CHAPTER

1

Anatomy of Human Skin

Akshita Anand Arora, Parul Singh

INTRODUCTION

Skin is the largest organ of the body with a surface area of 2 m^2 in a 70 kg individual. It accounts for 16 to 20% of the total body weight. Human skin is of two types: hair-bearing skin and non-hair-bearing (glabrous) skin as seen on palms and soles. The glabrous skin is marked by a series of ridges and grooves (sulci) with a configuration unique to each individual known as dermatoglyphics. Skin is primarily composed of the following:

1. Epithelial tissue (epidermis and dermis) (Table 1.1)
2. Adipose tissue (hypodermis)
3. Accessory structures (hair, nails, glands and sensory receptors).

DEVELOPMENT OF SKIN

Specification: The ectoderm on the sides of the neural plate becomes the epidermis; and mesenchymal and neural crest cells form the dermis. Formation of layers of skin and specialized structures takes place in this phase.

Morphogenesis: Morphogenesis takes 2–5 months. In this stage, different layers of the epidermis differentiate as do dermis and subcutaneous tissue. Development of subcomponents like epidermal appendages and vascularization of dermal tissue occurs in this phase.

Differentiation: Differentiation takes 5–9 months. There is further development and maturation of the tissue formed in morphogenesis.

Epidermis: It comprises of stratified squamous epithelium, which is 0.4 to 1.5 mm thick whereas the entire skin is up to 4 mm in thickness. It is composed of five layers (Table 1.2), which are as follows from below upwards (Fig. 1.1).

Table 1.1: Contents of epidermis and dermis

	Cells	*Other structures*
Epidermis	Keratinocytes, melanocytes, langerhans cells, merkel cells	Hair follicles, apocrine and eccrine glands
Dermis	Fibroblasts, mast cells, histiocytes, macrophages, lymphocytes	Matrix of polysaccharides and proteins containing collagen and elastin fibers

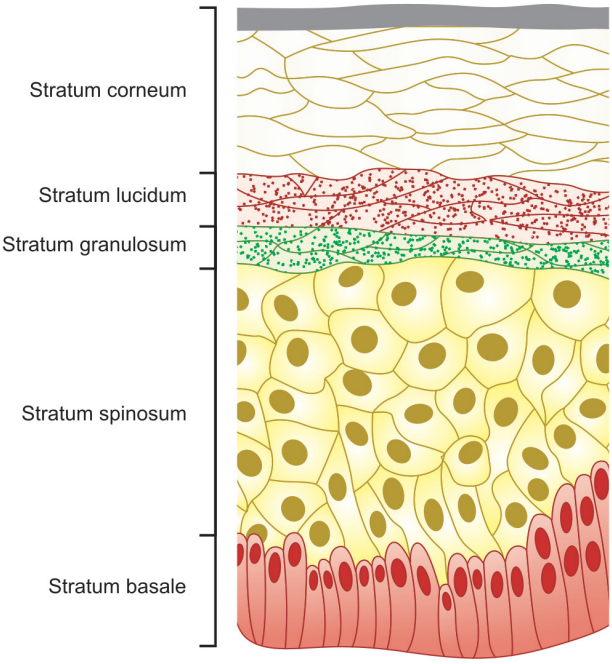

Fig. 1.1: Layers of epidermis

Table 1.2: Layers of the epidermis

- Stratum basale
- Stratum spinosum
- Stratum granulosum
- Stratum lucidum (present only on palms and soles)
- Stratum corneum

1. Stratum Basale or Stratum Germinativum

It is a single cell layer but may become 2–3 cells thick in hyperproliferative epidermis and glabrous skin. Morphologically, the cells of this layer are small and cuboidal (10–14 µm in diameter) with dense cytoplasm which contains tonofilament bundles, ribosomes and large, dark-staining nuclei. The cells are attached to each other through desmosomes and to the basement membrane zone (BMZ) with the help of hemidesmosomes via keratin filaments K5 and K14. Cell division at this level occurs every 18th to 19th day making it the primary site for mitotically active cells. Melanocytes are seen interspersed in the basal layer. Basal layer mainly consists of three types of cells—stem cells, transient amplifying cells and postmitotic cells.

2. Stratum Spinosum or Prickle Cell Layer

Stratum spinosum is immediately above the basal cell layer, wherein the basal keratinocytes increase in size and number to form 8–10 thick layer of prickle cells. Suprabasal spinous cells are polyhedral with a rounded nucleus. Cells in this layer are attached to adjacent cells with the help of desmosomes giving it the characteristic spinous shape and hence the name. These cells differentiate and move upwards to become flatter. K1 and K10 are keratin subtypes abundantly seen. Stratum basale and spinosum together form the malpighian layer.

3. Stratum Granulosum or Granular Layer

This layer lies above the stratum spinosum, and is called stratum granulosum because of the basophilic keratohyaline granules known as Odland bodies. Odland bodies are rich in histidine and are composed of profilaggrin, keratin filaments and loricrin. The cells are arranged in 2 to 5 layers.

4. Stratum Lucidum or Clear Cell Layer

The electron lucent layer sandwiched between stratum granulosum and stratum corneum, is seen only on the palms and soles. Nucleated cells in this layer are referred to as transitional cells.

5. Stratum Corneum or Dead Cell Layer

It is the outermost skin layer with thickness of 20–25 cells. Cells in this layer are known as corneocytes which are anucleate, flattened cornified cells that are a result of complete differentiation of granular cells. The cells that were originally attached by desmosomes, separate to become flattened; and are shed while moving towards the surface. The main function of this layer is to provide mechanical protection to the skin and act as a barrier to water loss and permeability of soluble substances from the environment. The various constituents of epidermal layers are mentioned in Table 1.3.

CELLS OF THE EPIDERMIS

1. Keratinocytes

Keratinocytes form the most abundant cells of epidermis. They are derived from ectoderm. Keratinocyte stem cells give rise to all layers of epidermis. A small percentage of keratinocytes in the basal layer constitute the transient amplifying cells and undergo mitotic divisions. The cells thus formed move upward from the stratum basale to stratum corneum over a period of 52 to 75 days. This is referred to as epidermal turnover time. This process of epidermopoiesis is regulated by a number of stimulatory factors (transforming growth factor alpha, epidermal growth factor, basic fibroblast growth factor), inhibitory signals (interferon alpha and gamma), integrins and apoptosis. Even a low calcium level inhibits differentiation.

Keratinocytes differentiate as the cells move from basal layer towards the surface. It involves formation

Table 1.3: Constituents of epidermal layers

Stratum corneum	Lipid bilayer, cross-linked cornified envelope, filaggrin
Granular layer	Tight junctions, lamellar granules, keratohyaline granules, keratin filament bundles, profilaggrin, loricrin, lipids
Spinous layer	Bundles of K1/K10-keratin filaments, intercellular junctions rich in desmosomes AP2, C/EBP, Hes1, Notch 1/3
Basal layer	K5/K14-keratin filaments, intercellular junctions rich in adherens junctions p63, EGFR, IGFR, TβRII, Delta1

*EGFR, epidermal growth factor receptor; IGF, insulin-like growth factor; IGFR, IGF receptor; TGF, transforming growth factor.

of keratin filaments (keratinization), development of keratinocyte granules and change in expression of other cell surface proteins, lipids and antigens.

Keratin filaments constitute the cytoskeleton of kertinocytes and are of two types-acidic (1 to 8) and basic (9 to 19). These are obligate heteropolymers. Simple epithelium contains keratin pair K8/K18, and the stratified squamous epithelium contains K5/K14. They maintain the architecture and function of epidermis.

Keratohyaline granules develop in the stratum granulosum and contain histidine rich protein fillagrin responsible for the adherence of cells of stratum corneum. Odland bodies are membrane coated granules seen mainly in the stratum granulosum and help in forming the cornified cell envelope.

The keratinocytes are linked to adjacent cells, basement membrane and are in close contact with the neural components with the help of intercellular junctions. They are responsible not only for the mechanical strength but also for biochemical and signaling interactions. Various types of intercellular junctions have been discussed below:

Desmosomes: Desmosomes are adhesion complexes which bind adjacent keratinocytes and keratin intermediate filaments to the cell membrane and thus provide a network of stability. The main components of desmosomes consist of desmosomal cadherins, desmogleins, desmocollins, desmoplakins, plakoglobin and other macroglobules.

Adherens junctions: These are transmembrane structures that are electron dense. They may exist separately or be associated with tight junctions and desmosomes. They help in adhesion, changes in cell shape, barrier formation and cell motility. They are composed of 2 components namely nectin and cadherin.

Gap junctions: These are made-up of connexons and allow transfer of ions and small molecules between two cells.

Tight junctions: These are key components of skin structure that help in regulation of permeability of epithelium which maintains barrier integrity and cell polarity. The main structural proteins are claudins, mainly 1 and 4 subtype.

2. Melanocytes

These are dendritic cells derived from neural crest. They are the melanin producing cells found in skin, inner ear, choroid and iris of the eye. Melanocytes are seen interspersed among it basal keratinocytes. Epidermal melanin unit is the term used for a group of 36 basal and suprabasal keratinocytes cells in contact with one melanocyte.

An individual cell consists of pale cytoplasm, ovoid nucleus and multiple melanosomes. Melanosomes are pigment producing granules within the melanocytes. It is the difference in size and distribution of melanosomes and not melanocytes which is responsible for variation in color of skin in different races. Melanosomes undergo different biochemical stages and are then transferred from the dendritic tips to the keratinocytes. There are two types of melanin produced namely, eumelanin and pheomelanin. α-MSH from pituitary gland controls melanin synthesis.

Melanocytes consists of melanocyte specific receptors which includes melanocortin-1 and melatonin receptors. Normal melanocyte function, skin color and photoprotection is regulated by activation or inhibition of melanocyte specific receptors. Alterations in melanocyte signaling pathways also contribute to common hair abnormalities such as hair graying.

3. Langerhans' Cells

Langerhans' cells are dendritic antigen-presenting and antigen-processing cells in the epidermis, derived from bone marrow. They are intraepidermal macrophages whose dendrites trap antigens among keratinocytes. The cells leave the epidermis to migrate via lymphatics to the regional lymph node and hence play an important role in antigen presentation, stimulation of T cell response and phagocytosis. These are present in basal, spinous and granular layer, contain pale cytoplasm and a convoluted nuclei.

Langerhans' or Birbeck granules (size from 100 nm to 1 μm) are rod or racquet shaped granules, present in the cytoplasm of Langerhans' cells with a principal function to sample and present antigens to T cells of the epidermis. Cross section show 'tennis racquet' appearance on electron microscopy. These granules are the most specific marker for Lagerhans' cells. Immunohistochemical markers for Langerhans' cells are CD1a, S-100 and langerin (CD207).

4. Merkel Cell

These are slow adapting, type 1 mechanoreceptors which constitute 0.2–5% of epidermal cells. They are located at the basal keratinocytes and are primarily found in the tactile areas of glabrous skin, hairy skin, taste buds, labial epithelium, anal canal and eccrine sweat glands; all regions of high tactile acuity. The density of these cells is approximately 50 per mm^2.

These cells contain pale cytoplasm with lobulated nuclei and spherical granules. The number of merkel cells in sun exposed skin is twice as compared to non-sun exposed skin. They are closely related to sensory nerve endings and secrete peptides. They express immunoreactivity for neuropeptides, such as metenkephalin, vasoactive intestinal polypeptide, neuron-specific enolase and synaptophysin-like and pancreastatin-like material. They also contain chromogranin A. These cells are grouped around unmyelinated sensory nerve endings, forming touch spots. These complexes are known as hair discs, touchdomes, touch corpuscles or Iggodiscs. Immuno-histochemical markers for merkel cells are K8, K18, K19 and K20 (most reliable). Merkel cell and its nerve complex are important for the sensation of touch and serve as mechanoreceptors.

HAIR FOLLICLES

Hair mainly develops from the epithelial cells whereas the papilla develops from the mesenchymal cells and fibroblast. Histologically hair follicle is divided into two parts: Upper part (infundibulum and isthmus) and lower part (stem and hair bulb). Part of the hair follicle from surface opening to the attachment of sebaceous gland is referred to as infundibulum. Isthmus is the part of the hair follicle beyond infundibulum up to the insertion of arrector pilli muscles. Lower part of the hair mostly contains the stem and the bulb or base of the follicle.

In cross section, hair shows three concentric layers which are as follows:

a. Medulla (central axis): Contains 2 to 3 layers of cell containing soft keratin
b. Cortex: Forms bulk of hair containing hard keratin
c. Cuticle: Single layer of cell containing hard keratin

Hair bulb consists of 5 major portions-dermal hair papilla, hair matrix, hair, inner root sheath (cuticle, Huxley's and Henley's layer) and outer root sheath. These layers extend up along the stem but the inner root sheath is present only up to the level of isthmus.

Hair Cycle

There are three phases of hair cycle, namely anagen, catagen and telogen. Anagen is the growing phase; comprising of 6 substages (I–VI), and this is the phase that defines the final length of a particular hair follicle. Anagen hair are pigmented, long, have a gelatinous root sheath and a hooked root end. This stage lasts for 3–5 years for an adult scalp. Anagen phase is followed by a phase of involution referred to as catagen, wherein the epithelial cell division reduces and stops. It lasts for 3 weeks and the hair shaft keratinizes to a club-shaped structure. Telogen phase is the phase one between follicular regression and commencement of next anagen phase and lasts for 3 months. At any point of time around 85–90% hair are in anagen phase, >1% in catagen phase and 13% in telogen phase, with an average hair growth of 0.4 mm per day in a normal scalp.

SEBACEOUS GLANDS

Sebaceous glands are holocrine glands where sebum is formed by autolysis of cells. Each gland consists of single or multiple lobules and a common excretory duct. These are the largest glands and are most numerous on face, scalp, upper trunk, external auditory meatus and anogenital surfaces. Sebaceous glands mature during the phase of follicular differentiation and are responsible for increased sebum production at puberty.

APOCRINE GLANDS

These are coiled tubular glands which open into the hair root above the opening of sebaceous glands or directly on the skin surface. They are present in axillae, genital and perianal areas. Every gland has three segments—interepidermal duct, intradermal duct and a secretory portion. Modified apocrine glands include ceruminous glands, Moll's glands and mammary glands.

ECCRINE GLANDS

These are coiled tubular glands. They open directly on the skin surface via sweat pores and consists of three segments. Secretory portion is present in lower

dermis, consisting of single layer of glycogen rich, large pale cells and small darker cells. Intradermal duct consist of two layers of cuboidal cells, lined by eosinophilic pseudo cuticle. The intraepidermal duct consists of inner layer of luminal cells and two to three outer layers of epithelial cells.

NAILS

Nail forms an important part of the digital tip. At 8–10 weeks of embryogenesis, nail structure appears at the dorsal digit region. Ectoderm buds turn inward at the proximal boundary of the early nail field, giving rise to the proximal nail fold. By the fourth month of gestation, nail plate grows out from the proximal nail fold, to completely cover the nailbed by the fifth month. Nails have an important role not only in cosmesis but more importantly in the tactile function of the fingertips, in peripheral thermoregulation and protecting the acral areas.

Nail Apparatus

The entire nail apparatus lies above the periosteum of distal phalanges. It consists of nail plate, nail folds, nail matrix, nailbed, eponychium and hyponychium (Table 1.4).

DERMOEPIDERMAL JUNCTION

It is 0.5 to 1 mm thick homogenous band that forms an interface between top layer of the dermis and lower part of epidermis. It comprises the dermal-epidermal basement membrane zone (BMZ). It plays a key role in epidermal-dermal interactions. The basement membrane consists of lamina densa and lamina lucida. Anchoring filaments traverse the lamina lucida through hemidesmosomes, and end in lamina densa. Beneath the lamina densa there are anchoring fibrils. The laminins in lamina lucida are composed of three chains (α, β and γ). Laminin bridges between the transmembrane hemidesmosomal molecules and the dermal matrix molecules. The intracellular plaque of the hemidesmosomes contains BP230 or BPAg1.

Other components are plectin. The transmembrane components of the hemidesmosome are BP180/collagen XVII and α6β4 integrin. These structures form the adhesion complex of DEJ.

Table 1.4: Structure of the nail apparatus

Nail plate	Keratinized structure, comprising of close-packed, adherent, interdigitating cells with absence of nuclei and organelles
Nail matrix	Helps in formation of hard keratin of nail plate
Cuticle (eponychium)	Narrowband of epidermis which extends onto the nail plate and adheres to it at the proximal part
Nailbed	Consists of dermis and soft tissue and lies beneath the nail plate
Nail groove	Anchors ligaments present between nail matrix and underlying bone
Proximal nail fold	Devoid of dermatoglyphic markings and pilosebaceous glands

DERMIS

It constitutes 15–20% of the total weight of human body. Dermal thickness may vary depending on the site, e.g. 5 mm over the back and 1 mm over the eyelids. It is a complex of fibrous, filamentous and amorphous connective tissue that consists of nerves, vessels, skin appendages, fibroblasts, macrophages, mast cells, lymphocytes, plasma cells and other leukocytes. Fibrous connective tissue includes collagen and elastic fibers. Non-fibrous connective tissue consists of fine filamentous glycoproteins, proteoglycans (PGs) and glycosaminoglycans (GAGs) of the ground substance. It forms the bulk of skin and provides flexibility, stretch and tensile strength.

Dermis is divided into papillary and reticular dermis. Subpapillary plexus of blood vessels is present between papillary and reticular dermis. Adventitial dermis comprises of papillary dermis and periadenexal dermis.

Papillary Dermis

It is superficial and thin part of dermis (1/10th) that is present on under surface of the epidermis and forms ridges. It consists of bundles of collagen fibrils (small) and oxytalan elastic fibers. It shows high fibroblastic activity, high metabolic rate and synthesizes different PGs.

Reticular Dermis

It comprises the lower 9/10th of the dermis and merges with the subcutaneous fat. Reticular dermis is subdivided into upper zone (intermediate size collagen fiber bundles and elaunin fibers) and deeper zone composed of large collagen fibrils.

GROUND SUBSTANCE

It is an amorphous matrix of dermis comprising of PG's and GAG's that enclose the fibrous components of dermis. Major PGs are chondroitin sulfates, dermatansulfates (biglycan, decorin, versican), heparan/HSPGs (perlecan, syndecan) and chondroitin-6 sulfate PGs. Hyaluronan is present in the dermis as a free GAG and as a component of PGs.

CONNECTIVE TISSUE MATRIX

Collagen tissue: It is the major component of dermis contributing 75% of the dry weight of skin. It is soft, flexible, strong and inelastic. Around 80–90% collagen fibers are type 1. Molecules are made up of three chains composed of proline, hydroxyproline and globular terminal domains.

Elastic tissue: It forms uninterrupted network that extends from dermis to the subcutis. It is 1–3 µm in diameter. These are thick and firm in lower dermis and become thinner near the epidermis. It is seen as dark stained fibrils existing both separately and with collagen fibrils and matrix.

CELLS OF THE DERMIS

Fibroblasts

Fibroblasts are derived from mesenchymal tissue. They are the most common cells found in the dermis. They are seen as bipolar spindle cells with ovoid nucleus. Fibroblasts cause production and degradation of fibrous and non-fibrous proteins of connective tissue and matrix and hence act as a source of ground substance. They also provide a structural framework and help in interactions between epidermis and dermis.

Monocytes, Macrophages and Dendrocytes

Monocytes, macrophages and dendrocytes together form a mononuclear phagocytic system. Monocytes differentiate into macrophages. They contain lysosomes and phagocytic vacuoles. Dendrocytes are stellate, dendritic or spindle-shaped cells. These cells are phagocytic.

Mast Cells

Ovoid or spindle-shaped cells seen in the dermis, mast cells are derived from pleuripotent cells in the bone marrow. Mast cells have secretory properties. They are oval-shaped with round nucleus, 6–12 µm in diameter and resemble a fried egg. Mast cells are of two types, those found in the dermis and submucosa (type 1)); and those found in the bowel and respiratory mucosa (type 2). They have a high content of heparin, histamine, neutrophil, eosinophil, chemotactic factors, tryptase, kininogenase and β-glycosaminidase. These cells consist of two components: lamellae (thick, curve, parallel filaments forming whorls) and fine granular material.

MUSCLES OF SKIN

Smooth muscles: The smooth muscles in the skin are arrector pili and tunica dartos. They lack striations and contain cigar-shaped central nucleus with round ends.

Striated muscles: They are present in the skin of neck (platysma) and face (muscles of expression). These muscles show cytoplasmic striations and nucleus lies at the periphery.

SUBCUTANEOUS TISSUE

Eighty percent of body fat is present in the subcutaneous tissue, rest protects the internal organs. Fat here comprises of lobules of adipocytes which are separated by fibrous septa through which the vessels pass. Adipocytes (mesenchymal cell) have their cytoplasm filled with lipids that shifts the nucleus eccentrically and gives it a fusiform shape. Subcutaneous fat provides insulation, mechanical cushion and has an endocrine function along with a role in angiogenesis and osteogenesis.

FURTHER READING

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