; innervated by **postganglionic sympathetic fibers**, which synapse with **muscarinic acetylcholine receptors** on the glands
    - Isotonic sweat secreted in secretory gland ➔ NaCl reabsorbed in duct ➔ **hypotonic sweat** is delivered to surface
      - ➔ ↑rate of sweating ➔ more isotonic solution (less time to reabsorb in duct)
      - ➔ Maximal rate of sweating ~ 3 L/hr
      - ➔ Merocrine secretion
    - Components (deep to superficial): secretory coil (deep dermis), intradermal/straight duct (eosinophilic cuticle seen on histology), and acrosyringium (intraepidermal portion; spiral duct that opens onto the skin surface)
    - Stains for S100, keratin, and CEA
  - Apocrine glands
    - Secretory exocrine glands with unclear function in humans, though in animals they mediate sexual attraction through pheromone release
      - ➔ Activity begins around puberty
    - Located primarily in **anogenital skin, axillae**, external ear canal, vermillion border, **periumbilical region**, eyelid margin, and breast
    - Empty into follicular infundibulum (above sebaceous duct)
    - Secretory control unclear ➔ glands noninnervated, but do have **β-adrenergic receptors**, which are likely **stimulated by circulating catecholamines**
    - Secretory products released through **decapitation secretion**: cholesterol and cholesterol esters, triglycerides, squalene, and fatty acids
      - ➔ **Lipofuscin** = pigmented mixture of lipids and proteins ➔ responsible for yellow-brown color of **chromhidrosis**
    - Initially odorless secretions ➔ later modified by surface bacteria ➔ results in body odor
    - Ectopic or modified apocrine glands: **mammary glands**, ceruminous glands of the external auditory canal, and **Moll's gland of the eyelids**
      - ➔ These empty directly to the surface
  - Sebaceous glands
    - Secretory exocrine glands found primarily on the scalp, face, and upper anterior trunk ("seborrheic areas")
      - ➔ NOT on the palms/soles