ABSTRACT

The skin is a large organ, weighing an average of 4 kg and covering an area of 2 m². Its major function is to act as a barrier against an inhospitable environment – to protect the body from the influences of the outside world. The importance of the skin is well illustrated by the high mortality rate associated with extensive loss of skin from burns.

The major barrier is provided by the epidermis. Underlying the epidermis is a vascularized dermis that provides support and nutrition for the dividing cells in the epidermis. The dermis also contains nerves and appendages: sweat glands, hair follicles, and sebaceous glands. Nails are also considered skin appendages. The third and deepest layer of the skin is the subcutaneous fat. The functions of all these components are listed in Table 2.1.

Skin disease illustrates structure and function. Loss of or defects in skin structure impair skin function. Skin disease is discussed in more detail in the other chapters.

EPIDERMIS

Key Points

1. Keratinocytes are the principal cell of the epidermis
2. Layers in ascending order: basal cell, stratum spinosum, stratum granulosum, stratum corneum
3. Basal cells are undifferentiated, proliferating cells
4. Stratum spinosum contains keratinocytes connected by desmosomes
5. Keratohyalin granules are seen in the stratum granulosum
6. Stratum corneum is the major physical barrier
7. The number and size of melanosomes, not melanocytes, determine skin color
8. Langerhans cells are derived from bone marrow and are the skin’s first line of immunologic defense
9. The basement membrane zone is the substrate for attachment of the epidermis to the dermis
10. The four major ultrastructural regions of the basement membrane zone include the hemidesmosomal plaque of the basal keratinocyte, lamina lucida, lamina densa, and anchoring fibrils located in the sublamina densa region of the papillary dermis

The epidermis is divided into four layers, starting at the dermal junction with the basal cell layer and eventually at the outer surface in the stratum corneum. The dermal side of the epidermis has an irregular contour. The downward projections are called rete ridges, which appear three-dimensionally as a Swiss cheese-like matrix with the holes filled by dome-shaped dermal papillae. This configuration helps to anchor the epidermis physically to the dermis. The pattern is most pronounced in areas subject to maximum friction, such as the palms and soles.

The cells in the epidermis undergo division and differentiation. Cell division occurs in the basal cell layer, and differentiation in the layers above it.
Basal Cell Layer

The basal cells are the undifferentiated, proliferating cells. Skin stem cells are located in the basal layer in the interfollicular epidermis, and they give rise to keratinocytes. For normal skin homeostasis, daughter cells from the basal cell layer migrate upward and begin the process of differentiation. In normal skin, cell division does not take place above the basal cell layer. It takes about 2 weeks for the cells to migrate from the basal cell layer to the top of the granular cell layer, and a further 2 weeks for the cells to cross the stratum corneum to the surface, where they finally are shed. Injury and inflammation increase the rate of proliferation and maturation (Fig. 2.1).

Stratum Spinosum

The process of differentiation continues in the stratum spinosum, or granular cell layer, in which the cells acquire additional keratin and become more flattened. In addition, they contain distinctive dark granules, seen easily on light microscopy, that are composed of keratohyalin. Keratohyalin contains two proteins, one of which is called profilaggrin, the precursor to filaggrin. As its name suggests, filaggrin plays an important role in the aggregation of keratin filaments in the stratum corneum. The other protein is called involucrin (from the Latin for “envelope”), and plays a role in the formation of the cell envelope of cells in the stratum corneum. Ichthyosis vulgaris (ichthys, Greek for “fish”) is an inherited dry skin condition secondary to deficient filaggrin production, as noted on light microscopy of a skin biopsy by a reduced or absent granular layer (Fig. 2.3).

Granular cells also contain lamellar granules, which are visualized with electron microscopy. Lamellar granules contain polysaccharides, glycoproteins, and lipids that extrude into the intercellular space and ultimately are thought to help form the “cement” that holds together the stratum corneum cells. Degradative enzymes also are found within the granular cells; these are responsible for the eventual destruction of cell nuclei and intracytoplasmic organelles.

Stratum Granulosum

The stratum granulosum lies above the basal layer and is composed of keratinocytes, which differentiate from the basal cells beneath them. The keratinocytes produce keratin, a fibrous protein that is the major component of the horny stratum corneum. The stratum spinosum derives its name from the “spines,” or intercellular bridges, that extend between keratinocytes and which are visible with light microscopy. Ultrastructurally, these are composed of desmosomes, which are extensions from keratin within the keratinocyte; functionally, they hold the cells together (Fig. 2.2).
Stratum Corneum

A remarkably abrupt transition occurs between the viable, nucleated cells at the top of the granular cell layer and the dead cells of the stratum corneum (Fig. 2.4). The cells in the stratum corneum are large, flat, polyhedral, plate-like envelopes filled with keratin. They are stacked in vertical layers that range in thickness from 15 to 25 layers on most body surfaces to as many as 100 layers on the palms and soles. The cells are held together by a lipid-rich cement in a fashion similar to “bricks and mortar.” The tightly packed, keratinized envelopes in the stratum corneum provide a semi-impenetrable layer that constitutes the major physical barrier of the skin.

The skin microbiome could be considered another outermost layer of the epidermis. With the better sequencing and metagenomics technologies, the role of the microbiome in human health and disease states is being actively investigated. It plays an active role in modulating the host’s immune response to pathogens.

The epidermis, then, is composed of cells that divide in the basal cell layer (basal cells), keratinize in the succeeding layers (keratinocytes), and eventuate into the devitalized, keratin-filled cells in the stratum corneum.

Other Cellular Components

In addition to basal cells and keratinocytes, two other cells are located in the epidermis: melanocytes and Langerhans cells.

Melanocytes

Melanocytes are dendritic, pigment-producing cells located in the basal cell layer (Figs. 2.4 and 2.5). They protect the skin from ultraviolet radiation. Individuals with little or no pigment develop marked sun damage and numerous skin cancers. The dendrites extend into the stratum spinosum and serve as conduits, through which pigment granules are transferred to their neighboring keratinocytes. The granules are termed melanosomes, and the pigment within is melanin, which is synthesized from tyrosine. Melanosomes are preferentially situated above the nucleus to protect the DNA.

People of all races have a similar number of melanocytes. The difference in skin pigmentation depends on (1) the number and size of the melanosomes and (2) their dispersion in the skin. In darkly pigmented skin, melanosomes are larger in size and more numerous compared with melanosomes in lightly pigmented skin. Sunlight stimulates melanocytes to increase pigment production and disperse their melanosomes more widely.

Langerhans Cells

Langerhans cells are dendritic cells in the epidermis that have an immunologic function (Fig. 2.4). They are
Langerhans cells are the first line of immunologic defense in the skin.

**Merkel Cells**
Merkel cells are located in the basal cell layer. They are more numerous on the palms and soles and are connected to keratinocytes by desmosomes. Merkel cells function as mechanoreceptors. Merkel cell carcinoma is a rare skin cancer with a high mortality rate, as discussed in Chapter 5.

**Dermal–Epidermal Junction – The Basement Membrane Zone**
The interface between the epidermis and dermis is called the basement membrane zone. With light microscopy, it is visualized only as a fine line. However, electron microscopic examination reveals four regions: (1) keratin filaments in the basal keratinocytes attach to hemidesmosomes (electron-dense units), which in turn attach to anchoring filaments in (2) the lamina lucida. The lamina lucida is a relatively clear (lucid) zone traversed by delicate anchoring filaments that connect hemidesmosome of basal cells to (3) the lamina densa; the lamina densa is an electron-dense zone composed primarily of type IV collagen derived from epidermal cells and (4) anchoring fibrils, which are thick fibrous strands, composed of type VII collagen, and located in the sublamina densa region of the papillary dermis. The basement membrane zone serves as the “glue” between the epidermis and dermis, and is the site of blister formation in numerous diseases (Fig. 2.6). Hence, its structure, composition, and immunologic make-up continue to be investigated intensely.

**Key Points**
1. Provides structural integrity and is biologically active
2. The primary components of the dermal matrix are collagen, elastin, and extracellular matrix
3. Collagen, the principal component of the dermis, represents 70% of skin's dry weight

The dermis is a tough, but elastic, support structure that contains blood vessels, nerves, and cutaneous appendages. It provides structural integrity and is biologically active by interacting and regulating the functions of cells (i.e., tissue regeneration). The dermis ranges in thickness from 1 to 4 mm, making it much thicker than the epidermis, which in most areas is only about as thick as this piece of paper (Fig. 2.7). The dermal matrix is composed primarily of collagen fibers (principal component), elastic fibers, and ground substance (now called extracellular matrix), which are synthesized by dermal fibroblasts. Collagen accounts for 70% of the dry weight of skin. Collagen and elastic fibers are fibrous proteins.
that form the strong, yet compliant skeletal matrix. In the uppermost part of the dermis (papillary dermis), collagen fibers are fine and loosely arranged. In the remainder of the dermis (reticular dermis), the fibers are thick and densely packed (Fig. 2.8). Elastic fibers are located primarily in the reticular dermis, where they are thinner and more loosely arranged than collagen fibers. The extrafibrillar matrix fills the space between fibers. It is a non-fibrous material made up of several different mucopolysaccharide molecules, collectively called proteoglycans or glycosaminoglycans. The extrafibrillar matrix imparts to the dermis a more liquid quality, which facilitates movement of fluids, molecules, and inflammatory cells.

Nerves and blood vessels course through the dermis, and a layer of subcutaneous fat lies below it (Fig. 2.9).

**Nerves**
The skin is a major sensory receptor. Without the sensations of touch, temperature, and pain, life would be less interesting and more hazardous. Sensations are detected in the skin by both free nerve endings and more complicated receptors that are corpuscular in structure. The free nerve endings are the more widespread and appear to be more important. The nerve supply of the skin is

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**Structural components of the dermis:**
1. Collagen
2. Elastic fibers
3. Extrafibrillar matrix

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**FIGURE 2.7** Systemic scleroderma – an increase in the number and activity of fibroblasts produces excessive collagen and results in dermal thickening.

**FIGURE 2.8** Papillary dermis – fine, loose collagen strands. Reticular dermis – thick and dense collagen strands.

**FIGURE 2.9** Dermis and subcutaneous fat.
SKIN APPENDAGES

Blood Vessels

The blood vessels in the skin serve two functions: nutrition and temperature regulation. The epidermis has no intrinsic blood supply and therefore depends on the diffusion of nutrients and oxygen from vessels in the papillary dermis. Blood vessels in the dermis also supply the connective tissue and appendageal structures located therein.

The vasculature of the skin is arranged into two horizontal plexuses that are interconnected. The superficial plexus is located at the lower border of the papillary dermis, and the deep plexus is located in the reticular dermis. Temperature regulation is achieved through shunts between the plexuses. Increased blood flow in the superficial plexus permits heat loss, whereas shunting of blood to the deep plexus conserves heat.

SKIN APPENDAGES

**Key Points**

1. Eccrine glands help to regulate body temperature
2. Apocrine sweat glands depend on androgens for their development
3. The stem cells of the hair follicle reconstitute the nonpermanent portion of the cycling hair follicle
4. Sebaceous glands are under androgen control
5. Nails, like hair, are made of keratin

The skin appendages are the eccrine and apocrine sweat glands, hair follicles, sebaceous glands, and nails. They are epidermally derived but, except for nails, are located in the dermis.

**Eccrine Sweat Glands**

For physically active individuals and for people living in hot climates, the eccrine sweat glands are physiologically the most important skin appendage. They are activated by emotional and thermal stimuli. Cholinergic innervation is responsible for physiologic eccrine secretion. Botulinum toxin type A (Botox) injected intradermally can treat axillary hyperhidrosis by blocking acetylcholine action. Eccrine sweat glands help to regulate body temperature by excreting sweat onto the surface of the skin, from which the cooling process of evaporation takes place. Two to three million eccrine sweat glands are distributed over the entire body surface, with a total secretory capacity of 10 L of sweat per day. The secretory portion of the sweat apparatus is a coiled tubule located deep in the dermis. The sweat is transported through the dermis by a sweat duct, which ultimately twists a path through the epidermis (Fig. 2.11). Sweat secreted in the glandular portion is isotonic to plasma but becomes hypotonic by the time it exits the skin as a result of ductal reabsorption of electrolytes. Hence, the sweat apparatus is similar to the mechanism in the kidney, that is, glandular (glomerular) excretion is followed by ductal reabsorption.

**Apocrine Sweat Glands**

In humans, apocrine sweat glands are androgen dependent for their development and serve no known useful function, although they are responsible for body odor. The odor actually results from the action of surface skin bacteria on excreted apocrine sweat, which itself is odorless. Apocrine sweat glands are located mainly in the axillary
and anogenital areas. The secretory segment of an apocrine gland is also a coiled tubule located deep in the dermis. However, unlike in eccrine glands, in which the secretory cells remain intact, in apocrine glands the secretory cells “decapitate” their luminal (apical) portions as part of the secretory product (see Fig. 2.11). The apocrine duct then drains the secreted sweat into the midportion of a hair follicle, from which it ultimately reaches the skin surface.

**HAIR FOLLICLE**

In most mammals, hair serves a protective function, but in humans it is mainly decorative.

Hair follicles are distributed over the entire body surface, except the palms and soles. Hair comes in two sizes: (1) vellus hairs, which are short, fine, light colored, and barely noticeable; and (2) terminal hairs, which are thicker, longer, and darker than the vellus type. Terminal hairs in some locations are hormonally influenced and do not appear until puberty (e.g., beard hair in males, and pubic and axillary hair in both sexes).

A hair follicle can be viewed as a specialized invagination of the epidermis (see Fig. 2.11), with a population of cells at the bottom (hair bulb) that are replicating even more actively than normal epidermal basal cells. These cells constitute the hair matrix. As with basal cells in the epidermis, the matrix cells first divide and then differentiate, ultimately forming a keratinous hair shaft. Melanocytes in the matrix contribute pigment, the amount of which determines the color of the hair. As the matrix cells continue to divide, hair is pushed outward and exits through the epidermis at a rate of about 1 cm per month. Hair growth in an individual follicle is cyclical, with a growth (anagen) phase, a transitional (catagen) phase, and a resting (telogen) phase. The lengths of the phases vary from one area of the body to another. On the scalp, for example, the anagen phase lasts for about 3 years, the catagen phase for about 3 weeks, and the telogen phase for about 3 months. The length of the anagen phase varies from individual to individual, explaining why some persons can grow hair longer than others.

Hair follicle stem cells, a new hair matrix is formed at the bottom of the follicle, and the cycle is repeated (Fig. 2.12). At any time, 80% to 90% of scalp hair is in the anagen phase and 10% to 20% is in the telogen phase, thus accounting for a normal shedding rate of 25 to 100 hairs per day.

As shown in Fig. 2.11, the hair follicle is situated in the dermis at an angle. Not shown is an attached arrector pili muscle. When this muscle contracts, the hair is brought into a vertical position, giving a "goose flesh" appearance to the skin. The stem cells of the hair follicle are located in the “bulge” area of the follicle, where the arrector pili muscle inserts into the hair follicle, and in the dermal papilla. The stem cells are important for reconstituting the nonpermanent portion of the cycling hair follicle and play a role in reconstituting the epidermal cells.

**Sebaceous Glands**

Sebaceous glands produce an oily substance termed sebum, the function of which is unknown. In fact, the skin of children and the palmar and plantar skin of adults function well without sebum.

Sebaceous glands are part of the pilosebaceous unit and so are found wherever hair follicles are located. In addition, ectopic sebaceous glands are often found on mucous membranes, where they may form small yellow papules called Fordyce spots. In the skin, sebaceous glands are most prominent on the scalp and face, and are moderately prominent on the upper trunk. The size and secretory activity of these glands are under androgen control. The sebaceous glands in newborns are enlarged owing to maternal hormones, but within months, the glands shrink (Fig. 2.13). They enlarge again in preadolescence from stimulation by adrenal androgens and reach full size at puberty, when gonadal androgens are produced.

Sebaceous glands are androgen dependent.
The lipid-laden cells in the sebaceous glands are wholly secreted (holocrine secretion) to form sebum. Triglycerides compose the majority of the lipid found in sebaceous gland cells. From the sebaceous glands, sebum drains into the hair follicle (see Fig. 2.11), from which it exits onto the surface of the skin.

**Nails**

Nails, like hair, are made of keratin, which is formed from a matrix of dividing epidermal cells (Fig. 2.14). Nails, however, are hard and flat, and lie parallel to the skin surface. Located at the ends of fingers and toes, they facilitate fine grasping and pinching maneuvers.

The **nail plate** is a hard, translucent structure composed of keratin. It ranges in thickness from 0.3 to 0.65 mm.

Fingernails grow at a continuous rate of about 0.1 mm/day, and toenails at a slightly slower rate.

Four epithelial zones are associated with the nail:

1. The **proximal nail fold** helps to protect the matrix. The stratum corneum produced there forms the cuticle.
2. The **matrix** produces the nail plate from its rapidly dividing, keratinizing cells. Most of the matrix underlies the proximal nail fold, but on some digits (especially the thumb) it extends under the nail plate, where it is grossly visible as the white lunula. The most proximal portion of the matrix forms the top of the nail plate; the most distal portion forms the bottom of the nail plate (Fig. 2.15).
3. The epithelium of the *nail bed* produces a minimal amount of keratin, which becomes tightly adherent to the bottom of the nail plate. The pink color of a nail is due to the vascularity in the dermis of the nail bed.

4. The epidermis of the *hyponychium* underlies the free distal edge of the nail plate. Stratum corneum produced there forms a cuticle to seal the junction of the distal nail bed and nail plate.

**Subcutaneous Fat**

A layer of subcutaneous fat lies between the dermis and the underlying fascia. It helps to insulate the body from cold, cushions deep tissues from blunt trauma, and serves as a reserve source of energy for the body. Biologically active fat cells play a role in hormone messaging, as evidenced by metabolic disturbances in obese children and adolescents with peripheral insulin resistance. Recent evidence supports the role of adipose-derived stem cells in wound healing, hair follicle support/growth, and protection against photoaging. Within the subcutaneous fat layer, aggregates of fat cells (lipocytes) are separated by fibrous septa that are traversed by blood vessels and nerves (Fig. 2.16).