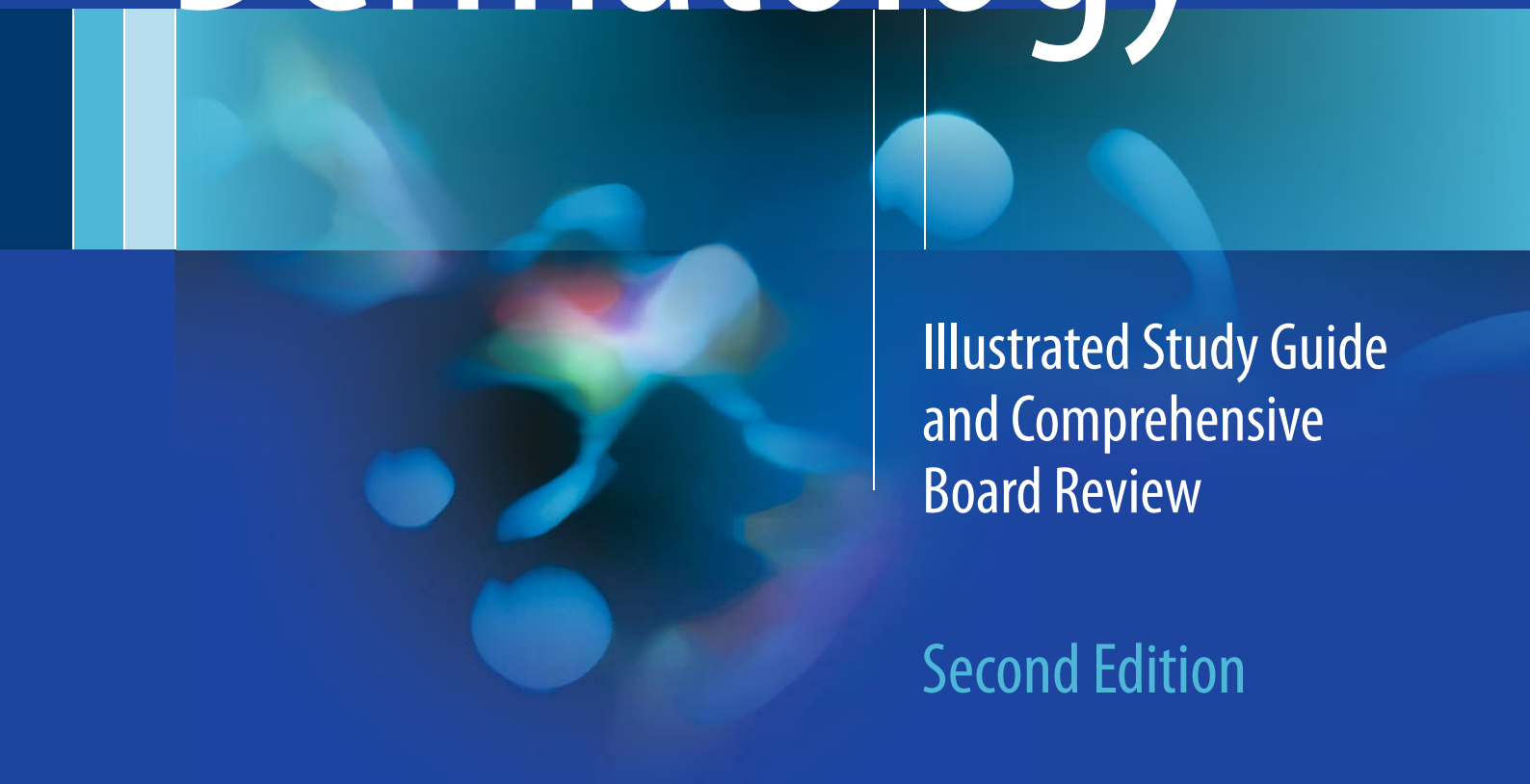
Sima Jain

Dermatology



Illustrated Study Guide and Comprehensive Board Review

Second Edition

Springer

Dermatology

Sima Jain
Author and Editor

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Illustrated Study Guide and Comprehensive Board Review

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To my parents, Manohar and Usha, to whom I owe so much. Thank you for teaching me the importance of hard work, for giving me strength during times of adversity and for your unconditional love and support.

To my incredible husband, Milind, for your love, patience, humor and ability to always keep me balanced. You are my everything and thank you for always believing in me.

To my beautiful children, Sahana, Sahil and Alina. You are the light of my life… my sunshine, my strength, and my treasure. I love you with all of my heart.

Foreword

I've known Dr. Sima Jain since 2003, when she visited the dermatology program at the University of Illinois at Chicago for an away elective as a medical student. Although our time together was relatively brief, Sima and I developed a connection around teaching, something which continues to drive our professional interests and contributions to the specialty. I appreciated Sima to have an indelible enthusiasm for sharing knowledge, and it seemed inevitable to me that she would create a ragingly popular review book to help residents and students learn dermatology.

In this second edition of *Dermatology: Illustrated Study Guide and Comprehensive Board Review*, Dr. Jain offers significant enhancements that will augment the dermatology resident's learning experience. The book is replete with high yield text and well-formatted tables that now also includes over 800 clinical and histological images. This is as comprehensive and accurate of a study guide as I have come across over the years, including those available to me during my own training. The chapters on Pediatric Dermatology and Pathology deserve special mention in this regard.

Dr. Jain has left no stone unturned in her effort to provide dermatology residents a high yield resource to help condense a seemingly endless amount of information. The second edition will no doubt have a permanent position in resident book bags with easy retrieval for individual study and for group fodder sessions. In my role as a program director and an educator, my interest is in helping residents apply book knowledge to routine practice, with the goal of achieving competence in dermatology and providing high quality care to patients. I believe the residents who will get the most out of Dr. Jain's book will engage in regular and intensive reading of textbooks and journal articles in dermatology, and will supplement their study with this high yield summary to effectively refresh and reinforce knowledge.

My hat goes off to Dr. Jain for supporting the training of numerous resident cohorts, both past and for years to come through providing an excellent review resource.

Respectfully,
Amit Garg, MD
Professor and Founding Chair
Department of Dermatology
Hofstra Northwell School of Medicine

Preface

I am flattered and humbled that the first edition of the book has been so well received and it is with this in mind that I have tried to make this new edition even more helpful and practical than the first edition. In this updated version I have added more than 300 images and I have tried to include any omissions, correct any errors and include any new treatments since the first edition was released.

As I wrote in the previous preface, the idea of writing this book arose when I was studying for my dermatology board examination. At the time, I was unable to find a comprehensive study guide containing both high yield text and corresponding clinical images. I ended up using multiple textbooks, atlases, and study guides to review for the exam, which proved to be quite challenging and time consuming. My goal was to create a practical review book with concise yet thorough text along with high-yield corresponding clinical images. Important concepts throughout the book are either underlined or highlighted in the text and tables are placed in as many chapters as possible for easy reading.

Another unique aspect of this book is the discussion of life after the dermatology board exam. Medical training, as it exists today, does not emphasize important post-residency concepts such as understanding the elements of a physician employment contract, proper coding and documentation, and choosing between different types of malpractice insurance. Most of us have had to learn this on our own without a specific resource to guide us, which is why I have included this information in the last chapter.

Ultimately, this book is intended as a board preparatory guide for dermatologists who are preparing for initial certification or recertification. Moreover, the topics addressed in this book are highly relevant to daily practice and may serve as an excellent reference for physicians in both dermatology and primary care. In summary, it is hoped that this will fill a real need for all dermatologists as an essential board review book and provide an indispensable resource for all physicians.

Acknowledgements

I would like to extend my sincerest thanks and appreciation to my developmental editor, Michael D. Sova, for being immensely patient with me throughout this process and for his tireless efforts to perfect this second edition into what I had envisioned, no matter how much work that entailed or how many hours we had to talk over the phone. Thank you for your constant attention to detail and your perseverance. And thank you to my wonderful editor, Rebekah Amos, for your unwavering support and guidance. You both have been incredible to work with.

I would also like to thank Dr. Paul Getz for his generous contribution of numerous photographs to this book and the first edition.

Lastly, I want to thank the dermatology residents who have helped update this book with their comments and suggestions, namely Euphemia Mu, Alex Maley, Vikas Patel, Aly Barland, Ryan Fischer and Anand Rajpara.

Author and Editor

Sima Jain is a board-certified dermatologist who currently practices in Orlando, Florida. She completed her undergraduate studies at Johns Hopkins University in Baltimore, Maryland and received her medical degree at the University of Florida in Gainesville, Florida. She then moved to Chicago, Illinois where she completed her dermatology residency at the University of Illinois at Chicago Medical Center, where she was chosen to be chief resident during her final year. During her last year she was awarded the annual Resident Teaching Award by the prestigious medical honor society, Alpha Omega Alpha, for providing excellent clinical teaching to residents and medical students. Since completing her training, she has continued to receive awards for excellence in patient care and has stayed involved in medical education. She is currently an Assistant Clinical Professor of Dermatology at the University of Florida, has authored multiple articles in peer-reviewed journals, and is the sole author of the first edition of the book, *Dermatology: Illustrated Study Guide and Comprehensive Board Review*, which was published in 2012 and quickly became the best-selling dermatology board review book in the country. In her free time, she enjoys teaching, reading, and spending time with her husband and three beautiful children.

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Basic Science and Immunology

Contents

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1.1 EMBRYOLOGY

Table 1-1: Development of Cutaneous Structures

	Gestational Age (Estimated)	Epidermal Development	Hair, Nail and Gland Development	Dermal/Subcutaneous Development
1st trimester	~3–4 weeks	Single layer of ectoderm		
	~6 weeks	Outer flattened periderm and inner, cuboidal germinal (basal) layer ← Germinal layer produces entire epidermis		Germinal layer in contact w/ underlying mesenchyme
	~7 weeks	Fetal **basement membrane**	Tooth primordia	
	~8–12 weeks	Epidermal stratification begins ~8 weeks ← Completed by 2nd trimester Appearance of → **Melanocytes** → **Langerhans cells** → **Merkel cells**		Dermal-subcutaneous boundary distinct
	~9–12 weeks	Appearance of anchoring filaments/hemidesmosomes	Hair follicle and nail primordia seen	
2nd trimester	~12 weeks	**Formation of dermo-epidermal junction** (DEJ)	**Nail bed starts to keratinize, proximal nail fold forms**	Type III collagen appears
	~12–14 weeks	Parallel ectodermal ridges (fingerprints)	Eccrine and sebaceous gland primordia seen	Fibroblasts actively synthesizing collagen and elastin in dermis
	~12–24 weeks	Melanin production (12–16 wks), melanosome transfer (20 wks)	Hair follicles differentiate during 2nd trimester (7 concentric layers present)	
	~15–20 weeks	Periderm is shed (periderm is part of vernix caseosa) [20–21 weeks]	Follicular keratinization, **nail plate completely covers nail bed**	Papillary/reticular boundary distinct, dermal ridges appear
	~22 weeks		Trunk eccrine gland primordia	Elastic fiber seen
	~22–24 weeks	**Mature epidermis complete** (w/ interfollicular **keratinization**)		Adipocytes appear under dermis

1.2 EPIDERMIS

- Functions as a mechanical and antimicrobial barrier; protects against water loss and provides immunological protection; thickness varies from 0.04 mm (eyelid skin) to 1.5 mm (palmoplantar skin)
- Divided into four layers (each with characteristic cell shape and intracellular proteins): stratum corneum, stratum granulosum, stratum spinosum, and stratum basale (germinativum); of note, stratum lucidum is additional layer in palmoplantar skin

Keratinocytes

- **Ectodermal derivation**; keratinocytes comprise approximately 80–85% of epidermal cells
- Total epidermal turnover time: average 45–60 days (30–50 days from stratum basale to stratum corneum and approximately 14 days from stratum corneum to desquamation)
- Epidermal self-renewal maintained via stem cells in basal layer of interfollicular epithelium and the bulge region of hair follicles (latter location only activated with epidermal injury)
- Keratinocytes produce keratin filaments (syn: intermediate filaments or tonofilaments), which form the cell's cytoskeletal network; this provides resilience, structural integrity, along with serving as a marker for differentiation (ie. basal layer: K5/14)
  - Six different types of keratin filaments: type I/II are epithelial/hair keratins, type III-VI include desmin, vimentin, neurofilaments, nuclear lamins, and nestin
  - >50 different epithelial/hair keratins, expressed as either type I (acidic) or type II (basic), and type I/II coexpressed together as a heterodimer (i.e., K5/14)
    - Type I (acidic) epithelial keratins: K9–28, chromosome 17
    - Type I (acidic) hair keratins: K31–40 *(old nomenclature: hHa1–hHa8, Ka35, Ka36)*
    - Type II (basic) epithelial keratins: K1–8 and K71–80, chromosome 12
    - Type II (basic) hair keratins: K81–86 (*old nomenclature: hHb1–hHb6*)

Of note, second cytoskeletal network formed by actin filaments

Table 1-2: Keratin Filament Expression Pattern

Type II	Type I	Location of expression	Associated diseases
1	10	Suprabasal keratinocytes	Epidermolytic hyperkeratosis, Unna-Thost PPK
1	9	**Palmoplantar** suprabasal keratinocytes	Vorner PPK
2 *(2e)*	10	Granular and upper spinous layer	Ichthyosis bullosa of Siemens
3	12	Cornea	Meesman corneal dystrophy
4	13	Mucosal epithelium	White sponge nevus
5	14	**Basal keratinocytes**	Dowling-Degos disease, EBS
6a	16	Outer root sheath	Pachyonychia congenita I
6b	17	**Nail bed**	Pachyonychia congenita II
8	18	Simple epithelium	Cryptogenic cirrhosis
K81 K86		Hair	Monilethrix
	19	Stem cells	

Do not confuse Dowling-Degos with Degos disease:
Dowling-Degos: AD, reticulated pigmentation over skin folds
Degos (malignant atrophic papulosis): occlusion + tissue infarction

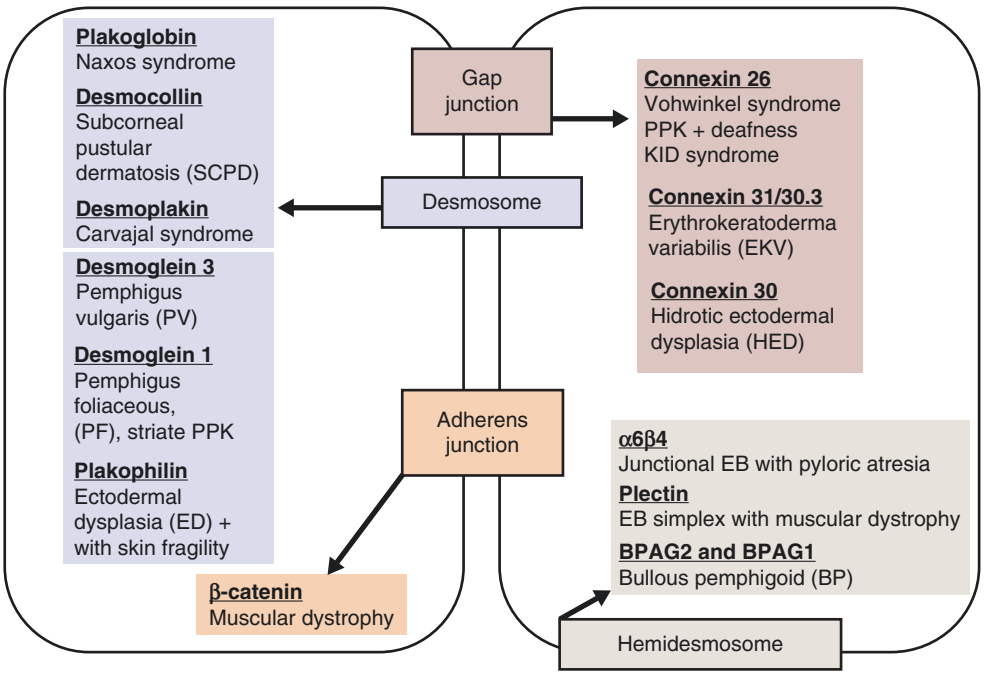
Stratum Basale (Germinativum)

- Basal layer just above basement membrane; contains keratinocytes, melanocytes, merkel cells and Langerhans cells (latter mainly in stratum spinosum)
- 10% of cells in basal layer are stem cells
- Expression of ornithine decarboxylase (ODC), which is a marker for proliferative activity
- (ODC stimulated by UVB and partially blocked by retinoic acid/corticosteroid/vitamin D_3)
- De novo expression of K5/14 occurs, forming keratin filaments which insert into both desmosomes and hemidesmosomes and form keratinocyte cytoskeleton
- Hemidesmosomes allow attachment of basal keratinocyte to basement membrane

Stratum Spinosum

Flegel's disease, Harlequin ichthyosis: ↓ lamellar granules (LG)
X-linked ichthyosis: absent steroid sulfatase in LG.
Congenital ichthyosiform erythroderma: ↑ LG but structurally abnormal

- Polyhedral-shaped cells with round nucleus and 'spiny' appearance on H&E (due to desmosomal attachments between cells); layer contains keratinocytes and Langerhans cells
- New synthesis of K1/K10; K5/14 still present (not de novo)
- Cells contain lamellar granules (syn: lamellated bodies or odland bodies): intracellular lipid-carrying granules formed w/in Golgi in upper spinous layer; contain glycoproteins and lipid precursors which are discharged into intercellular space between granular and cornified layer; forms lamellar sheets (ceramide) or 'mortar' which acts as intercellular cement for corneocytes ('bricks'), thus contributing to formation of cutaneous lipid barrier
- Types of cell junctions prominently seen in this layer and in granular layer (Figure 1.1):
  - **Desmosomes:** calcium-dependent cell-cell adhesion molecules between keratinocytes; serve as attachment sites for cytoskeleton (intermediate filaments); each desmosome made up of several proteins:
    - Transmembrane proteins: desmoglein 1/3, desmocollin 1/2 (desmosomal cadherins)
    - Desmosomal plaque proteins: plakoglobin (γ-catenin), desmoplakin 1/2, keratocalmin, desmoyokin, band 6 protein, envoplakin
  - **Adherens junctions** (zonula adherens): transmembrane classical cadherins (namely E and P) linked to actin cytoskeleton via cytoplasmic plaque proteins (α, β, γ-catenin)
  - **Tight junctions** (zonula occludens): seal intercellular space, prevent diffusion of solutes between cells and maintain cell polarity; major constituents are claudins and occludins
  - **Gap junctions**: transmembrane channels formed by six connexin monomers, allows for cytoplasmic continuity and communication between cells
- Know particular diseases associated with defects or antibodies against certain cell junction proteins (Figure 1.1)



Plakoglobin: only common protein between adherens junction and desmosome

Figure 1.1:
Skin diseases associated with cell junctions

Stratum Granulosum

Ichthyosis vulgaris: ↓ profilaggrin, ↓ KHG
Lamellar ichthyosis: ↑ profilaggrin, ↑ granular cell layer
Psoriasis: ↑ involucrin, ↓ loricrin, ↑ K6/16

- Cells with more flattened appearance; contain dense keratohyalin granules
- Granular cells start to lose their nuclei but retain dense keratin filaments
- Expression of K2 (modified from K1) and K11 (modified from K10)
- **Keratohyalin granules** (KHG): dense stellate globules which contain profilaggrin, loricrin, and involucrin (latter two function in cornified cell envelope)
  - **Filaggrin**: keratin **fil**ament **aggr**egating prote**in** in KHG; binds intermediate filaments and organizes into fibrils; initially cleaved from profilaggrin (when granular layer transformed into cornified layer) and is degraded into free amino acids
- **Cornified cell envelope** [CE] (Figure 1.2): highly cross-linked lipid-rich flexible structure enveloping corneocytes; serves as insoluble exoskeleton and rigid scaffold for internal keratin filaments; provides both mechanical and water permeability barrier
  - CE assembly begins in granular layer where several proteins cross-linked by transglutaminase into γ-glutamyl lysine isopeptide bonds → rendering CE insoluble
  - CE comprised of lipid layer and several covalently cross-linked proteins: involucrin, loricrin, filaggrin, small proline-rich proteins (SPRs), envoplakin, and serine proteinase inhibitor called skin-derived anti-leukoproteinase (SKALP)
    - **Loricrin**: major protein component of CE, appears in granular layer within KHG along with profilaggrin, cross-links with involucrin
    - **Involucrin**: substrate for transglutaminase cross-linking in granular layer; forms insoluble cell boundary; early differentiation marker and upregulated in psoriasis

Stratum Corneum

- Provides mechanical protection, impermeability and barrier to water loss
- Brick and mortar model: lipid-depleted, protein-rich corneocytes ('bricks') surrounded by extracellular lipid-rich matrix ('mortar')
- Corneocytes composed of high weight keratins embedded in filaggrin-rich matrix
- **Urocanic acid** (UCA): filaggrin degradation product found naturally in the cornified layer; absorbs/blocks UV radiation and forms natural moisturization factor (NMF) with other filaggrin degradation products (amino acids, pyrrolidone carboxylic acid); NMF allows stratum corneum to remain hydrated even in drying conditions
- Ceramide is a major lipid barrier of skin; other barrier lipids include cholesterol, cholesterol sulfate, and fatty acids

Of note, steroid sulfatase cleaves cholesterol sulfate to cholesterol; enzyme abnormal in X-linked ichthyosis

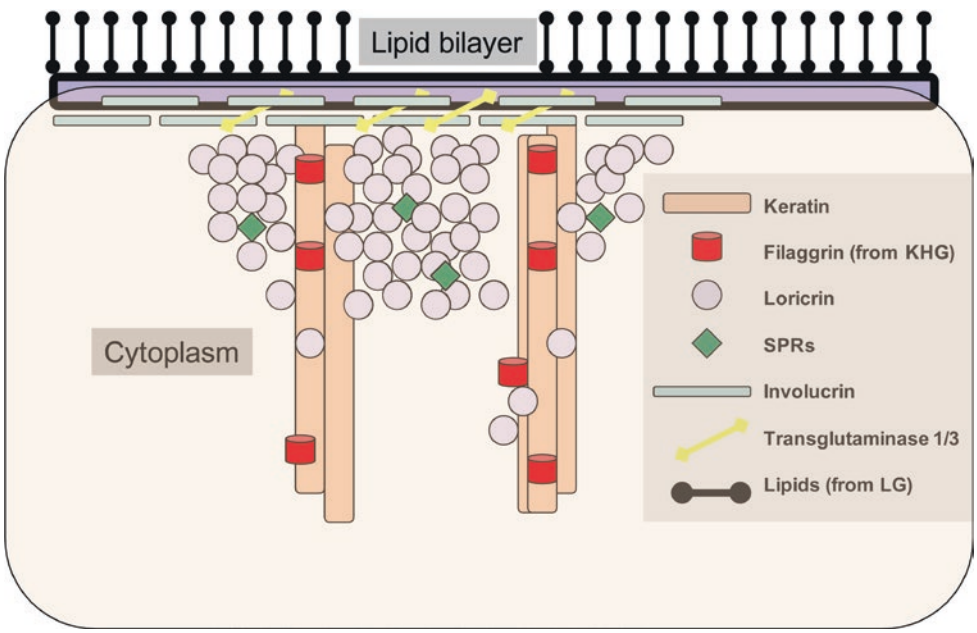


Figure 1.2: Cornified envelope (CE)

1.3 BASEMENT MEMBRANE ZONE (BMZ)

- Selective barrier between the epidermis and dermis; allows for interaction between the two areas and provides anchoring of epidermis to dermis
- Skin has 2 main BMZs: dermo-epidermal junction (major BMZ) (Figure 1.3) and dermal blood vessels
- Contains 4 distinct zones on electron microscopy (EM): inferior portion of basal keratinocyte, lamina lucida, lamina densa and sublamina densa

Be able to identify BMZ components on electron microscopy (EM) (Figure 9.7A)

Table 1-3: Macromolecules in BMZ

Layer of BMZ	Structure	Associated Macromolecules
Basal keratinocyte/ Plasma membrane	Hemidesmosome	BPAG1 (230kDa), BPAG2 (180kDa), α6β4 integrin, plectin
Lamina lucida	Anchoring filaments	Laminin, portion of BPAG2
Lamina densa	Anchoring plaque	Type IV collagen, laminins, heparan sulfate
Sublamina densa	Anchoring fibril	Type VII collagen, fibrillin, anchoring plaque (type IV collagen), type I and III collagen

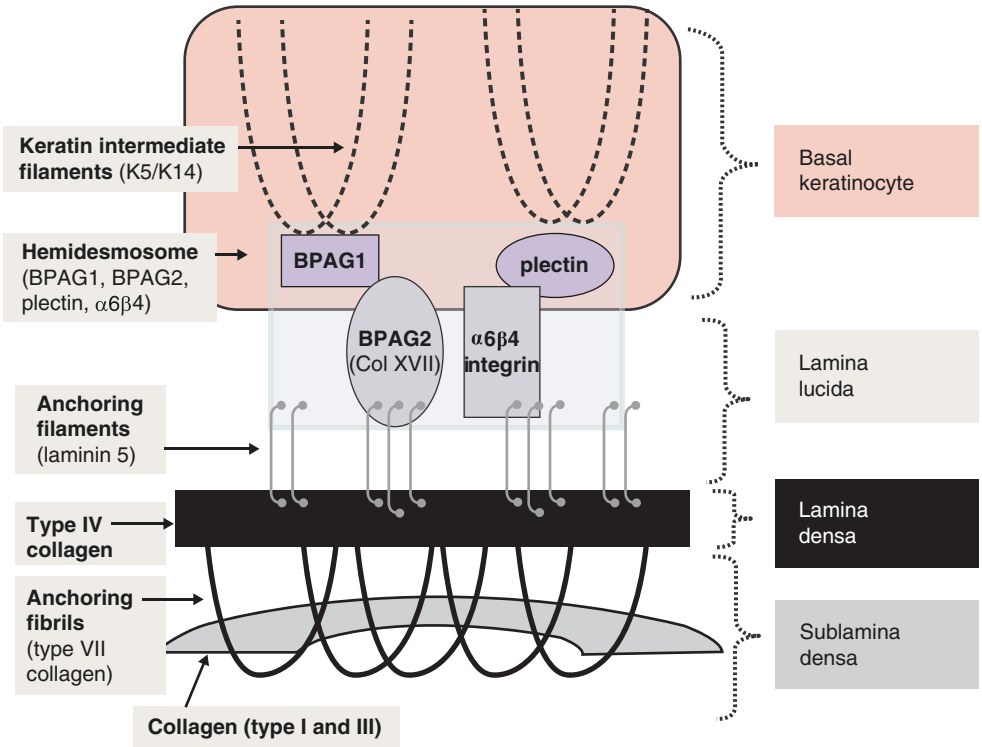


Figure 1.3:
Dermo-epidermal junction zone (DEJ)

A. INFERIOR PORTION OF BASAL KERATINOCYTE

Hemidesmosome (HD)

- Appears as thickened area interspersed along plasma membrane of basal keratinocyte; provides attachment between basal keratinocyte and extracellular matrix
- Composed of following macromolecules: BPAG1, BPAG2, integrin, and plectin
- Tonofilaments (or keratin filaments) insert into hemidesmosomes

BPAG1 (230 kDa)

- Intracellular glycoprotein in plakin family which is associated with the cytoplasmic plaque domain of hemidesmosomes; promotes adhesion of intermediate filaments with plasma membrane (likely binds or anchors filaments to HD)

BPAG2 (180kDa, Collagen XVII)

- Transmembrane (mainly extracellular) protein belonging to collagen family; interacts with BPAG1, β4 integrin, and plectin
- Divisions of protein: amino terminus (intracellular), transmembrane portion, extracellular carboxy terminus (in lamina lucida); most antibodies in bullous disorders target extracellular domain (proximal NC16A and distal carboxy terminus)
  - NC16A domain (1st extracellular segment): typically targeted by bullous pemphigoid (BP), pemphigus gestationis, linear IgA bullous dermatosis (LABD)
  - Carboxy terminus (C-terminal): cicatricial pemphigoid (CP) tends to target this portion

Three target antigens seen in CP: BPAG2, laminin-5 (epiligrin), α6β4 integrin

Integrin

- Transmembrane cell receptor consisting of two subunits (α and β); located at basal layer of epidermis and promotes both cell-cell and cell-matrix interactions
- α6β4: hemidesmosome-associated integrin; binds intermediate filaments intracellularly, laminin-5 (now called laminin-332) in lamina lucida, and HD proteins (plectin, BPAG2)

Autoantibody to β4 → CP (ocular); β4 mutation → JEB with pyloric atresia

Plectin

- Intracellular protein belonging to plakin family; associated with cytoplasmic plaque domain of hemidesmosome; links intermediate filaments to plasma membrane and cross-links HD proteins

Plectin mutation → EBS w/ muscular dystrophy

B. LAMINA LUCIDA

- Electron-lucent zone under hemidesmosome on EM; weakest link of BMZ
- Comprised of anchoring filaments (laminin-332), laminin-1, fibronectin, nidogen (entactin), uncein and portion of BPAG2

Anchoring Filaments

- Delicate filaments emanating perpendicularly from HD which stretch from plasma membrane to lamina densa; product of basal keratinocytes; smaller than anchoring fibrils
- Laminin-332: also known epiligrin (truncated laminin), laminin-5, kalinin, and nicein; glycoprotein serving as major component of anchoring filaments; major attachment factor for keratinocytes and binds α6β4 integrin at hemidesmosome

C. LAMINA DENSA

- Electron-dense zone below lamina lucida appearing as dense line with closely stippled dots on EM
- Type IV collagen: major component and characteristic collagen of BMZ; highly cross-linked sheet-like pattern provides flexibility to basement membrane
- Additional components: laminins, entactin (nidogen-1), and heparan sulfate (negatively-charged hydrophilic proteoglycan which provides selective permeability barrier)

D. SUBLAMINA DENSA

- Contains anchoring fibrils, anchoring plaques, elastic microfibrils (without elastin), and linkin

Anchoring Fibril

- Primary constituent is type VII collagen; appears larger than anchoring filaments and emanates perpendicularly down from lamina densa into papillary dermis
- Connects lamina densa to anchoring plaques (type IV collagen) in dermal matrix
- Intercalation with banded collagen fibrils of papillary dermis: forms fan-shaped clumps

Type VII collagen autoantibodies in both EB acquisita (EBA) and bullous SLE; type VII mutation in dystrophic EB (DEB)

Anchoring Plaque

- Primary component is type IV collagen; site where anchoring fibrils attach from above and fibrillar collagen (type I and III) attach from below; electron-dense oval structures seen under lamina densa on EM

Table 1-4: Diseases Associated with Epidermal/Dermal Proteins

Protein	Associated Disease
Plectin	EBS with muscular dystrophy, paraneoplastic pemphigus (PNP)
α6β4 integrin	JEB with pyloric atresia, cicatricial pemphigoid (CP) - ocular
BPAG1	Bullous pemphigoid (BP), PNP
BPAG2	NC16A → BP, linear IgA bullous dermatosis (LABD), pemphigoid gestationis Carboxy terminus → CP
Laminin-332 (5)	JEB (Herlitz), CP (↑ risk of cancer)
Type VII collagen	Dystrophic EB (mutated), EBA, bullous SLE
Plakoglobin	Naxos disease
Desmocollin 1	Subcorneal pustular dermatosis (type of IgA pemphigus)
Desmoglein 1	Striate PPK, pemphigus foliaceous, pemphigus vulgaris (mucocutaneous), bullous impetigo, staphylococcal scalded skin syndrome (SSSS), PNP
Desmoglein 3	Pemphigus vulgaris (mucosal-dominant and mucocutaneous), PNP
Desmoglein 4	Monilethrix (autosomal recessive)
Desmoplakin 1/2	Carvajal syndrome, striate PPK, skin fragility/woolly hair syndrome, PNP
Plakophilin	Ectodermal dysplasia/skin fragility syndrome
Connexin 26	KID syndrome, Vohwinkel syndrome, PPK with deafness
Connexin 30	Hidrotic ectodermal dysplasia (HED)
Connexin 30.3/31	Erythrokeratoderma variabilis (EKV)
β-catenin	Pilomatricoma (multiple may be associated with myotonic dystrophy)
Loricrin	Vohwinkel (variant), progressive symmetric erythrokeratoderma
Filaggrin/KHG	Atopic dermatitis, ichthyosis vulgaris
Transglutaminase	TG3 → dermatitis herpetiformis, TG1 → lamellar ichthyosis

1.4 MELANOCYTES, LANGERHANS, AND MERKEL CELLS

Melanocyte

- Pigment-producing dendritic cell derived from neural crest; found in skin, hair, uveal tract of eye (choroid, iris, ciliary body), leptomeninges, and inner ear (striae vascularis of cochlea)
- Survival/migration during embryogenesis depends on specific interactions such as *c-kit* activation contributing to migration and development of melanocytes and melanoblasts
- Resides in basal layer with ratio of 1 melanocyte to 10 basal keratinocytes (do not confuse with epidermal melanin unit where 1 melanocyte in contact with 36 keratinocytes)
- Melanocytes do not form junctions with keratinocytes (hence, artifactual halo on H&E)
- Function: production of melanin pigment with subsequent transfer to keratinocytes, absorption of UV radiation and protection from UV-induced mutations
- Melanin: synthesized in melanosome (specialized type of lysosome) and passes through series of stages (I to IV) before melanosome transferred to keratinocyte via phagocytosis of melanocyte tips (apocopation); melanin precursors acted upon by copper-dependent enzyme tyrosinase; two types of pigment (Figure 1.4):
  - **Pheomelanin**: red-yellow in color, synthesized in pheomelanosomes (spherical structure, microvesicular internal structure)
  - **Eumelanin**: brown or black in color, eumelanosome (oval-shaped, longitudinally oriented with lamellar internal structure)

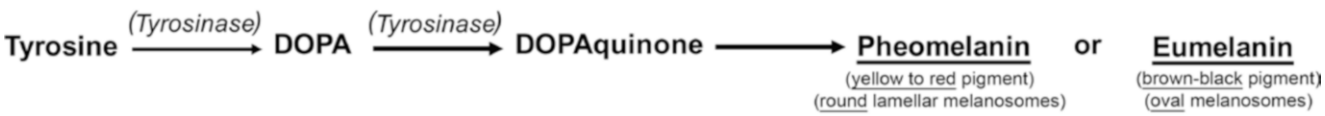


Figure 1.4: Melanin biosynthetic pathway

- Melanin stimulated by melanocyte-stimulating hormone (MSH), which is derived from larger precursor propiomelanocortin (POMC); POMC also a precursor for ACTH, which is why ↑ hyperpigmentation seen in Addison's disease
- Melanocortin-1 receptor (MC1R) controls which type of melanin is produced by melanocytes; loss of function in MC1R results in ↑ pheomelanin (red hair) and ↓ eumelanin; thus, fair skin without the more protective pigment and more prone to damage from UV radiation with subsequent ↑ risk for melanoma
- Hair melanocytes: one melanocyte to 5 keratinocytes; graying caused by gradual decrease in number of follicular melanocytes
- Chronic sun exposure results in melanocytes creating larger melanosomes
- Racial differences NOT due to differences in number of melanocytes, but rather the size, distribution and number of melanosomes (all races have SAME melanocyte density)
  - Dark-skinned: larger melanosomes, ↑ melanization, ↓ melanosome degradation, and melanosomes transferred as individual organelles
  - Light-skinned: smaller melanosomes and transferred as membrane-bound clusters (with 3–6 melanosomes)

Be able to identify EM image of Langerhans cell (Figure 9.7B)

Langerhans Cell (LC)

- Bone marrow-derived dendritic cell with monocyte-macrophage lineage found in stratum spinosum; constitutes 3–5% of cells of epidermis; contains actin and vimentin
- Critical in recognizing and presenting foreign antigens to specific T lymphocytes
- Connected to keratinocytes via E-cadherin receptors
- On EM, Langerhans cell with folded nucleus and distinct intracytoplasmic organelles (Birbeck granules: striated appearance with either rod-shape and/or tennis-racquet-shape)
- Exposure to UV radiation causes depletion of LCs and decreases ability to present antigen

Langerhans cell histiocytosis:
Letterer-Siwe – acute disseminated
Eosinophilic granuloma – bone (cranium)
Hand-Schuller-Christian – diabetes insipidus, exophthalmos, bone lesions
Hashimoto-Pritzker – self-healing

Merkel Cell

- Ectoderm-derived cell (less likely neural crest-derived) functioning as mechanoreceptor (slow adapting, type I); found among basal keratinocytes
- Found in areas with high tactile sensitivity (lips, fingers, ORS of hair follicle, oral mucosa)
- EM shows microvilli at cell surface with dense core granules, lobulated nucleus, and intermediate filaments assuming whorled arrangement near nucleus (dot-like pattern)
- Markers: cytokeratin (CK) 20 (specific for merkel cells in skin), also contain CK8, 18, and 19
- Contain battery of neuropeptides and neurotransmitter-like substances:
  - Neuron-specific enolase (NSE), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), chromogranin A, synaptophysin, and met-enkephalin

Know neuropeptides found within merkel cells

1.5 DERMIS

- Mesoderm-derived components
- Divided into superficial papillary dermis and deep reticular dermis (latter with larger collagen bundles and mature branching elastic fibers)

Collagen

- Family of fibrous proteins, 20+ genetically distinct types identified; provides structural stability and accounts for 70–80% dry weight of dermis; major dermal constituent
- Composed of 3 chains combined into a triple helix configuration; contains Gly-x-y repeats (glycine always 3rd residue, x frequently proline, y often hydroxylysine or hydroxyproline)
- Collagen degraded by interstitial collagenases (metalloproteinases or MMPs)
- Collagen synthesis stimulated by: retinoic acid
- Collagen synthesis inhibited by: IL-1 (↑ MMP expression), glucocorticoids, IFNγ, TNFα, D-penicillamine, UV irradiation

Glycine is most abundant amino acid in collagen

Table 1-5: Types of Collagen

Collagen	Location	Associated Diseases
I	Dermis, bone, ligament/tendon	Ehers-Danlos syndrome, arthrochalasia (EDS type VII), osteogenesis imperfecta
II	Vitreous humor, cartilage	
III	Fetal skin, blood vessels	EDS vascular (type IV)
IV	Basement membrane	Alport and Goodpasture syndrome
V	Ubiquitous	EDS classic (type I/II)
VI	Aorta, placenta	Congenital muscular dystrophy
VII	Anchoring fibrils (BMZ)	Dystrophic EB (DEB)
VIII	Cornea (Descemet's membrane)	Corneal dystrophy
IX–XII	Cartilage	–
XV–XVI	Placenta	–
XVII (BPAG2)	Hemidesmosome	Junctional EB (JEB)

Descemet's membrane: basement membrane between corneal proper substance and endothelial layer

Marfan's → **fibrillin 1** mutation, congenital contractural arachnodactyly → **fibrillin 2**
Buschke-Ollendorf → ↑ **desmosine**, anetoderma → ↓ **desmosine**

Elastic Tissue

- 4% dry weight; provides elasticitiy to skin (able to return to normal shape after deformation)
- Continuous network spanning from lamina densa of DEJ throughout dermis
  - **Oxytalan fibers**: thin fibers running perpendicular to skin surface in papillary dermis
  - **Eulanin fibers** – thicker fibers parallel to skin surface in reticular dermis
- Elastic tissue is an aggregate of two components: core of elastin (amorphous protein) surrounded by protein filaments (fibrillin)
- Desmosine and isodesmosine unique to elastic fibers; lysyl oxidase (copper-dependent enzyme) necessary for formation of elastic-specific amino acids and cross-linking
- Elastic fibers damaged by UV radiation; dermal elastosis hallmark of photodamage

Ground Substance

- Amorphous gel-like material in which connective tissue fibers are embedded
- Primarily composed of proteoglycans: core protein complexed with glycosaminoglycan (GAG such as hyaluronic acid, dermatan sulfate, heparan sulfate, chondroitin sulfate)
- Function includes water absorption (may absorb up to 1,000 times its volume), shock-absorbing properties, and lubrication between collagen and elastic fibers
- Aging results in ↑ dermatan sulfate and ↓ chondroitin sulfate
- Pathological accumulation seen in acid mucopolysaccharidoses due to deficiency of lysosomal hydrolases that normally cleave GAGs

Glomus Cells

- Modified smooth muscle cells found in dermis; allows shunting of blood from arterioles to venules without going through capillaries; glomus body consists of afferent arteriole, Sucquet-Hoyer canal, efferent arteriole and nerve fibers

1.6 APPENDAGEAL GLANDS AND NERVES

A. GLANDS

Presence of eosinophilic cuticle helps distinguish eccrine duct from coil histologically

Eccrine Glands

- Most important function is to regulate body temperature through evaporative heat loss
- Composed of three sections:
  - **Acrosyringium**: intraepidermal spiral duct opening to surface of skin
  - **Straight duct**: within dermis and consisting of double layer cuboidal epithelium lined by eosinophilic cuticle on luminal side
  - **Secretory eccrine coil**: within deep dermis/subcutaneous fat and consists of 2 different cells (glycogen-rich, pale cells and smaller darker cells) which appear to fit together in one layer, outer portion contains myoepithelial cells
- Positive for S100, keratin, and carcinoembryonic antigen (CEA)
- Found everywhere except: clitoris, glans penis, labia minora, external auditory canal, and lips
- Eccrine glands possess cholinergic innervation (acetylcholine) but paradoxically derived from sympathetic outflow (which typically uses norepinephrine, not acetylcholine), thus functionally cholinergic but anatomically sympathetic; merocrine secretion

Apocrine Glands

- Generally confined to axillae, breast (mammary gland), anogenital region, external auditory canal (ceruminous gland) and eyelids (Moll's gland)
- Secretion via decapitation (portion of cell pinched off and enters lumen)
- Responds mainly to sympathetic adrenergic stimuli

Sebaceous Glands

- Formed initially as outgrowth from upper portion of hair follicle; contains lobules of pale-staining cells characterized by lipid vacuoles; holocrine secretion with distention of sebocytes (filled with lipid vacuoles) until shed into lumen
- Found throughout skin except palms and soles
- Always associated with follicles except following locations ('free' sebaeceous glands):
  - **Gland of Zeis** → found on superficial eyelid margin (near Moll's gland)
  - **Meibomian gland** → tarsal plate of eyelids (behind Moll's gland)
  - **Montogomery tubercle** → nipple and areola
  - **Tyson's gland** → external fold of prepuce (genitalia)
  - **Fordyce spot** → vermilion border of the lips and buccal mucosa
- Gland under adrenergic hormonal control; enlargement at puberty due to ↑ androgens
- Lipid composition of sebum: 57% triglycerides, 25% wax esters, 15% squalene, <3% cholesterol and cholesterol esters

B. NERVES

- Sensory receptors divided into corpuscular (which contains non-nervous components) and free nerve endings; positive for S100 and contains neurofilaments
- Two main types of corpuscular endings: nonencapsulated (merkel cells) and encapsulated (Meissner's and Pacinian corpuscles)
- Pain detected by nociceptors via either Aδ-type fibers (large) or C-type fiber

Non-Encapsulated Endings

- **Free nerve endings**: rapidly adapting receptors; majority consist of non-myelinated C-type fibers and some myelinated Aδ-type fibers; terminal endings within epidermis and papillary dermis; mainly detects touch, pressure and pain
- **Merkel cells**: found in basal layer and makes close contact with sensory nerve terminal (Merkel disc), detects touch

Encapsulated Endings

- Vater-Pacini (Pacinian) corpuscle
  - Rapidly adapting mechanoreceptor resembling an onion; found in deep dermis/subcutis
  - Detects deep pressure and vibration; increased concentration in palms/soles, nipples, anogenital region
- Meissner's corpuscle
  - Elongated mechanoreceptor detecting light touch (resembles pine cone); located just below DEJ (dermal papillae) and highest density in palmoplantar skin
- Ruffini corpuscle
  - Thin, encapsulated, fluid-filled slow adapting receptor; found in deep dermis and detects continuous pressure
- Mucocutaneous end organs (Krause end bulbs)
  - Mucocutaneous receptors found on vermilion lip, perianal region, glans penis, clitoris and labia minora

1.7 HAIR AND NAILS

Hair

- Hair is derived from ectoderm, but dermal papilla is of mesoderm-derivation
- Hair follicle is positioned at an angle; base of follicle typically within the subcutaneous fat
- Longitudinal anatomy (Figure 1.5A):
  - **Infundibulum:** upper portion of follicle extending from surface of epidermis to opening of sebaceous gland
  - **Isthmus**: middle portion extending from opening of sebaceous gland duct to insertion of arrector pili muscle (bulge), lined by outer root sheath (ORS), no inner root sheath (IRS)
  - **Inferior segment or lower hair follicle:** extending from base of isthmus to hair bulb; consists of matrix cells and envelops dermal papilla; lined by IRS; ORS present but not keratinized; widest diameter termed critical line of Auber (below this is where bulk of mitotic activity occurs); melanocytes in bulb provide melanosomes for hair color
- Cross-sectional anatomy (Figure 1.5B) from outer to inner layer:
  - Glassy membrane → ORS → Henle's layer (IRS) → Huxley's layer (IRS) → cuticle (IRS) → hair shaft cuticle → cortex → medulla

Know layers in order

- Important sites:
  - **ORS**: extends entire length of hair follicle; undergoes trichilemmal keratinization (no keratohyalin granules) in isthmus but changes to normal epidermal keratinization (with KHG) in infundibulum; ORS basal layer contiguous with keratinizing epidermal cells
  - **IRS**: cuticle of IRS interlocked with cuticle of hair shaft; IRS is present until bulge area, at which point it disintegrates; contains KHG in cytoplasm
  - **Cortex**: contains majority of hair keratins; **cuticle** maintains integrity of hair fibers
  - **Bulge**: thickened area of follicle wall, contains stem cells; insertion site of arrector pili
  - **Dermal papilla**: collection of mesenchymal cells which protrudes into hair bulb
- Different hair cycles (not synchronous): anagen → catagen → telogen
  - **Anagen:** hair growth phase, duration of phase determines length of hair, duration 2-6 years on scalp; 85% of hairs in this cycle at any one time
  - **Catagen**: transitional phase (regression); bulb regresses and IRS lost, 2-4 week duration on scalp; 2% hairs in this cycle
  - **Telogen**: resting phase, proximal hair terminal is club-shaped instead of bulb-shaped, duration of cycle approximately 3 months in scalp; 15% of hairs in this cycle; dermal papilla located higher up in dermis during telogen

Telogen: resting or '**t**ired' phase

- Growth: 0.4 mm/day, 1.2 cm/month
- Average number of hairs on scalp: 100,000 (new follicles cannot develop in adult skin); 100 hairs normally lost each day
- Curly versus straight hair depends on shape of follicle (round follicle results in straight hair, oval follicle in curly hair)
- Proteins containing sulfur impart stability in keratins within the hair shaft (disulfide bonds)
- Melanocytes found in matrix area of follicle and pigment production coupled with anagen phase; no melanin formation in telogen and catagen phase

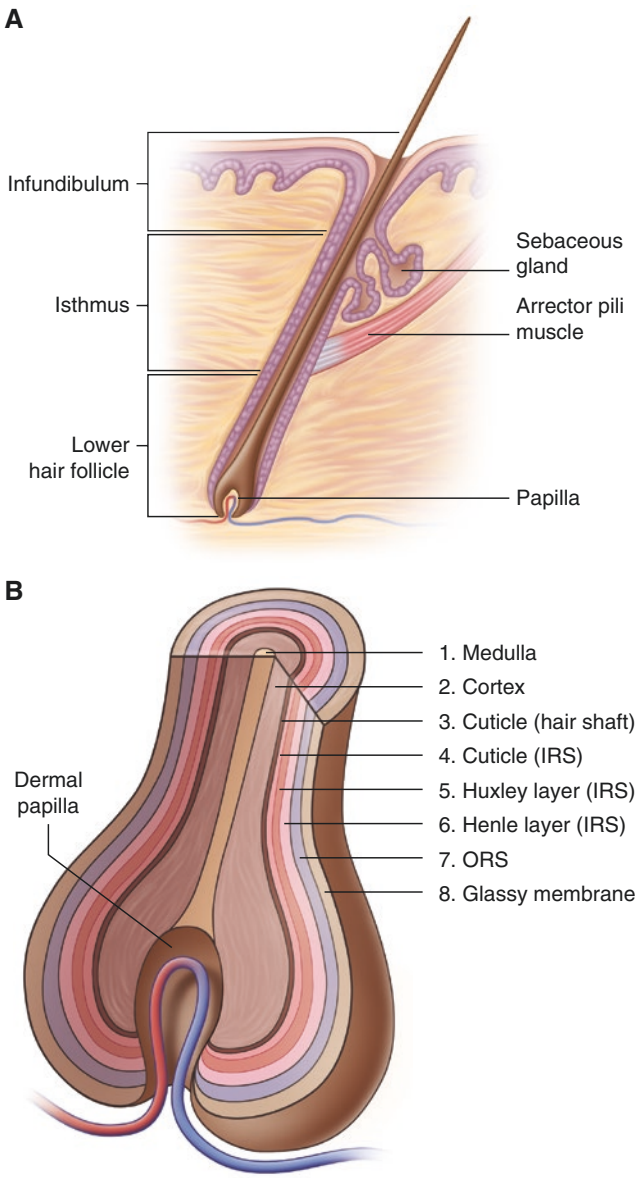


Figure 1.5: **A: Longitudinal section of hair follicle, B: Cross-section of hair follicle**

Nails *(Figure 1.6, Figure 1.7)*

- Nail plate
  - Consists of fully cornified cells (onychocytes); created by the nail matrix epithelium
  - Proximal nail matrix synthesizes the dorsal aspect of nail plate; distal nail matrix creates the ventral surface of the nail plate
  - Pink color of nail plate due to longitudinally situated subungual capillaries
  - Nail plate has firm attachment to underlying nail bed
- Cuticle or eponychium: prevents separation of nail plate and proximal nail fold
- Nail matrix:
  - Wedge-shaped area of specialized epithelium, divided into proximal and distal portion
  - Lunula demarcates distal portion of nail matrix
  - Melanocytes found in high concentration in nail matrix (mainly seen in the distal matrix)
- Growth rate of fingernails 2-3 mm/month; toenails 1 mm/month
- Complete replacement of nail requires 6 months for fingernail and 18 months for toenail

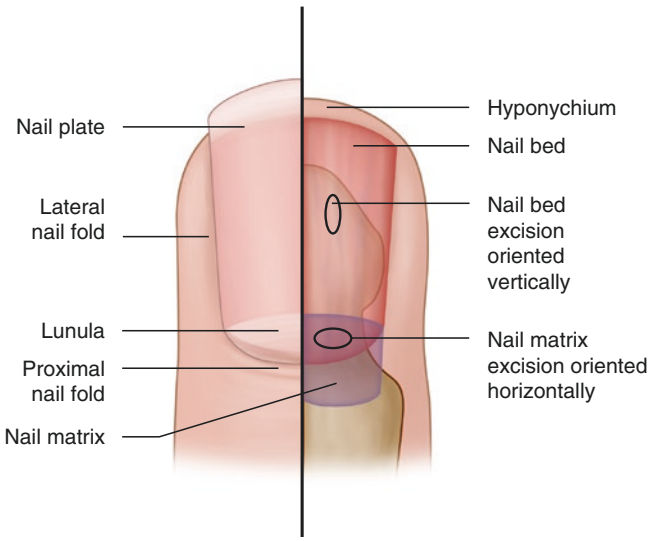


Figure 1.6: Nail anatomy

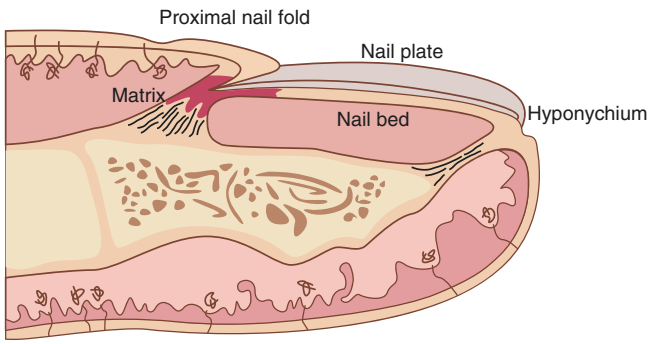


Figure 1.7:
Drawing of the nail apparatus in transverse section, showing the four structures that contribute to nail plate formation and growth: proximal nail fold, nail matrix, nail bed, and hyponychium. Note the proximity of the nail apparatus with the bone of the distal phalanx and the two ligaments that link them together.
(Reprint from Piraccini BM, (ed). Nail Disorders: A Practical Guide to Diagnosis and Management. Milan, Italy: Springer; 2014.)

1.8 WOUND HEALING AND CYTOKINES

Wound Healing

- Different overlapping events: inflammatory phase, proliferative phase and tissue remodeling; some sources cite vascular phase (hemostasis) as first phase

Table 1-6: Stages of Wound Healing

PHASE I: INFLAMMATION *(first 6-8 hours)* Clot formation → neutrophils/macrophages debride wound
⇒ **Platelets (main player)** Release chemotactic factors (fibrinogen, fibronectin, thrombospondin, vWF, ADP) attracting other platelets, WBCs and fibroblasts; produces **fibronectin** which acts as provisional matrix for fibroblast migration; also releases PDGF, TGFα and TGFβ
⇒ **Neutrophils** Appears first and in greater numbers than macrophages; attracted by fibrinogen, fibrin split products, leukotrienes and C5a; important in **tissue debridement and bacterial killing**
⇒ **Macrophages** Becomes predominant leukocyte as process continues; aids in tissue debridement and **critical** for wound healing as helps transition from inflammation to repair; attracted by fibrin degradation products, fibronectin, fragments of collagen, TGF-β; release growth factors which stimulate fibroblasts and extracellular matrix (ECM) production
PHASE 2: GRANULATION TISSUE FORMATION (5-7 days but may last longer) Keratinocyte re-epithelialization + granulation tissue formation + angiogenesis
⇒ **Keratinocytes (main player)** Re-epithelialization begins several h**ours** after injury; keratinocytes **leapfrog** over each other from wound edges and adnexal structures; collagenase produced and aids in migration
⇒ **Fibroblasts** Migrates to wound 48 hrs after injury, move along fibronectin matrix from initial clot; type III collagen in early wound; contraction by myofibroblasts (typically second week of healing)
⇒ **Blood vessels** Stimulation of new vessel growth via VEGF, TGF-β, thrombospondin, angiotropin, angiogenin, SPARC (secreted protein acidic and rich in cysteine)
PHASE 3: TISSUE REMODELING *(after 3rd week)* Granulation tissue becomes mature scar tissue
⇒ **Fibroblasts (main player)** Produces fibronectin, hyaluronic acid, collagen → key role in cell migration/tissue support; fibronectin for cell migration and template for collagen deposition
⇒ **Collagen** Granulation tissue initially composed of type III collagen; gradually replaced by type I collagen and scar's tensile strength increases; final strength only 70-80% preinjured skin

Scar strength: 5% at 1 week, 20% at 3 weeks, 70-80% at 1 year

1.9 IMMUNOLOGY

- Immune system divided into innate and adaptive immunity based on specificity of response and presence/lack of immunologic memory

Table 1-7: Innate and Adaptive Immune System

Innnate immunity	Adaptive Immunity
First line defense; rapid but less controlled	Delayed initial response but more specific
No memory	Memory
Nonspecific receptors (R) recognize non-self pathogens	Gene rearrangement specific for individual antigen (Ag)
Cannot bind to self antigens	Can bind to self and nonself antigens
Noncellular Components	
Antimicrobial peptides: **canthelicidins** and **defensins**	Antibodies
Cytokines (IL-1, IL-10, IL-12, IFNα, IFNβ)	Cytokines (IL-2, IL-4, IL-5, IFNγ, TGF-β)
Complement	Complement
Toll-like receptors (TLR) and nucleotide oligomerization domain (NOD) receptors: recognize pathogen-associated molecular pattern (PAMPs)	
Cellular Component	
Macrophages, neutrophils, NK cells, mast cells, eosinophils	T cells, B cells and Langerhans cells

A. NON-CELLULAR COMPONENT

Cytokines *(Table 1-8)*

- Cytokines are small proteins secreted by cells that modulate functional properties of the cytokine producing cell or other local/distant cells (autocrine, paracrine or endocrine manner); plays crucial role in intercellular communication and affects proliferation and differentiation of cells; vast majority of cytokines produced by T cells
- Cytokines classified as interleukins, lymphokines or chemokines based on their function and cellular source; chemokine is a specific class of cytokines with ability to stimulate leukocyte mobility (chemoattraction) and direct migration (chemotaxis)
- Keratinocytes: major source of cytokines in skin, including TNFα, IL-1, IL-6, IL-7, IL-8, IL-10, IL-18

Toll-Like Receptors (TLR) *(Table 1-9)*

- Family of receptors recognizing conserved patterns in microorganisms (PAMP on surface of pathogen); each TLR has multiple leucine-rich repeats and binds multiple PAMPs
- TLRs primarily expressed in immune cells and serve as first line defense; activation of TLR signaling induces expression of proinflammatory cytokines, chemokines, and plays role in adaptive immunity (dendritic cells present pathogen-derived antigen from TLR to T cells)
- TLRs bridge innate immune system to adaptive immune system
- TLR pathway results in NFκB activation

NFκB: protein complex that controls transcription of DNA

Complement System *(Figuer 1.7)*

- Small proteins found either circulating in blood or on the surface of cell membranes
- Function to destroy invading microorganisms but leave host tissue intact; occurs via opsonization (complement proteins coat pathogenic organism to enhance phagocytosis) and direct membrane damage; plays role in both innate and adaptive immune system
- Complement cascade: proteins circulate as proenzymes, which upon activation are able to cleave/activate next protein in cascade; one enzyme can cleave many substrates, resulting in massive amplification

Table 1-8: Cytokines

Cytokine	Produced by	Function
IL-1	Monocytes, macrophages, keratinocyte	**Proinflammatory** Corticosteroid downregulates IL-1 production Triggers host innate inflammatory response (i.e. macrophages), induces fever, ↑ production of acute phase reactant, vascular endothelial cells with ↑ expression of adhesion molecules (↑ chemotaxis)
IL-2	Activated T cells	**T cell stimulator** ↑ Growth and activation of T, NK and B cells
IL-3	T cells	Growth of mast cells and enhanced basophil production, stimulates myeloid cells
IL-4	T_H2 cells	**↑ T_H2 response** Stimulates B/T cells (T_H2), induces B-cell class switching to IgE, ↑ MHC II production
IL-5	T_H2 cells, mast cells	**Eosinophil stimulator** Also stimulates B cells and Ig production (↑ IgA production)
IL-6	Mainly lymphoid cells, endothelial cells	**Proinflammatory** Produces acute phase proteins, stimulates B cells to differentiate to plasma cells and ↑ antibody secretion, ↑ neutrophil production
IL-8	Keratinocyte, endothelial cells	**Neutrophil chemotaxis** Member of CXC chemokine family
IL-10	T_H2 cells, keratinocytes	**Anti-inflammatory** Inhibits proinflammatory cytokines along with inhibition of macrophages/ dendritic cells; activates B cells, downregulates T_H1 response
IL-12	Mononuclear phagocytes, dendritic cells	**↑ T_H1 response** Proinflammatory cytokine, induces cell-mediated immunity (ie. NK cells), ↑ synthesis of IFNγ and TNFα
IL-15	Mononuclear phagocytes	**Proliferative** ↑ NK cell proliferation, ± T cell growth factor
IL-18	Activated T cells	**Proinflammatory** IFNγ-inducing factor
TNFα	T cell, mononuclear phagocyte, mast cell, keratinocytes	**Proinflammatory** Releases other proinflammatory cytokines (IL-1, IL-6), ↑ MHC I/II, activates T/B cells, induces fever and catabolism (cachexia)
IFNα IFNβ	Leukocytes, fibroblasts	**Antiproliferative** Antiviral, anti-oncogenic, ↑ MHC I/II expression, activation of NK cells, antifibrotic properties, inhibits angiogenesis
IFNγ	T cells, NK cells	**↑ T_H1 response** Primes macrophages, causes B cell switching to produce Ab, good for opsonization, ↑ MHC expression, inhibit T_H2 response
TGF-β	Activated platelets, keratinocyte	**Anti-inflammatory** Induces apoptosis, inhibits growth of many cell types, counteracts proinflammatory cytokines

Of note, aberrant TGF-β expression is implicated in the pathogenesis of fibrosis in systemic sclerosis (SSc)

- Otber roles include chemotaxis, immune complex solubilization and removal, B cell activation, anaphylaxis (via degranulation of neutrophils and mast cells)
- 3 complement pathways: classical, alternative and mannose-binding lectin pathway
- All three pathways form membrane attack complex or MAC (C5b-C9), which is the cytolytic end-product of the complement pathway; MAC causes insertion of molecules into the lipid bilayer and forms pores (transmembrane channels), resulting in osmotic lysis of cell