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An Overview on Histology of the skin

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Abstract:

The skin, the largest organ in the human body, plays a vital role in protecting internal structures, regulating temperature, and enabling sensory perception. Histologically, the skin is composed of three main layers: the epidermis, dermis, and hypodermis (subcutaneous tissue), each with specialized cells and structures that contribute to its diverse functions. The epidermis is a stratified squamous keratinized epithelium predominantly made up of keratinocytes, along with melanocytes, Langerhans cells, and Merkel cells. It undergoes a continuous process of renewal through keratinization. Beneath it lies the dermis, a connective tissue layer rich in collagen and elastic fibers, housing blood vessels, nerves, hair follicles, and glands. The hypodermis consists mostly of adipose tissue, serving as insulation and energy storage. This layered organization allows the skin to act as both a barrier and a dynamic interface with the external environment. Understanding the histological structure of the skin is fundamental for diagnosing dermatological diseases and for advancing fields such as dermatopathology, cosmetic science, and wound healing.

Keywords: Skin histology, Epidermis, Dermis, Hypodermis, Keratinocytes, Skin layers, Skin structure, Histological features, Human skin, Dermatopathology.

Introduction:

The skin is the largest and most accessible organ of the human body, accounting for approximately 15% of total body weight and serving as a protective interface between the internal environment and the outside world. It plays critical roles in thermoregulation, immune defense, sensory reception, and the prevention of water loss and pathogen entry **(1).**

Histologically, the skin is composed of three main layers: the epidermis, a stratified squamous keratinized epithelium that provides a protective barrier; the dermis, a connective tissue layer that supports vascular, neural, and appendageal structures; and the hypodermis, primarily composed of adipose tissue that provides insulation and energy storage. Each layer contains specific cell types and extracellular components essential for maintaining skin integrity and function. A solid understanding of skin histology is vital for medical education, clinical diagnosis of dermatological conditions, and advancements in fields such as wound healing, regenerative medicine, and cosmetic dermatology **(2).**

Histology of the skin:

The skin is known as cutaneous or integumentary and its appendages (hair follicles, hairs, nails, sweat, and sebaceous glands) constitute the integumentary system. Under the skin is the hypodermis, it is not a part of the skin and is equivalent to the subcutaneous fascia, sandwiched between the dermis and skeletal muscles. It is

composed primarily of adipose tissue arranged into lobules that are separated by connective tissue septa. The hypodermis serves as physical protection, allows the skin mobility, serves an energy reserve and source of insulation and thermal regulation **(2).**

The epidermis is composed of a keratinized stratified squamous epithelium that grows continuously and simultaneously maintains its normal thickness by the process of desquamation **(3).** The dermis is composed of connective tissue. Epidermis and dermis interdigitate with each other by the formation of epidermal ridges and dermal papillae, where the two are separated by a basement membrane. Frequently, a dermal papilla is subdivided into two secondary dermal ridges with an intervening interpapillary peg from the epidermis **(4).**

Epithelial cells of the epidermis rest on a basement membrane that contains glycosaminoglycans and proteoglycans, glycoproteins, and collagen. By electron microscopy, this membrane has three laminae; the lamina lucida just next to basal epithelial cell membranes is a pale zone of low density (10-50nm wide), an intermediate zone, wider and more electron dense, is the lamina densa (20-300nm). Type IV collagen in both layers is a fine meshwork embedded in an amorphous matrix. The third lamina is reticular and consists mostly of a delicate network of reticular fibers. Epithelium produces the lamina densa, but fibroblasts elaborate the reticular lamina, which provides an underlying foundation for the cells **(5, 6).** The cells are anchored to this basement membrane by hemidesmosomes that are clearly visible at electron microscopy. The hemi-desmosomes are attached by fine filaments of laminin and fibronectin that cross the lamina lucida and contact the type IV collagen fibers of the lamina densa **(7).**

There are two locations where skin is different in both gross and histological preparation; the palms of the hands and soles of the feet are examples of thick skin, and elsewhere the integument is made up of thin skin. Thick skin has a thicker epidermal layer that includes five well-developed layers: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. But the epidermis of thin skin has thinner all layers and also lacks stratum lucidum **(4, 8).**

Stratum basale, also known as stratum germinativum, is the deepest layer. Its primary cell type is the keratinocyte, which produces the keratin protein- a crucial component of the skin's protective barrier. These cells are attached to each other and to the overlying spinosum cells by desmosomes and to the basement membrane by hemidesmosomes. Histologically, this stratum is a single layer of columnar or cuboidal cells with large, ovoid nuclei and basophilic cytoplasm. Their cytoplasm is electron dense and contains numerous ribosomes, mitochomdria and tonofilament. Some of these cells can act like stem cells with the ability to divide and produce new cells, and they are sometimes called basal keratinocyte stem cells. The epidermal keratinocytes are renewed constantly, with the top layer of cells continually being shed and new cells from the stratum basale replacing them. It takes about 3-4 weeks for keratinocytes to finish their renewal cycle. This turnover is vital for the constant renewal of the skin's surface and plays a critical role in the wound healing **(5, 9*).*** Other types of cells found within the stratum basale are melanocytes and Merkel cells **(10).**

The second layer, the stratum spinosum, is composed of 8-10 layers of keratinocytes, formed as a result of cell division in the stratum basale. Their cells are polyhedral with large pale-staining nuclei as they are actively synthesizing fibrillary proteins, known as cytokeratin, which build up within the cells, aggregating together and forming tonofibrils. The tonofibrils go on to form the desmosomes, which allow for strong connections between adjacent keratinocytes. Their cytoplasm is rich in tonofilaments, organelles, and membrane-coating or lamellar granules. During tissue fixation for histologic microscopy, the cells shrink but remain tightly bound to each other through the desmosomes, and thereby the sites of connection between cells appear like spines or prickles. Another cell, as Langerhans, is also found in this layer **(4, 9).**

The stratum granulosum is the most superficial layer of the non-keratinized portion of the epidermis. It has a grainy appearance due to further changes to the keratinocytes as they are pushed from the stratum spinosum. Keratinocytes in this layer are arranged in 3-5 layers, flattened and basophilic, and contain shrunken nuclei and large, deeply basophilic keratohyalin granules (KHGs) and also lamellar granules in their

cytoplasm. As keratinocytes mature and migrate upward to the stratum corneum, they begin to prepare for the dissolution of their nuclei and other organelles **(8).**

Keratohyalin granules (KHGs) are irregular in shape and variable in size. They comprise keratins and a keratin-binding protein such as loricrin, filaggrin (FLG), and trichohyalin. Two types of KHGs are expressed: P-granules enriched with loricrin, and F-granules enriched with FLG which is produced from profilaggrin, is one of the major intermediate filament-associated proteins that aggregates keratin filaments, conferring the stratum corneum with tensile strength. During maturation, KHGs associate with an actin network and are elongated and expanded to provide access to FLG-processing enzymes such as retroviral-like aspartic protease 1 (ASPRV1), profilaggrin endopeptidase. With the progression of epidermal differentiation, KHGs migrate toward the nucleus to enhance differentiation-related signaling, thereby producing FLG monomers to aggregate keratin filaments **(11) .**

Other types of granules can be seen by electron microscopy and immunohistochemical techniques. Theses granules called lamellar granules (LGs), or membrane-coating granules (MCGs), keratinosomes, or Odland bodies. They are round to ovoid in shape, with a diameter of about 200-500nm. They have a bounding membrane surrounding a stack of internal lipid lamellae. Isolated LGs contain phosphoglycerides, sphingomyelin, and the most unusual lipid component is a linoleate-containing glucosylceramide. They also contain acid hydrolases, β-glucocerebrosidase, sphingomyelinase, and phospholipase-A, proteases and antimicrobial peptides **(7, 12, 13).**

In this context, these granules are first seen in the spinous layer and accumulate with differentiation in the granular layer. In the uppermost granular cells, the bounding membrane of the LGs fuses into the cell plasma membrane, and the internal contents are extruded into the intercellular space **(12).** Lipids secreted by LGs are processed by enzymes, β-glucocerebrosidase and acidic sphingomyelinase, to generate ceramides and other lipophilic components. The lipid processing enzymes are active at acidic pH and are inhibited at higher PH. The initially extruded contents rearrange to form the intercellular lamellae of the stratum corneum and are responsible for the permeability barrier function of the stratum corneum **(13, 14).**

The fourth layer is the stratum lucidum, relatively thin and readily visible by light microscopy only in areas of thick skin. It usually appears as a thin, translucent region, interposed between the strata granulosum and the corneum. It is composed of 3-5 layers of dead, flattened keratinocytes, which are densely packed together and lie beneath the stratum corneum. These keratinocytes are filled with eleidin, an intermediate form of keratin in which the process of keratinization is well advanced. Also, they are surrounded by an oily substance that is the result of the exocytosis of lamellar bodies. Its thickness is controlled by the rate of mitotic activity of the epidermal cells **(4, 5, 8).**

The fifth layer is the stratum corneum, which serves as the body's first barrier from the external environment. It is the outermost layer of the epidermis and marks the final stage of keratinocyte maturation and development. Keratinocytes at the basal layer of the epidermis are proliferative, they migrate upwards, and as their appearance changes, they produce and accumulate the building blocks of keratin. These cells are finally differentiated, enucleated, they are termed corneocytes and retain only keratin filaments embedded in a filaggrin matrix, and cornified lipid envelopes replace their plasma membranes. These cells are flattened, connecting to each other with corneo-desmosomes and stacking as layers (15 or more) to form the stratum corneum **(7).** The corneocytes divided into two layers; the stratum disjunctum and compactum. The stratum disjunctum is the uppermost and loosest layer, and skin’s protective acid mantle and lipid barrier sit on top of this layer. As this stratum continues to lose adhesiveness secondary to decreased inter-corneocyte adhesion, the cells desquamate. Also, yhey are larger, more rigid, and hydrophobic than that of the stratum compactum. While the stratum compactum is the deep, dense, or compacted, and more cohesive layer **(15).**

Other than the keratinocytes, there are other cells such as melanocytes, Merkel cells and Langerhans cells. Melanocytes are specialized cells located primarily in the basal layer of the epidermis, responsible for the production of melanin, the pigment that gives skin its color. UVB light stimulates melanin secretion, which is protective against UV radiation, acting as a built-in sunscreen. Melanin is produced during the conversion of tyrosine to DOPA by the enzyme

tyrosinase. Melanin then travels from cell to cell by a process that relies on the long processes extending from the melanocytes to the neighboring epidermal cells. Melanin is transferred to neighboring keratinocytes by "pigment donation" which involves phagocytosis of tips of melanocyte processes by keratinocytes **(10, 16).**

Merkel cells (MCs) are oval-shaped modified epidermal cells localized in the basal layer. They are distributed in both skin and mucosal tissues, the palms, finger pads, feet, toes, oral mucosa and also in the male prepuce and clitoris. Its morphologic description is principally by using electron microscopy. The cell is elliptical, with a length of about 10–15μm, a large, pale, lobulated nucleus, with few nucleoli and microvilli-like projections. The most characteristic feature is the electron-dense cytoplasmic granules, surrounded by narrow electron-lucent spaces and bounded by simple membranes. They are situated away from the Golgi and are concentrated near the juncture with the nerve ending. Intermediate keratin filaments are discerned that may sometimes form tonofibril-like aggregates around the nucleus. They intertwine with the surrounding keratinocytes by comparatively small, few desmosomes (**10, 17).** Due to their interactions with slowly adapting type 1 (SA1) Aβ low-threshold mechanoreceptor (Aβ-LTMRs) afferents neurons, they are considered to be part of the main tactile organ involved in the light touch sensation **(18).**

Langerhans cells (LCs) were first described by Paul Langerhans, as dendritically shaped cells, that were located in the epidermis. Later on, these cells were identified in all stratified squamous epithelium of mammals. They constitute 3% of the cell population in the epidermis. They are the first line defenders and play a significant role in antigen presentation. These cells express both MHC I and MHC II molecules, uptake antigens in the skin and transport them to the regional lymph node. These cells are of mesenchymal origin, derived from CD34-positive stem cells of bone marrow, and are part of the mononuclear phagocytic system **(10) .**

In histological sections stained with hematoxylin and eosin Langerhans cells are seen as 'clear cells'. They can be visualized as cells with their bodies generally in the stratum spinosum with delicate dendritic processes that can often be observed extending to the stratum corneum and usually directed towards the epithelial surface. According to morphology, LCs have been classified into two types: Type1, which are pyramidal in shape, located in the suprabasal layer, and Type2, which are spherical in shape, and located in the basal layer. Type 1 contains numerous Birbeck granules, electron-lucent cytoplasm, and long-branched dendritic processes, whereas Type 2 cells have fewer granules, electron dense-cytoplasm, and shorter dendritic processes. Among all the markers used, CD1a immunolabeling is the most reliable method to identify the human LCs. Recent studies have shown that Langerin seems to be the more specific marker **(19).**

The dermis is located deep to the epidermis and separated from it by a basement membrane. The dermis is composed mostly of dense, irregular, collagenous connective tissue. It contains capillaries, nerves, sensory organs, hair follicles, sweat and sebaceous glands, as well as arrector pili muscles. It is divided into two layers: a superficial papillary and a deeper reticular layers. The papillary layer is thin and located immediately under the epidermis. It hosts randomly distributed connective tissue cells, intermixed collagen chiefly type III, a network of loose elastic fibers, and many looped capillaries that nourish the epidermis and regulate body temperature **(4, 20).** The reticular layer is composed of dense, irregular, collagenous connective tissue containing cells, blood, and lymphatic vessels. Sweat glands and cutaneous nerves are also present and their branches extend into the papillary layer and into the epidermis **(4) .**

Derivatives of skin include sweat glands, sebaceous glands, hair, and nails. These structures originate from epidermal down growths into the dermis and hypodermis while maintaining their connection to the outside. Eccrine sweat glands do not develop in association with hair follicles. These are simple, coiled, tubular glands whose secretory units produce sweat, which is delivered to the surface of the skin by long ducts. Myoepithelial cells surround the secretory portion. These glands are important in regulating body temperature; they are found in both the thin and thick skin**.** The apocrine sweat glands are also called sexual scent glands; their function in humans is not clear. They may be involved in thermoregulation and are found only in some special regions of thin skin, such as the axilla, nipple, and perianal and genital areas **(4, 5).**

Sebaceous glands are absent in the hairless, thick skin of the palms and soles. They derive from hair follicles and more frequently in the dermis of the face, forehead, and scalp. Usually more than one gland opens to one third of the upper portion of the hair follicles. Also, sebaceous glands are found in the hairless skin of the lips, the glans penis, the prepuce, the areola of the nipples, and the labia minora; their excretory ducts open directly to the surface. This distribution highlights the unique functional roles of sebaceous glands in different skin areas, providing lubrication and protection. Their presence in both hairy and hairless regions underscores their importance in maintaining skin health and integrity **(20) .**

The acini of sebaceous glands are the classic example of holocrine secretion. They have a basal layer of flattened epithelial cells on the basal lamina, which proliferate and are displaced centrally, undergoing terminal differentiation as large, lipid-producing sebocytes filled with small fat droplets. Their nuclei shrink and undergo autophagy along with other organelles, and near the duct the cells disintegrate, releasing the lipids as the main secretory product. This product, called sebum, gradually covers the surfaces of both the epidermis and hair shafts. Sebum serves as a natural moisturizer and protective barrier for the skin and hair, helping to prevent dryness and maintain overall health. Additionally, it plays a role in the skin's antimicrobial defense, contributing to the skin's resilience against pathogens **(21).**

Hair follicles are dynamic structures embedded in the skin that produce hair. They are composed of multiple layers and cell types, each with specific functions. Below is a breakdown of their histological structure**:** Hair shaft**,** hair root, hair bulb, and the layers of hair follicle. The shaft is the visible part of the hair that extends above the skin surface. It composed of keratinized cells arranged in three layers: Medulla is a central core (absent in fine hairs); cortex is a middle layer containing keratin and melanin (provides color and strength) and cuticle is an outermost layer of overlapping, scale-like cells that protect the hair. The root is an embedded part within the follicle, where it receives nutrients and signals for growth. The bulb**,** located at the base of the follicle. It contains the matrix cells (germinative cells) that divide and differentiate to form the hair shaft and inner root sheath. The dermal papilla (a small, nipple-like structure) projects into the bulb. The papilla plays a crucial role in hair development by supplying essential nutrients and growth signals to the matrix cells. This interaction is vital for the formation and health of the hair shaft **(8, 21**, **22).**

The layers of the hair follicle are: Internal root sheath surrounds the hair root and helps mold the hair shaft. It is composed of three layers: The cuticle is the innermost layer, interlocking with the hair cuticle; Huxley's layer is the middle layer with flattened cells, and Henle's layer is the outermost layer, a single row of cuboidal cells. The external root sheath is a continuation of the epidermis into the hair follicle. It is composed of keratinocytes that provide structural support. The external root sheath also plays a role in hair growth and regeneration by housing stem cells that can differentiate into various cell types needed for hair production. This dynamic structure is essential for maintaining healthy hair follicles and ensuring proper hair development. The last one is a glassy membrane (basement membrane): a thick, clear layer separating the external sheath from the surrounding connective tissue. This membrane plays a crucial role in providing a barrier between the follicle and the surrounding tissues, ensuring that the follicle remains protected and supported. Additionally, it helps to regulate the interaction between the hair follicle and its environment, contributing to overall hair health **(Diagram 1) (23, 24).**

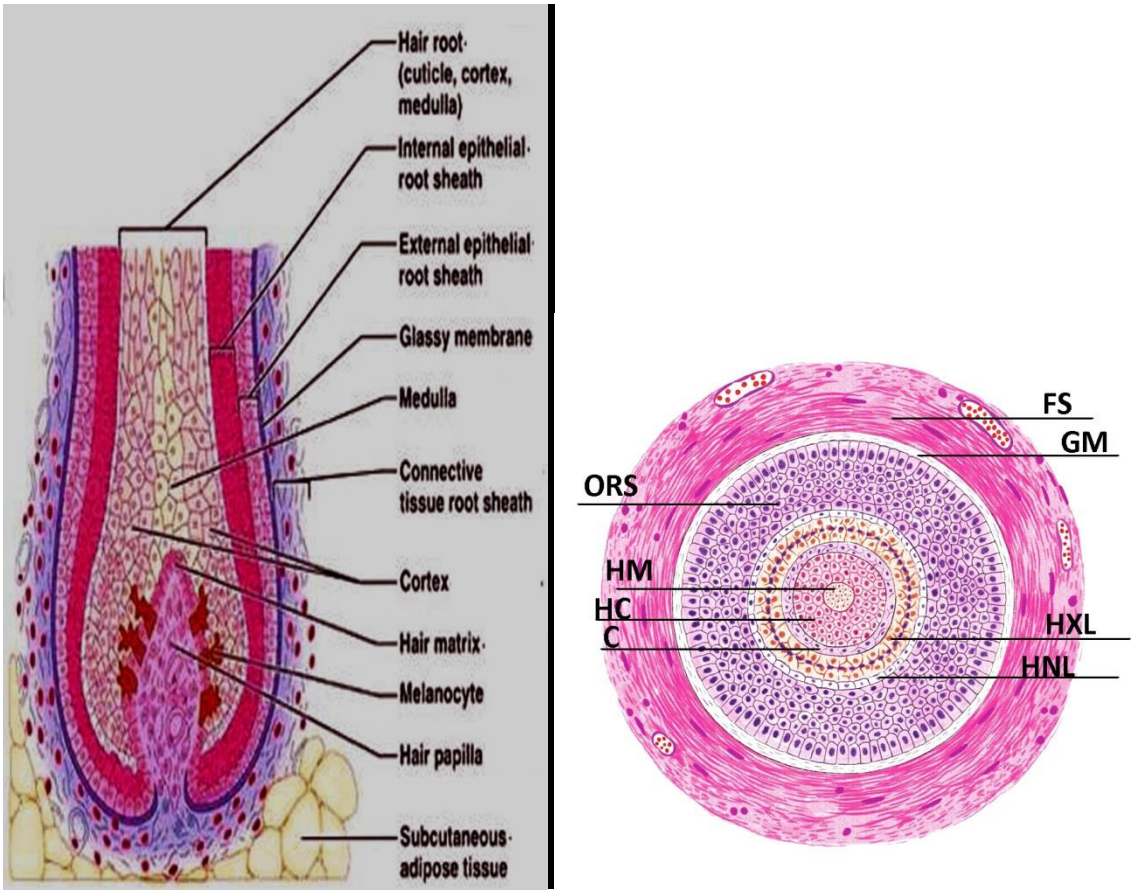

Diagram (1): Longitudinal and transverse section of the hair follicle at lower segment from inside to outside; the hair root (inner medulla (HM), outer cortex (HC), hair cuticle (C), the inner root sheath (inner cuticle (C), Huxley's layer (HXL), Henle's layer (HNL), the outer root sheath (ORS), Glassy membrane (GM), and connective tissue or dermal sheath (FS).

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