CHAPTER 1

Structure and function of the skin

The skin is the largest organ of the human body, covering a surface area of approximately 1.6 m^2 and accounting for about 16% of an adult's body weight. The skin is in direct contact with the outside environment and helps maintain four key functions:

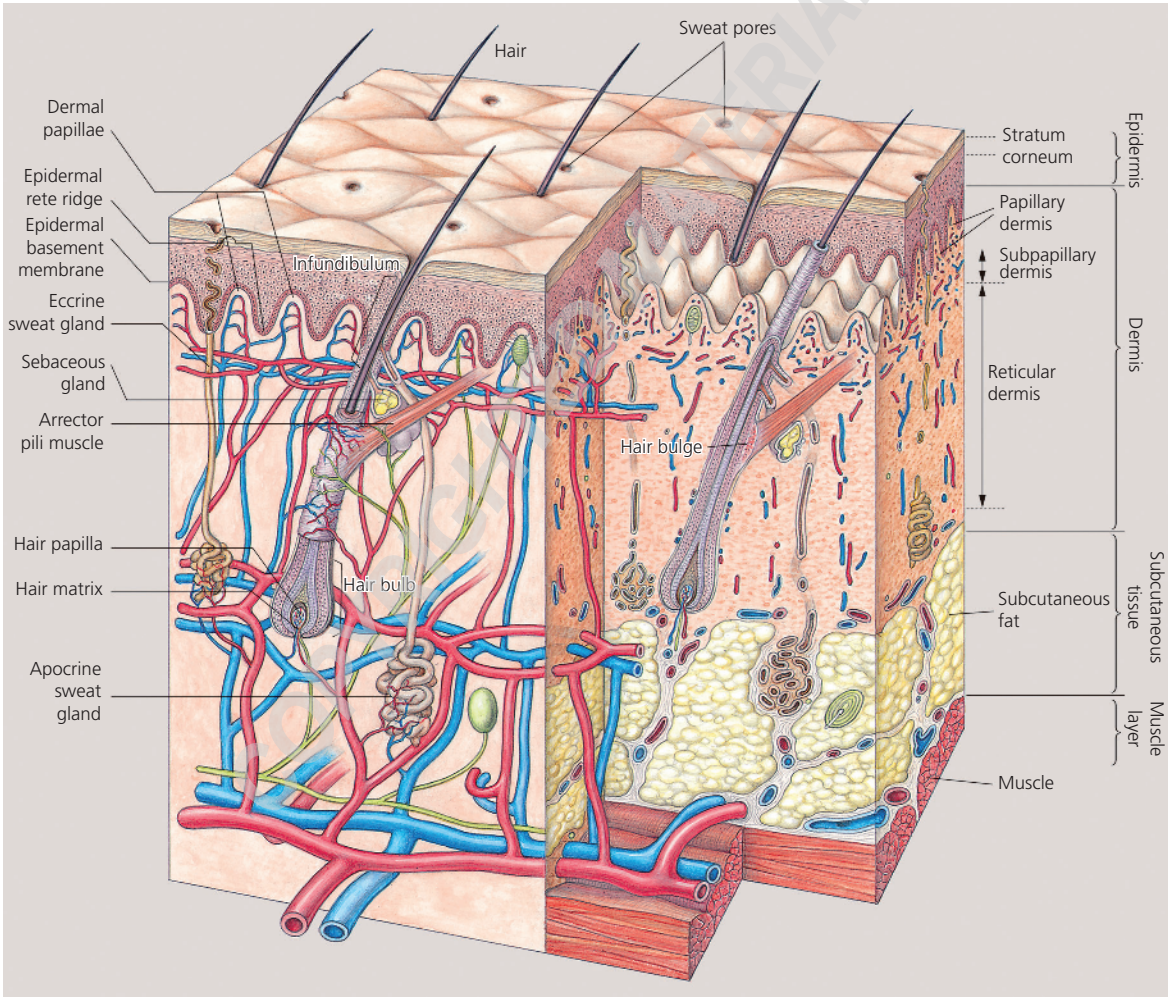


Fig. 1.1 Structure of the skin.

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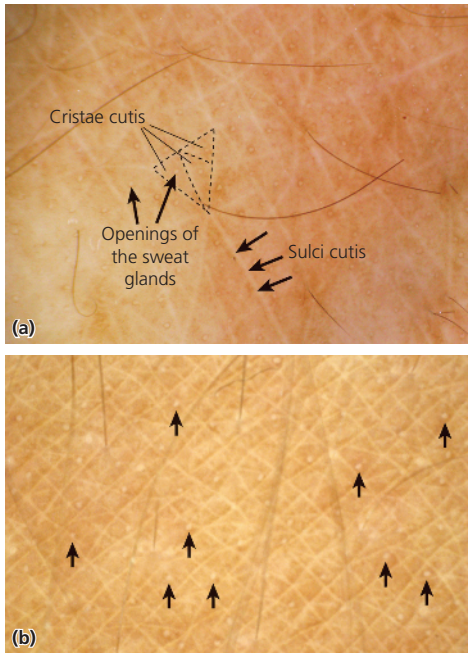


Fig. 1.2 Appearance of the skin surface. a: Cristae cutis (triangle), sulci cutis and openings of the sweat glands. b: Sweat pores fed by sweat glands open to the cristae cutis (arrows).

- retention of water and other molecules
- regulation of body temperature
- protection of the body from invading microorganisms and other harmful external factors
- sensory perception.

The horny cell layer plays a crucial role in maintaining the human body's water balance. To gain insight into cutaneous biology and skin diseases, an understanding of the structure and functions of normal human skin is essential. This chapter discusses the structure and function of normal skin and skin appendages, and the basics of immune mechanisms that mainly relate to the skin.

Overview of the skin

The skin is the largest human organ in both area and weight. It has the important function of separating the body from the external environment and maintaining homeostasis in the body. In order to achieve this, the skin has a complicated structure and various functions. Skin consists of a three-layer structure of epidermis, dermis, and subcutaneous tissue (Fig. 1.1). The cells in the epidermis are keratinocytes (~95%), melanocytes

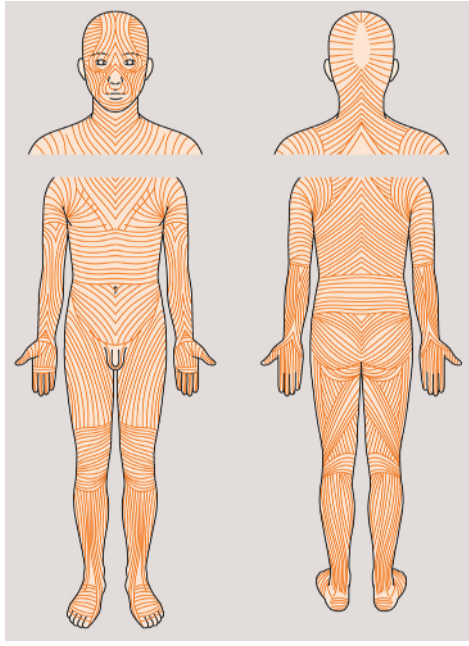


Fig. 1.3 Cleavage lines (Langer cleavage lines).

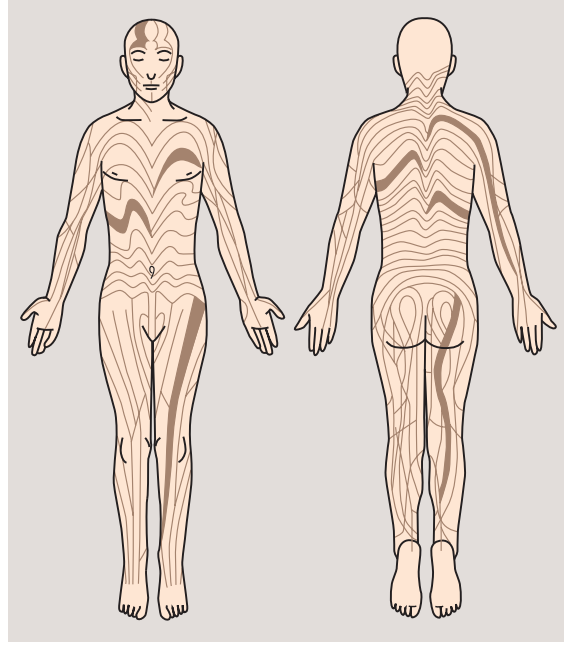


Fig. 1.4 Blaschko's lines.

(~5%), and Langerhans cells. The horny cell layer, formed by the keratinization of keratinocytes, is the outermost skin layer and is in direct contact with the external environment. It has the important functions of moisture retention and protection against the external environment, such as foreign substances and ultraviolet radiation. The major dermal components are collagen fibers, elastic fibers, blood vessels, and the components that maintain the skin, such as the extracellular matrix. The dermal appendages include the sweat glands, sebaceous glands, and hair follicles. At the boundary between the epidermis and dermis are finger-like projections, called dermal papillae, that project into the epidermis (see Fig. 1.1). The epidermis also projects into the dermis, producing the epidermal rete ridge. The main component of subcutaneous tissue is fat tissue, which stores neutral fat and provides protection from external impacts and heat/cold.

The skin surface is not smooth; it is laced with networks of fine shallow and deep grooves called sulci cutis. Sweat ducts open onto the skin surface in the center of the crista cutis, which is formed by the borders of the sulci cutis (Fig. 1.2).

The orientation of the sulci cutis is site dependent and is called the dermal ridge pattern. Fingerprints and patterns on the palms and soles, which are unique to each person, are formed by the sulci cutis. Langer's lines, also called cleavage lines, is a term used to define the direction within the human skin along which the skin has the least flexibility (Fig. 1.3). Elastic fibers are aligned in specific site-dependent orientations in the dermis. Several skin diseases, such as epidermal nevi, occur along specific lines called Blaschko's lines. These lines are distributed all over the body (Fig. 1.4) and are thought to be associated with the direction taken by the migrating differentiated cell clones during fetal skin development.

Epidermis

Structure and cells of the epidermis

The epidermis is approximately 0.2 mm thick. It consists mainly of keratinocytes (~95%), which proliferate and divide in the basal layer and move outward as they mature to form the cornified layer. This process takes 45 days in normal skin. In the epidermis, keratinocytes are therefore at different stages of maturation and are arranged in four main layers (Fig. 1.5 and

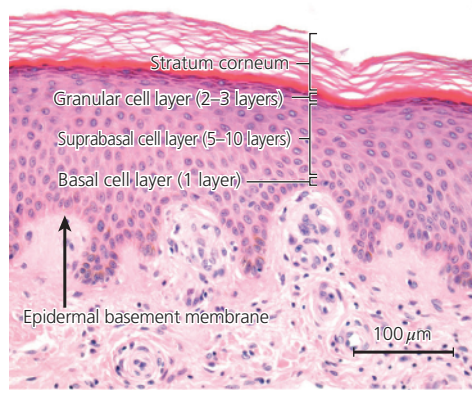


Fig. 1.5 The four layers of the epidermis.

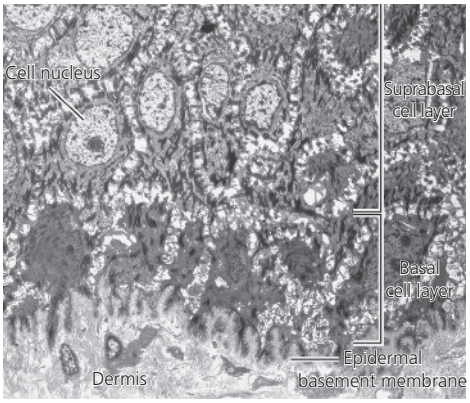


Fig. 1.6 Ultrastructural anatomy of the epidermis.

Fig. 1.6). Cytokeratins such as keratin intermediate filaments and tonofilaments are found abundantly in the cytoplasm of many epidermal keratinocytes and are distributed in bundles around the nuclei, from which they distally connect with hemidesmosomes and desmosomes to form a rigid and robust cellular cytoskeleton.

Basal cell layer

The basal cell layer, or stratum basale, consists of a single layer of cubical and/or columnar cells that replicate and migrate outward. It also comprises the epidermal stem cell subpopulation. Basal cells contain a basophilic (or darkly staining) cytoplasm and an elliptical nucleus rich in chromatin. These cells have desmosomes for cell-to-cell attachment, gap junctions for cell communication and hemidesmosomes for connection with the extracellular matrix and the underlying basal membrane (Fig. 1.7).

Prickle cell layer

The prickle cell layer, or stratum spinosum, consists of 5–10 layers that appear connected to each other by

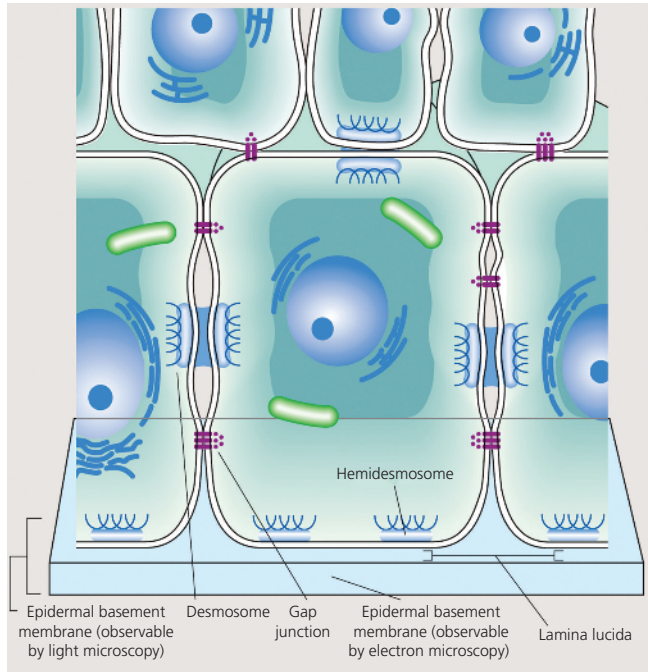


Fig. 1.7 Intercellular positions of desmosomes, gap junctions, and hemidesmosomes.

prickle-like structures that correspond to the location of desmosomes. Prickle cells in the lower layer are polygonal and those in the upper layers have a flattened morphology. They are larger than basal cells and contain small amounts of chromatin in their round nuclei.

Granular cell layer

The granular cell layer, or stratum granulosum, consists of two or three layers of cells containing basophilic keratohyalin granules. Granular cells and their nuclei are even flatter than those in the suprabasal layer. Spherical lamellar granules (also known as Odland bodies or keratosomes) have a diameter of approximately 300 nm and can be observed in the granular cell layer by electron microscopy. The main component of lamellar granules is stratum corneum lipid, which is released into the intercellular space of horny cells.

Horny cell layer

The horny cell layer, or stratum corneum, consists of about 10 sublayers. Enucleated keratinocytes become membranous and multilayered, resembling fallen leaves; they exfoliate sequentially from the outermost layer. The horny cell layer, which is very thick in the palms and soles, is underlain by the stratum lucidum (Fig. 1.8). Horny cells are flat, and their cytoplasm is filled with aggregated keratin fibers. The stratum corneum appears as an eosinophilic layer in hematoxylin and eosin staining. The horny cells gradually change into membranous structures in the upper layers. By electron microscopy, the clear contrast between electron-dense interfibrous substances and electron-sparse keratin fibers is called the keratin pattern.

The cell membrane is thickest in the horny cell layer and forms the cornified cell envelope or marginal band (Fig. 1.9 and Fig. 1.10). The protein component of the cornified cell envelope is extremely stable against physicochemical degradation.

Other cells

Keratinocytes account for 95% of all epidermal cells. The remaining 5% consists of melanocytes, Langerhans cells, and Merkel cells, which are respectively involved in melanin formation, antigen presentation, and sensation.

Adhesion of keratinocytes

The epidermal basement membrane plays a key role in dermal-epidermal adhesion.

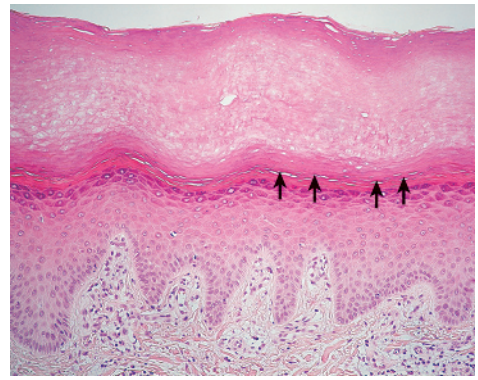


Fig. 1.8 The stratum lucida, which is found in the palms and soles (arrows).

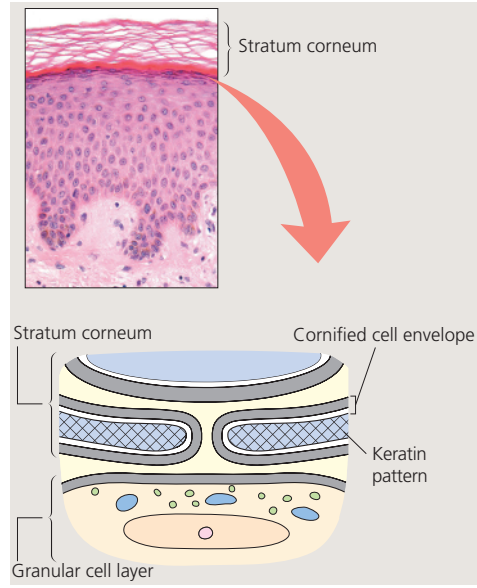


Fig. 1.9 Stratum corneum.

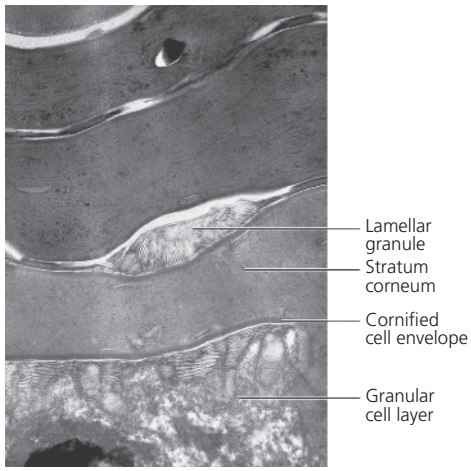


Fig. 1.10 Electron microscopy of the border between the granular cell layer and the stratum corneum.

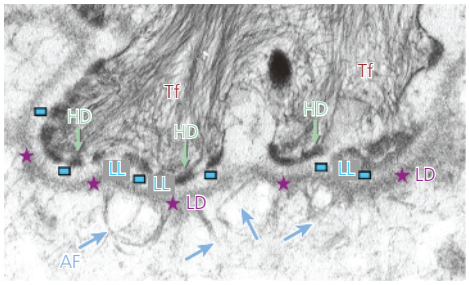


Fig. 1.11 Electron microscopy of the epidermal basement membrane.
AF, anchoring fibril; HD, hemidesmosome; LD, lamina densa; LL, lamina lucida; Tf, tonofilament.

Epidermal basement membrane

This underlies the epidermis and is revealed by periodic acid–Schiff (PAS) staining under light microscopy. The structure of the epidermal basement membrane includes the lamina densa (LD) and the lamina lucida (LL), which are observed by electron microscopy (Fig. 1.11 and Fig. 1.12).

The lamina densa is approximately 60–80 nm thick and consists mainly of fibronectins, heparan sulfate proteoglycan, type IV collagen, and laminin-332. By electron microscopy, it appears as an electron-dense lattice network. While desmosomes are important for cell-to-cell adhesion, hemidesmosomes mediate adhesion between the basal cells and the underlying lamina densa. Although a hemidesmosome resembles a bisected desmosome, its molecular composition is very different from that of a desmosome. Keratin fibers within the basal cells link hemidesmosomes, which maintain the structure of the cell (Fig. 1.13).

The lamina lucida is composed of a large glycoprotein called laminin-332, in addition to type XVII collagen (BP180; BPAG2). Type XVII collagen projects directly into the lamina lucida/lamina densa interface and connects hemidesmosomes with the lamina densa. Anchoring fibrils, which form semi-circular loop structures, link the dermis with the lamina densa by associating with type I and III collagens.

Adhesion between keratinocytes

Intercellular adhesion between keratinocytes is mediated by several cell-to-cell junctions, including desmosome junctions, adherens junctions, gap junctions, and tight junctions.

The desmosome consists of an inner and an outer plaque (attachment plaque) that are mainly composed

MEMO 1–1 Blister formation caused by inherited abnormalities or autoantibody deposition

Blisters can form as a result of an inherited abnormality or autoantibody deposition targeting various components of the cutaneous basement membrane which weakens the dermal-epidermal junction. For example, autoantibodies against type XVII collagen and BP230, which are components of hemidesmosomes, result in bullous pemphigoid. Inherited mutations in *KRT5*, *KRT14*, *COL17A1* encoding BP180, laminin-332, or *COL7A1* encoding type VII collagen cause epidermolysis bullosa (see Chapter 14). Blisters can also form as a result of weakened intercellular adhesion in the epidermis resulting from autoantibody deposition against desmogleins, which are structural components of desmosomes. Autoantibodies targeting desmoglein 1 cause pemphigus foliaceus whilst autoantibodies against desmoglein 3 result in pemphigus vulgaris.

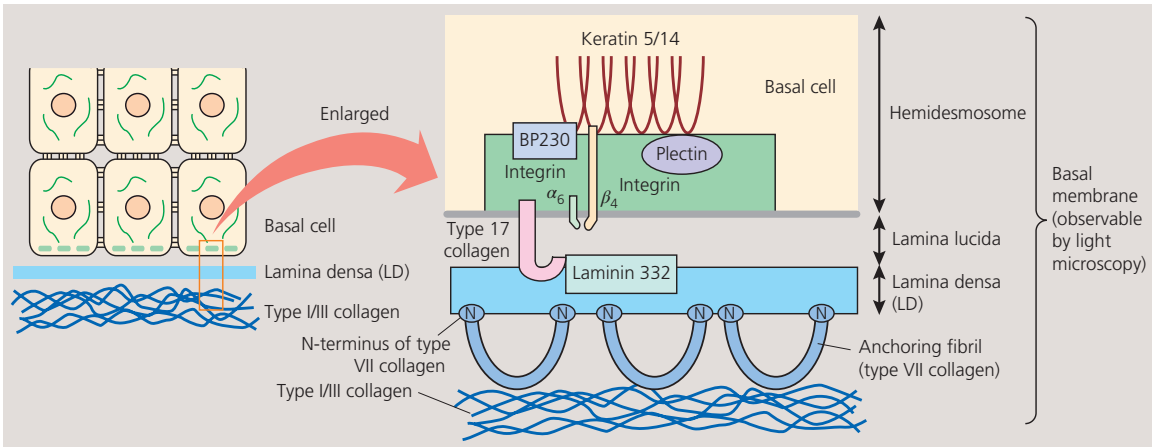


Fig. 1.12 Microstructure of the basement membrane zone.

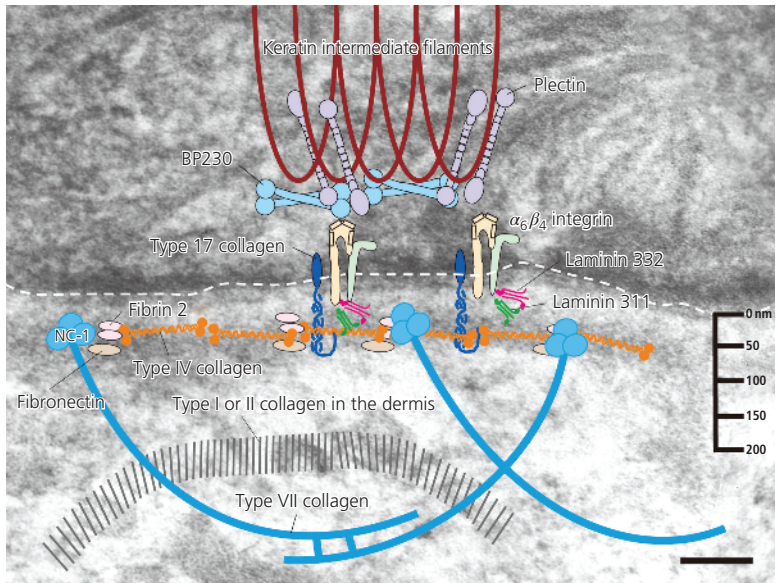


Fig. 1.13 Electron microscopy of the basement membrane zone.

of desmoplakin. Desmoplakin connects keratin fibers and strengthens the cytoskeleton. Transmembrane proteins such as desmogleins and desmocollins form homophilic connections to the same molecules by a calcium ion-dependent mechanism (Fig. 1.14).

The gap junction consists of several connexin subunits (forming a connexon) and has a structure in which cell membranes are linked with each other by a 2–3 nm gap. Gap junctions are involved not only in connecting cells but also in transporting small molecules and ions between cells (Fig. 1.15).

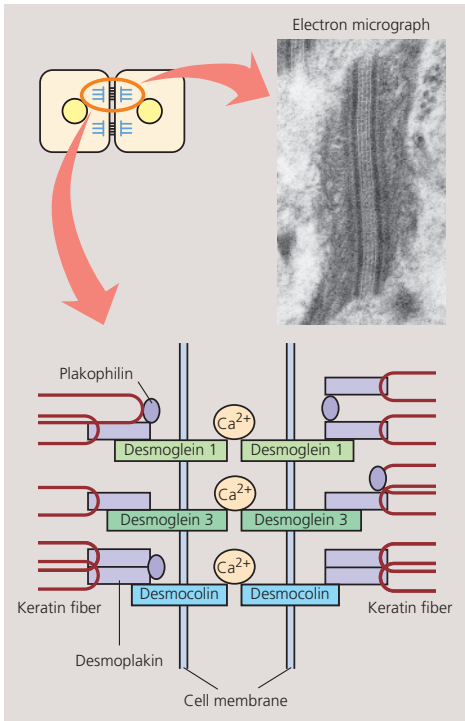


Fig. 1.14 Ultrastructural image and illustration of the desmosome.

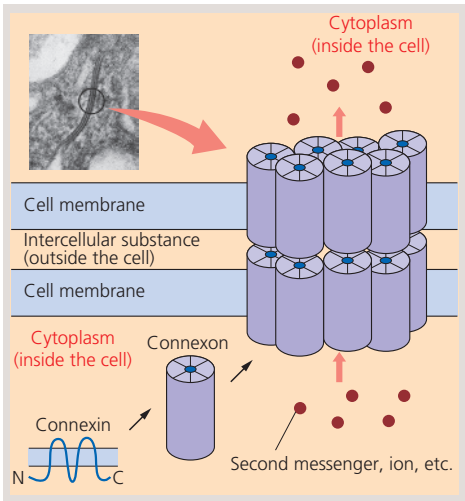


Fig. 1.15 Molecular components of the gap junction.

Keratinocyte cell membranes in the granular cell layers are connected by tight junctions consisting of membrane proteins called occludins and claudins. Tight junctions prevent fluids from leaking between cells (tight conjugation).

Keratinization

The horny cell layer acts like a film of plastic wrap, its main functions being to allow the underlying skin to retain moisture and to protect it from external factors such as microbes. Extensive loss or defect in the horny cell layer may cause severe dehydration, leading to death within 24 h if treatment is not promptly initiated. The cornified layer consists of several components, including keratins (produced by epidermal keratinocytes) and lipids. During keratinization, the epidermal keratinocytes divide in the basal layer, produce keratins, undergo differentiation, and migrate to the upper layers as they mature. Studies have demonstrated that epidermal keratinocytes secrete various cytokines.

Keratin

Keratin tonofilaments form a cytoskeletal network that is essential for maintaining the structure of the keratinocyte. Keratins are classified as type I (acidic) or type II (neutral to basic). Type I and type II keratins bind to each other in pairs to form intermediate filaments. Keratins can associate with each other to form keratin pairs, and this process is dependent on the state of differentiation of the keratinocytes. For example, K5/K14 pairs are found in basal cells whereas K1/K10 pairs are present in the suprabasal cell layers (Table 1.1, Fig. 1.16).

When keratinized, keratin fibers in the granular cell layer aggregate in association with filaggrin to form a characteristic condensed keratin pattern. Profilaggrins, abundantly present in keratohyalin granules, are cleaved into filaggrins by the action of the protease peptidylarginine deiminase during keratinization (Fig. 1.17). Released filaggrins aggregate keratin fibers in the horny cell cytoplasm, and the keratins are converted into amino acids in the upper layer of the stratum corneum. The cleaved filaggrins, which function in moisture retention and ultraviolet absorption, are called natural moisturizing factors (NMF).

Table 1.1 Expression regions of main keratin pairs, and congenital disorders from mutations of keratins.

Keratins	Main area of expression	Genetic disorder	Indirect reference
K1, K10	Suprabasal cell layer	Epidermolytic ichthyosis	Chapter 15
K2	Granular cell layer	Superficial epidermolytic ichthyosis	Chapter 15
K3, K12	Anterior epithelium of the comea	Juvenile epithelial corneal dystrophy (Meesman)	
K4, K13	Mucosa	White spong nevus (on tongue)	Chapter 22
K5, K14	Keratinocytes in the basal cell layer	Epidermolysis bullosa simplex	Chapter 14
K6, K16	Nails	Pachyonychia congenita	Chapter 19
K9	Keratinocytes in the suprabasal cell layer and granular cell layer on the palmoplantar region	Palmoplantar keratoderma (Vömer)	Chapter 15

Cornified cell envelope

The cornified cell envelope (marginal band) is an extremely large, strong and insoluble structure lining the horny cell membrane. By electron microscopy, it appears as an electron-dense structure at the periphery of the horny cells (Fig. 1.18). The main structural components of the cornified cell envelope are involucrins, produced in the lower keratinocyte prickle cells, and loricrins, produced by keratinocytes in the granular layer. The cornified cell envelope forms when these proteins are successively cross-linked by enzymes such as transglutaminases during keratinization. Transglutaminases are calcium-dependent enzymes that are activated by calcium influx into cells that undergo apoptosis during keratinization.

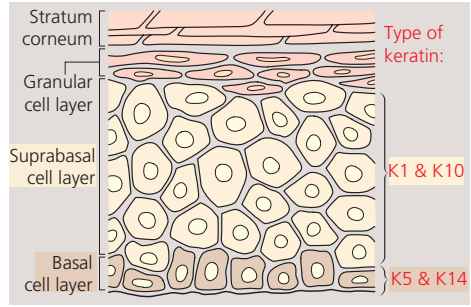


Fig. 1.16 Expression of keratin types in the epidermis.

MEMO 1–2 Ichthyosis caused by enzyme deficiency

- **Transglutaminase 1:** this is an enzyme that allows cell membrane components to link with protein molecules such as loricrin, involucrin, cystatin-α, and small proline-rich proteins. Without this activity, a normal cornified cell envelope does not form. For example, deficiency of transglutaminase 1 results in various ichthyoses, such as autosomal recessive lamellar ichthyosis and bathing suit ichthyosis (see Chapter 15).
- **ABCA12:** deficiency of the lipid transporter ABCA12 results in abnormal production of lamellar granules and incomplete formation of intercellular lipids, which is the underlying molecular basis of harlequin ichthyosis (see Chapter 15). The skin thickening seen in this condition is thought to result from a compensatory increase in the number of horny layer cells or an inhibition of the normal exfoliative process.
- **Steroid sulfatase:** deficiency of steroid sulfatase, which metabolizes sulfate cholesterol, inhibits normal exfoliation of horny cells and causes X-linked recessive ichthyosis (see Chapter 15).

MEMO 1–3 Activities of vitamin A

Vitamin A inhibits cholesterol sulfotransferases and decreases cholesterol sulfates, which is thought to stimulate exfoliation of the horny cell layers.

MEMO 1–4 Ceramide and its moisturizing function

The ceramide content of the horny cell layer is reduced in patients with atopic dermatitis. Ceramide is thought to be involved in disorders of dry skin and skin barrier function. In 2006 it was clarified that 20–50% of patients with atopic dermatitis had mutations in filaggrin genes, which reduces skin moisture retentivity (see Chapter 7).

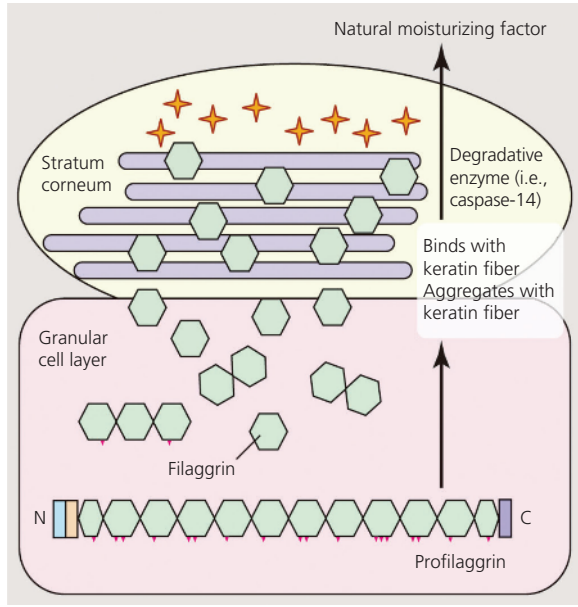


Fig. 1.17 Profilaggrin and filaggrin. Profilaggrin, which is in phosphorylated form, is stored in the keratohyalin granules of the granular cell layer. Profilaggrin is degraded into filaggrin through the process of dephosphorylation at the time of keratinization. Filaggrin aggregates and binds with keratin fibers in the stratum corneum to form the keratin pattern. Filaggrin ultimately degrades to low molecular weight substances such as urocanic acid and becomes a natural moisturizing factor that is involved in moisture retention and ultraviolet absorption.

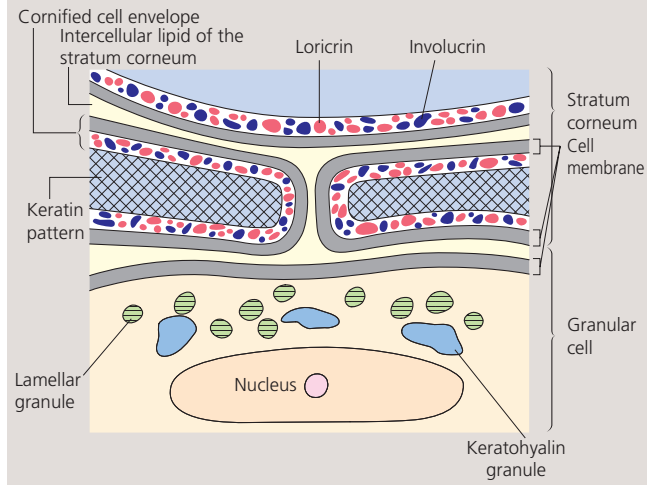


Fig. 1.18 The border between the epidermis and stratum corneum.

Horny layer (stratum corneum intracellular lipids)

The main function of intercellular lipids in the stratum corneum is to prevent excessive transepidermal water loss. These lipids consist mainly of ceramides (~50%), followed by cholesterols (~30%), free fatty acids, and cholesterol sulfates. Lamellar granules are found abundantly in the cytoplasm of the granular cell layers. These granules are released when the granular cells undergo apoptosis. The enzyme ABCA12 plays a significant role in the release of lipids from lamellar granules in granular cells. Ceramides are released by lamellar granules; free fatty acids are secreted from granular cell membranes. Cholesterol sulfates connect and stabilize the lipid structures between horny cells.

Exfoliation of horny cells

A key factor in the exfoliation of the stratum corneum is the degradation of horny cell intercellular lipids by lipases, a group of catabolic lipid enzymes and steroid sulfatases. Adhesion between keratinocytes is subsequently disrupted by proteases in the upper skin surface, resulting in the gradual exfoliation of the horny cell layer.

Melanocytes and melanin synthesis

Form and distribution of melanocytes

Melanocytes (pigment cells) are neural crest (ectoderm)-derived dendritic cells found in the basal cell layer and hair matrix (Fig. 1.19). Melanocytes (and Langerhans cells) are referred to as clear cells, since their cytoplasm contracts during dehydration and fixation in hematoxylin and eosin staining. Melanocytes display a characteristic brownish-black color in dopa oxidase staining. Approximately 1000–1500 melanocytes are seen per square millimeter of skin. An increase in melanocyte density is found in sun-exposed sites of the body, such as the face, and in physiologically pigmented sites, such as the external genitals.

The Golgi apparatus in the melanocyte is well developed and contains melanosomes in various stages of development (stages I, II, III, and IV). Melanin is produced in melanosomes from the amino acid tyrosine. Mature melanosomes are packaged and transported to the neighboring basal cells and suprabasal cells. Melanosomes transported to

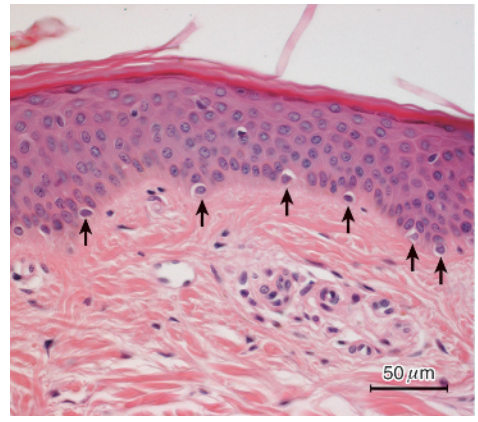


Fig. 1.19 Melanocytes. Melanocytes are seen as clear cells (arrows) under hematoxylin and eosin staining, because the cytoplasm of melanocytes shrinks during fixation.

MEMO 1–5 Causes of enhanced pigmentation

Adenocorticotropic hormones (ACTH), melanocyte-stimulating hormones (MSH), thyroid hormones, estrogens, ultraviolet rays, and X-rays are known to increase pigmentation of the skin.

MEMO 1–6 Association of tyrosinase with albinism

A child that has a congenital lack of tyrosinase is born with pale skin due to the lack of melanins (oculocutaneous albinism). In patients with Menkes' disease, there is extreme copper deficiency, which causes tyrosinase activity to decrease, resulting in reduced pigmentation

MEMO 1–7 Increase of 5-S-cysteinyl dopa (5-S-CD) in serum

In malignant melanomas, there is generally an increase in pheomelanin production, resulting in an increase of 5-S-CD in blood and urine. Therefore, an increase of 5-S-CD in the blood indicates metastasis of a malignant melanoma and its degree of spreading.

the basal epidermal keratinocytes aggregate in the upper part of the cytoplasm of the basal cells, forming a melanin cap to protect their DNA from UV radiation.

Racial differences in skin color are determined by the number and size of melanosomes. There is no difference in the distribution or density of melanocytes between races.

Biosynthesis of melanin

Melanin is a generic term for a group of substances called pigmented molecular phenolic polymers, which are indole compounds synthesized from tyrosines through polymer formation (Fig. 1.20).

Melanins in humans are broadly classified as eumelanin (black or intrinsic melanin) and pheomelanin (yellow melanin). Melanins in human skin and hair are complexes of these two types, and their ratio determines skin and hair color.

Tyrosines are supplied by blood, are subsequently oxidized by tyrosinase, which contains copper, and are finally metabolized into dopas and then into dopaquinones. Tyrosinase is the rate-limiting enzyme that catalyzes these two reactions during melanin synthesis (see Fig. 1.20).

Dopaquinones are automatically oxidized to become indole compounds that bind together to synthesize eumelanins. The presence of cysteine at this stage enables the conversion of dopaquinones, through their binding to cysteine, into 5-S-cysteinyldopa, which polymerizes to produce pheomelanins.

Melanosomes

These subcellular organelles are enclosed by a lipid double membrane in which melanins are exclusively produced. Melanin synthesis occurs when tyrosinases, which are synthesized by the Golgi apparatus, are carried to premelanosomes in the agranular endoplasmic reticulum. As melanin production increases, melanosomes enlarge. The formation of melanosomes is divided into stages I–IV by the degree of melanin deposition (Fig. 1.21). For example, a melanosome in stage IV is football shaped and measures approximately 500–700 nm along its major axis. It is transported from the dendrites to the neighboring epidermal keratinocytes.

Functions of melanin

The most important role of melanin is to confer protection to the skin from UV irradiation and thus to reduce the occurrence of malignant tumors and sunlight injury. The darker the skin, the lower the incidence of skin cancer caused by UV light.

Exposure to sunlight darkens the skin, and this process can occur rapidly due to oxidation of melanins or can happen several days after exposure, when there is an increase in melanin synthesis and mature melanosome formation.

Melanins can also absorb harmful active enzymes, metals, and drugs.

Langerhans cells

Langerhans cells are bone marrow-derived dendritic cells specific to stratified squamous epithelia such as the skin. Discrete Langerhans cells are frequently seen in the middle and upper suprabasal cell layers (Fig. 1.22). The cells are distributed at a density of 400–1000/mm^2. They lack tonofilaments and cell attachment structures, such as desmosomes, and they migrate. By electron microscopy, a few fibrillary components and Birbeck granules, whose cross-section is a characteristic tennis racket shape, are observed in the cytoplasm (see Fig. 1.55). Birbeck granules may be either Golgi apparatus derived or membrane derived, and are thought to be involved in receptor-mediated endocytosis.

Langerhans cells present antigens to T cells and can be easily distinguished from other cell types since they are ATPase, CD1a and S-100 protein positive.

Merkel cells

Merkel cells are found in the epidermal basal cell layer and are involved in touch sensation. They are seen at particularly high density in the finger pulps, oral mucosa, and hairy areas (the hair roots). They have angular plasma membrane projections and connect to adjacent keratinocytes by desmosomes (Fig. 1.23). Sensory (free) nerve endings are connected by synapses beneath the Merkel cells. Multiple dense-core granules (Merkel cell granules) are found in the cytoplasm. Following physical stimulation, they secrete neurotransmitters that convey tactile information to the underlying sensory nerve.

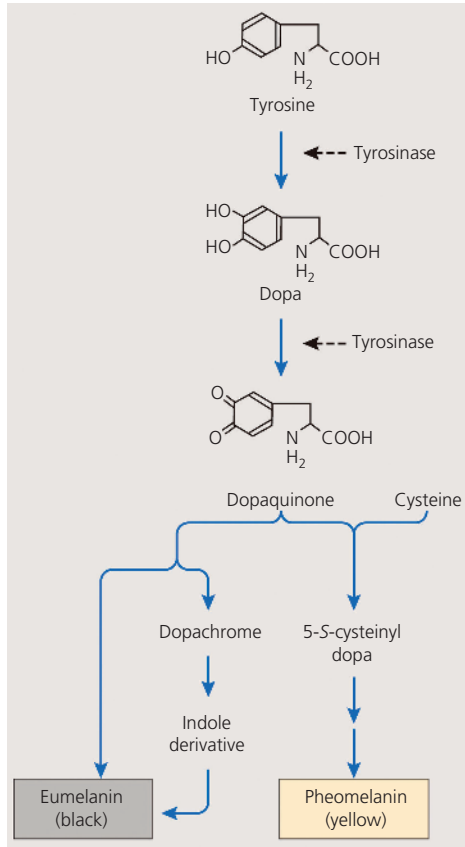


Fig. 1.20 Biosynthesis of melanin.

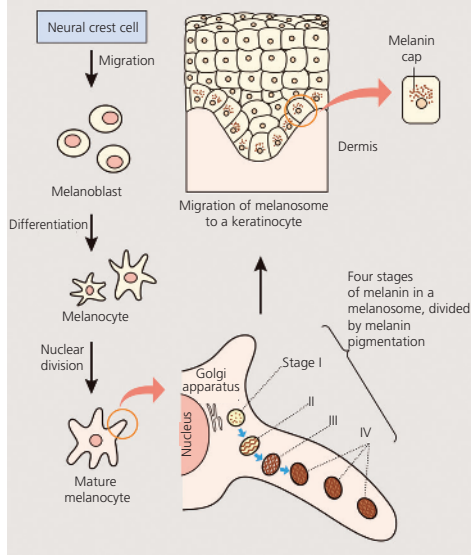


Fig. 1.21 Maturation of melanosomes.

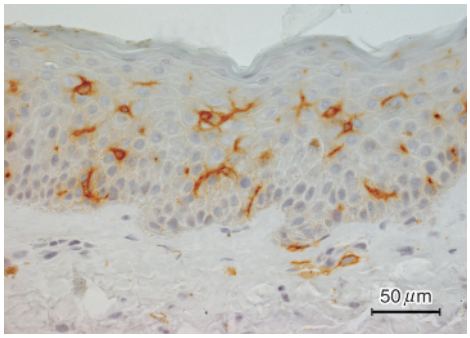


Fig. 1.22 **Langerhans cell (immunostaining against CD1a).**

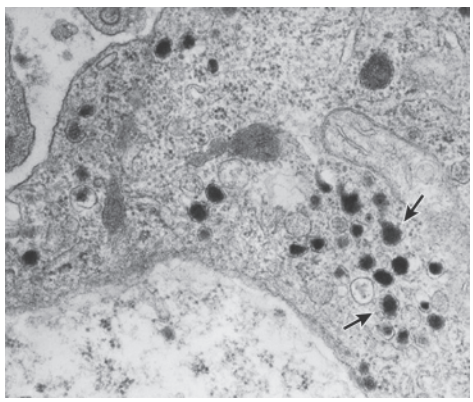


Fig. 1.23 **Birbeck granules of Langerhans cell (arrows).**

Dermis

Structure of the dermis

The dermis is the structure beneath the epidermis, and the two are separated by the basement membrane (see Fig. 1.1). The dermis is approximately 15–40 times thicker than the epidermis and consists of three layers.

- **Papillary layer:** this is the dermal area that projects between the epidermal ridges. It consists of thin fiber components and sensory nerve endings and is richly supplied with capillary blood vessels.
- **Subpapillary layer:** this area is subjacent to the epidermis and has the same components as the papillary layer.
- **Reticular layer:** this layer accounts for the largest part of the dermis. It has dense connective tissue consisting of fiber components. The lowermost part is in contact with the subcutaneous fat. There are also blood vessels and nerves in parts of the reticular dermis.

The dermis is composed of fibrous tissue and dermal matrix formed by cells in the interstitium (Fig. 1.24). The major dermal components are collagen fibers (mainly collagen types I and III), with smaller amounts of elastic fibers, reticular fibers, and matrix. Fibroblasts, macrophages, mast cells, plasma cells, endothelial cells, and nerve cells make up the cellular composition of the dermis.

Interstitial components

Collagen fibers

Collagen fibers account for 70% of the weight of dry dermis (Fig. 1.25) and appear white to the naked eye. The collagen fibrous component is poorly extensible; however, it is extremely tough and especially resistant to tension applied parallel to the fibers. This characteristic is important in maintaining the dynamic strength of the skin.

Collagen fibers form from aggregations of thin fibrils. The strength and thickness of the collagen fiber correlate with the number of fibrils. Thin collagen fibers are sparsely seen in the papillary and subpapillary layers; however, collagen bundles with thick, fully developed collagen fibers are densely distributed in the reticular upper dermal layers.

By light microscopy, the proteinaceous collagen fibers appear pink with hematoxylin and eosin staining, red with Elastica van Gieson staining, and blue with Azan

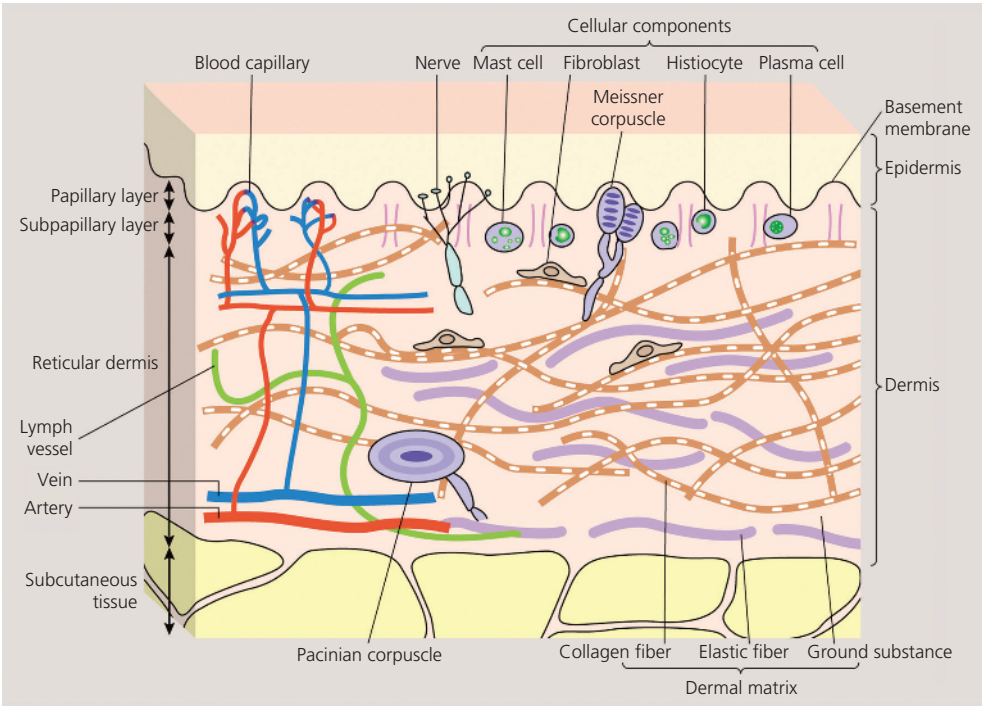


Fig. 1.24 Structure of the dermis.

or Masson trichrome staining. By electron microscopy, collagen fibrils appear as long fibers with a diameter ranging between 100 and 500 nm and display cross-striations that repeat at intervals of 60–70 nm (see Fig. 1.25). Fibrils become collagen fibers by aggregating with glycoproteins. A thick collagen bundle can reach a diameter of 2–15 µm.

Collagens are produced in the rough endoplasmic reticulum of fibroblasts. Helical procollagens with three α-chains are first secreted, and their molecular ends are cut by procollagen peptidase to become tropocollagens. The molecules then cross-link to each other with regular gaps that form the striped collagen fiber (Fig. 1.26).

Twenty subtypes of collagen molecules with α-chains of different molecular structures have been discovered (Table 1.2); however, type I collagen accounts for 80% of the collagen fibers that make up the dermis. Reticular fibers, which are distributed in the perivascular regions, are thin argyrophilic fibers that do not form thick fiber bundles. They are composed of type III collagen and account for about 15% of all fibers. The remaining 5% of collagen fibers are thought to be type V collagen. Types

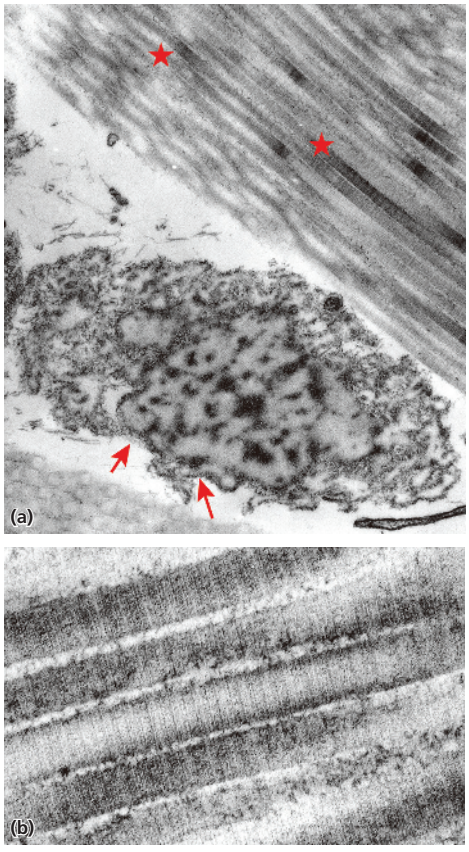


Fig. 1.25 Electron microscopy of the dermal matrix. a: Collagen fibers (stars) and elastic fibers (arrows). b: High-power magnification of collagen fibers. Stripes approximately 60–70 nm in width are seen.

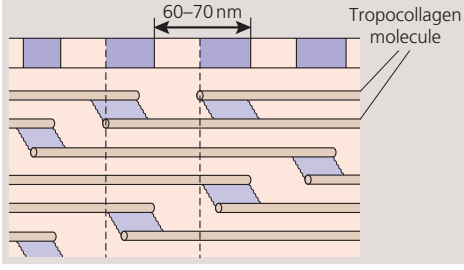


Fig. 1.26 Stripes of collagen fibers. Fine fibrils (tropocollagens) have cross-links, giving the fibers the appearance of stripes with intervals of 60–70 nm.

Table 1.2 Types of collagen fibers.

Fiber	Type
Fibrillar	I (dermis), II, III, V, XI
Basement membrane	IV
Anchoring fibril	VII (basement membrane)
Network-forming	VIII, X
FACIT*	IX, XII, XIV, XVI, XIX, XX
Microfibril	VI
Multiplexin	XV, XVIII
Other	XIII, XVII (basement membrane)

* Fibril associated collagen with interrupted triple helix.

IV, VII, and XVII are mainly found in the basal membranes in association with epidermal keratinocytes.

Elastic fibers

Elastic fibers are not as tough as collagen fibers; however, they are extremely elastic and are found abundantly in the dermis of the scalp and face, as well as in extensible structures such as arteries and tendons.

Elastic fibers found in the reticular dermis tend to be thicker than those in the papillary dermis. In the reticular layers, elastic fibers are scattered among collagen bundles and are orientated parallel to the skin surface. In the papillary layer, elastic fibers tend to be thinner and are orientated perpendicular to the skin surface. Nearer the skin surface, the elastic fibers form arches from which thin fibers project perpendicularly to reach the lamina densa. Elastic fibers are also connected to the lamina densa of sweat ducts, smooth muscle, nerves, and blood vessels.

Elastic fibers vary between 1 and 3 μm in diameter. They cannot be differentiated from collagen fibers by hematoxylin and eosin staining. Elastic fibers stain black in Elastica van Gieson or Weigert staining, and reddish-violet in aldehyde fuchsin staining. By electron microscopy, the striped pattern that characterizes collagen fibers is not observed (see Fig. 1.25).

Ground substance (extracellular matrix)

Ground substance (extracellular matrix) is a gelatinous amorphous compound of sugar and proteins that is found between fibers and cells in the dermis. The

components of ground substance are principally proteoglycans and glycoproteins whose molecular weights range from 150,000 to 250,000 kDa and whose sugar content is between 2% and 15%.

These molecules stabilize the dermal fibers to give flexibility to the skin. Fibronectin is a glycoprotein that contains a domain connecting fibrin, heparin, and collagen. It also binds integrin receptors on the cell surface and is involved in cell proliferation, differentiation, and wound healing. In addition to proteoglycans and glycoproteins, lymph-derived tissue fluid and blood make up the remainder of ground substance and are involved in the transport of substances essential to cellular activities and metabolism.

Proteoglycans are large molecules made up of multiple glycosaminoglycans (mucopolysaccharides) connected with backbone proteins. Glycosaminoglycans are mostly produced by fibroblasts in the dermis and are rich in hyaluronic acids, which are associated with moisture retention.

Cellular components

Fibroblast

Fibroblasts originate from mesenchymal cells and produce collagen and elastic fibers as well as glycosaminoglycans. They appear as thin spindle-shaped cells interspersed amongst collagen fibers (Fig. 1.27). By electron microscopy, multiple Golgi apparatuses and granular endoplasmic reticuli are seen in fibroblast. When collagen fibers are produced and the dermis matures, fibroblasts stop their activities and become fibrocytes. At this stage, their cell nuclei shrink and fewer endoplasmic reticuli are seen. Adrenal cortex hormones and thyroid hormones are involved in this process.

Histiocytes

Histiocytes are macrophages that are involved in antigen presentation to T cells. They are broadly distributed in the connective tissue and intermingle with fibroblasts on the outside of endocapillary cells (Fig. 1.28). By light microscopy, histiocytes are seen to have a large spindled or star shape with a small, round nucleus. By electron microscopy, concave nuclei and pseudopodial protrusions are observed. Histiocytes contain Golgi apparatuses, smooth and rough endoplasmic reticuli, and lysosomes. The lysosomes contain hydrolases and active acid phosphatases. Histiocytes release

MEMO 1–8 Abnormalities of elastic fibers or collagen fibers

If elastic fibers are decreased, lost or denatured, dermatolysis or senile cutis rhomboidalis nuchae may occur. Congenital abnormalities of the fibrillin protein result in Marfan syndrome (see Chapter 18). Abnormalities in dermal collagens may cause Ehlers–Danlos syndrome.

MEMO 1–9 Histiocytes, monocytes, macrophages

Macrophages are large phagocytic cells of which there are two types.

- **Free macrophages:** e.g., monocytes in blood, and migrating macrophages in granulomas.
- **Fixed macrophages:** e.g., histiocytes in the dermis and subcutaneous tissue, and Kupffer cells.

MEMO 1–10 Histiocytes, the key to pathological diagnosis

Epithelioid cells, Touton giant cells, xanthoma cells, and foreign body giant cells in an epithelioid cell granuloma are histiocytes that are pathologically present in an atypical form (see Chapter 2).

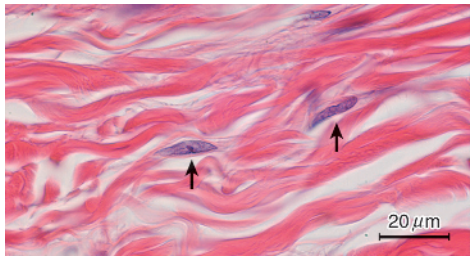


Fig. 1.27 **Fibroblasts (arrows).**

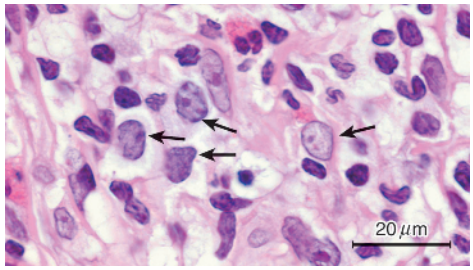


Fig. 1.28 **Histiocytes (arrows).**

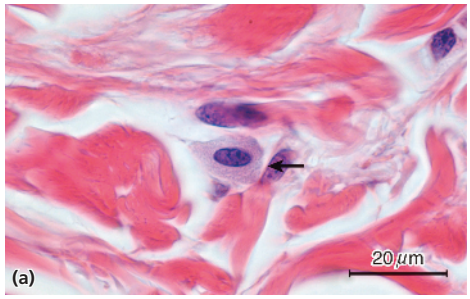
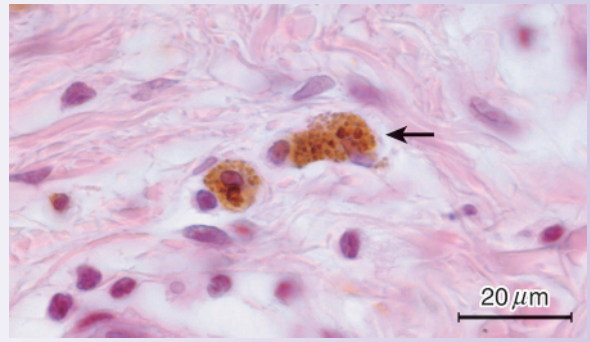


Fig. 1.29 **Mast cells.** a: Hematoxylin and eosin staining. b: Metachromasia is seen by toluidine blue staining.

MEMO 1–11 Melanophages

Melanin granules that have exfoliated from the epidermis to the dermis are often phagocytosed by histiocytes. Histiocytes that become brownish-red after repeatedly phagocytosing melanin granules are called melanophages.



collagenase and lysosomal enzymes, such as elastase, to digest the interstitium. They are also involved in organ repair, and they degrade and phagocytose foreign bodies and present them as antigens to T cells.

Mast cells

Mast cells are found in the dermis around capillaries and in the periphery of subcutaneous tissue. The shape is round to spindled, and the diameter is 10 μm (Fig. 1.29). Mast cells produce various vasodilatory and hyperlucent chemical mediators. Mast cell granules stain reddish-violet in toluidine blue and methylene blue, and exhibit metachromasia. Cutaneous mast cells resemble basophils in form and function; however, their characteristics differ slightly from those of other organs, because they differentiate in skin during intrauterine life.

Mast cells contain intracytoplasmic granules that appear by electron microscopy as round structures, each with a diameter of 0.3–0.5 μm, evenly distributed in the cytoplasm. Chemotransmitters in the granules are released outside the cell under various stimuli, such as in type I allergic reactions (Fig. 1.30). The main components of the released substances are histamines and heparins, followed by enzymes, including neutrophil chemotactic factors (NCF), eosinophil chemotactic factors of anaphylaxis (ECF-A), tryptase, chymase, and

tumor necrosis factor (TNF)-like substances. The mast cell may also produce and release inflammatory substances such as prostaglandins, leukotrienes, and platelet-activating factors.

Plasma cells

Plasma cells are differentiated B cells that have been stimulated by an antigen. They produce antibodies and are involved in humoral immunity. The shape varies from round to pear-shaped, and the diameter ranges from 8 to 14 μm, which is twice that of a leukocyte. They have a wheel-shaped nucleolus and many Golgi apparatuses (Fig. 1.31).

Dermal dendrocytes

Dermal dendrocytes are found in the dermal upper layer (in and between the papillary layer and the reticular layer). Thought to be immunocompetent cells, they are characterized by the presence of clotting factor XIIIa.

Vascular channels and nerves

Blood vessels

Arterial branches distributed in the skin (Fig. 1.32 and Fig. 1.33) are connected with each other in the deep dermal layer to form a horizontal network (subcutaneous plexus). From the subcutaneous plexuses, branches ascend to form a second vascular network in the lower papillary layer (subpapillary plexus). These

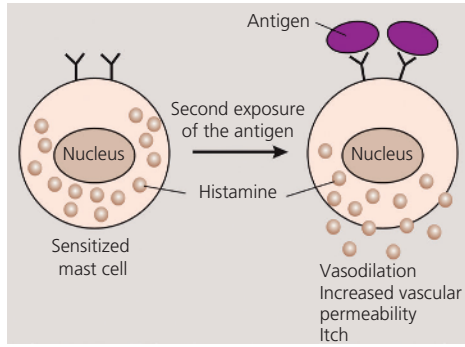


Fig. 1.30 Mast cell sensitization.

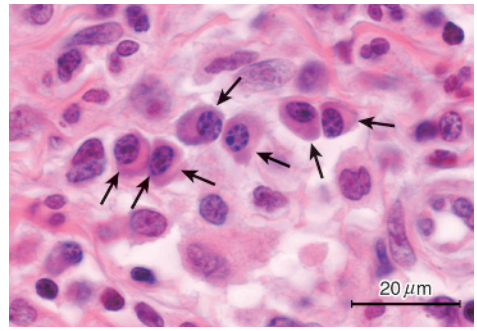


Fig. 1.31 Plasma cells (arrows).

MEMO 1–12 Discriminating between blood vessels and lymph vessels

The important points in discriminating between these are tabulated below.

Item	Blood vessel	Lymph vessel
Podplanin	Negative	Positive
Factor VIII	Positive	Basically negative
Basal layer	Extended and multi-layered	Intermittent
Intercellular connection	Developed	Weak
Lumen shape	Round	Irregular
Elastic fiber stain	Arteries: Positive in the internal elastic layer Veins: Negative	Negative

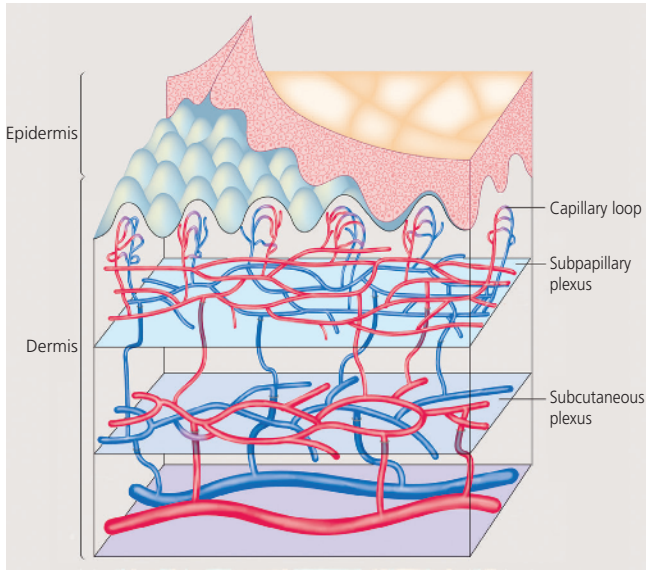


Fig. 1.32 Distribution of blood vessels in the dermis.

arteries in the dermis are arterioles. The subpapillary plexus gives rise to arterioles that ascend through the papillary layer, forming capillary loops in the upper papillary layer before anastomosing with venules that connect to each other to form two types of venous plexuses, whereby the blood flows into the cutaneous veins (see Fig. 1.32).

There are also distinctive vascular plexuses in the vicinity of the cutaneous appendages. For example, the peripheral regions of the eccrine glands are particularly rich in vascular networks, which control blood flow volume and body temperature. Moreover, hair follicles in the anagen (growth) stage are richly supplied with blood vessels in the surrounding dermal tissue.

Blood can also circulate directly from arteries to veins by means of arteriovenous anastomoses, which are supplied by sympathetic nerves. These anastomoses control peripheral blood flow and are involved in the regulation of body temperature. Glomus apparatuses, which have spherical anastomotic branches, are widely seen in the skin. They are particularly well developed in the fingers, at the apical ends of the toes and below the nails.

By electron microscopy, endothelial cells, pericytes, and the multilayered basement membrane in the peripheral interstitium may be observed in the

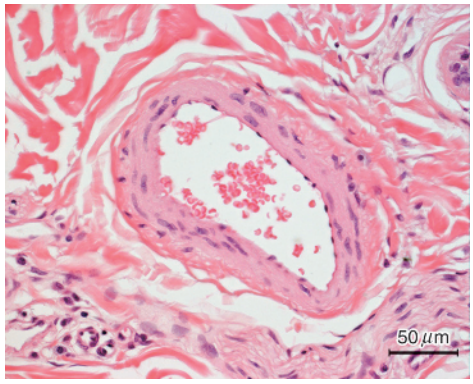


Fig. 1.33 Cross-section of a blood vessel (hematoxylin and eosin).

capillaries. In the endothelial cells, stick-shaped Weibel–Palade granules (diameter ~200 nm; length ~1 μm) containing factor VIII associated with histamines and blood coagulation may be seen. Pericytes have a vasoconstrictive effect and are observed along the walls of endothelial cells.

Lymphatic vessels

Lymphatic vessels are distributed around the subpapillary layer and are categorized as postcapillary, dermal or subcutaneous. The endothelial cells of the lymph capillaries are thin and are not associated with pericytes or the basal membrane. They are partly ruptured and are surrounded by loose collagen and elastic fibers (Fig. 1.34). The structure of lymph vessels is not as regular as that of blood vessels. Aggregated cutaneous lymphatic fluid passes through the regional lymph nodes and flows into the blood vessels. Podplanin is known to be a lymphatic endothelial cell marker.

Nervous system

The nerve fiber bundle is covered with a membrane in the lower dermal layers. The nerve fibers change from myelinated to non-myelinated in the upper dermal layers, where the nerve bundles branch into numerous fibers that then innervate the superficial dermis and peripheral appendages (Fig. 1.35). sensory nerves transmit tactile, pressure, pain, and temperature sensation. Autonomic nerves innervate blood vessels, sweat glands, and other appendages.

Sensory nerves

Sensory nerve structures include free nerve endings, which sense pain, Merkel cells (described earlier), which perceive tactile sensation in the epidermal basal layers, and nerve end bulbs, which transmit tactile, pressure, and vibration sensation.

Free nerve endings

Free nerve endings are distributed in the upper dermal and papillary layers. Some adhere to Merkel cells in the dermal papillary layer, whereas others infiltrate the dermis directly. Non-myelinated nerves transmit pain sensation.

End corpuscles

The end corpuscle is a specific sensory nerve terminal that consists of different types as described below.

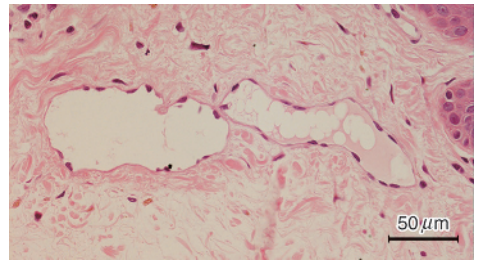


Fig. 1.34 Cross-section of lymphatic vessels (hematoxylin and eosin).

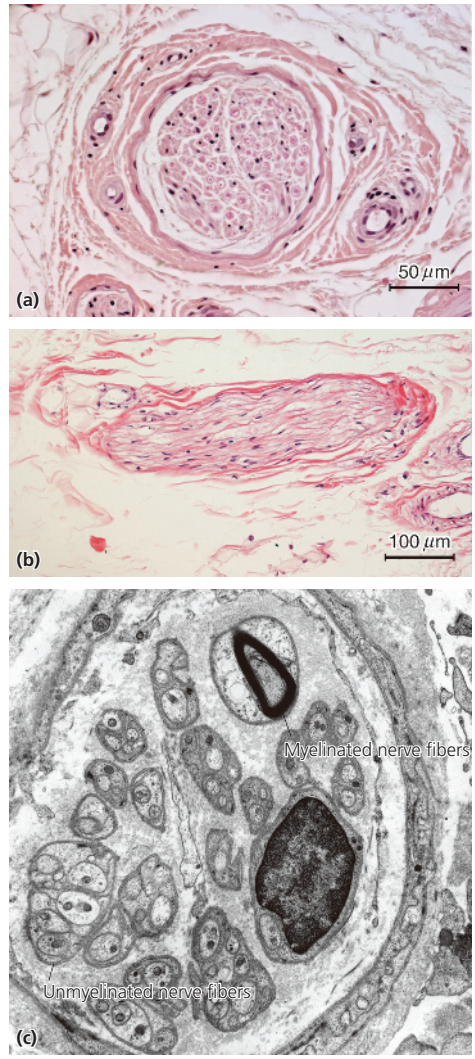


Fig. 1.35 Cross-section of nerve fibers. a: Myelinated nerve fibers. b: Unmyelinated nerve fibers. c: Electron microscopy.

MEMO 1–13 Sympathetic nerves distributed in the eccrine sweat glands

The sympathetic nerves are generally adrenergic; however, sympathetic innervation in the eccrine glands is cholinergic.

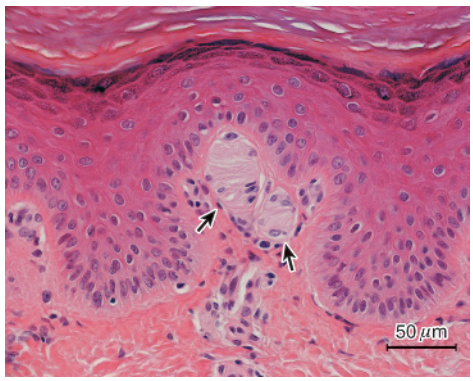


Fig. 1.36 Meissner corpuscles (arrows).

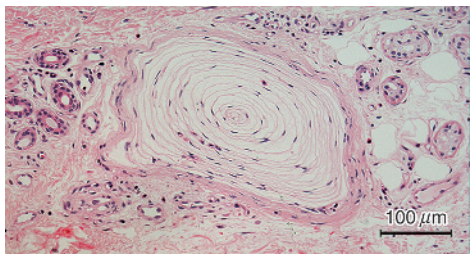


Fig. 1.37 Pacinian corpuscle (hematoxylin and eosin staining).

Meissner end corpuscles are present in the dermal papillae of the palms, soles, lips of the mouth, and external genitals. They perceive tactile and pressure sensations (Fig. 1.36). Pacinian corpuscles are seen in the deep dermal layer and subcutaneous tissue of the palms, soles, and external genitalia. They have an oval structure, measure approximately 1 mm along the major axis and can be clearly observed by light microscopy (Fig. 1.37). The central nerve fiber has a multilayered concentric structure. They are involved in vibratory perception.

Autonomic nerves

Autonomic nerves are principally distributed in the sweat glands, arrector pili muscles, blood vessels, and glomus apparatus. They control the functions of these structures. Cholinergic non-myelinated sympathetic nerves are distributed in the eccrine sweat glands. The adrenergic sympathetic nerves are distributed in the arrector pili muscles and blood vessels.

Subcutaneous fat tissue

The subcutaneous tissue is the layer between the dermis and the fascia. It cushions the skin against external physical pressure, retains moisture, and generates heat.

The subcutaneous tissue is largely composed of fat cells. Assembled fat cells are separated by a connective fibrous septum to form fat lobules. Fiber bundles called retinaculae cutis produced in the dermis firmly connect the dermis to the underlying fascia and periostea. These bundles run through the subcutaneous tissue. The main component of the fat droplet is triglyceride, composed of olein acid and palmitin acid. Since a large droplet accounts for most of the contents of the cellular cytoplasm in the fat cell, other cellular organelles are pushed to the edge. Multiple smooth muscles called tunicae dartoses are characteristically seen in the dermal deep layers and subcutaneous tissues of the scrotum, penis, labia majora, and nipples (Fig. 1.38). The boundary between the subcutaneous tissue and skeletal muscle is called the musculus cutaneous. It is not apparent at sites where muscles of expression (e.g., the face) are found.

The thickness of the subcutaneous tissue depends on several factors, including the body site and age.

The subcutis is particularly thick in the cheeks, breasts, buttocks, thighs, palms, and soles; it is thin in the eyelids, dorsal aspect of the nose, lips of the mouth, and labia minora, and absent in the foreskin. Subcutaneous tissue tends to develop and enlarge in newborns and at puberty. In embryos and newborn infants, heat is produced at a rapid rate by brown fat tissue in the dorsal region.

Appendages

Hair apparatus

The hair apparatus protects the scalp from external forces such as sunlight and controls the amount of heat produced in the head. Eyelashes protect the eyes from dust, and armpit and pubic hair absorb mechanical friction. The number of hairs on the scalp averages 100,000. The hair apparatus, which consists of hair and hair follicles, is distributed throughout the skin, except on the lips of the mouth.

Hair follicle

The structure that encloses the hair shaft is the hair follicle. It is aligned oblique to the skin surface. Part of the hair follicle is slightly enlarged to form a hair bulge to which the base of the arrector pili muscle is connected (Fig. 1.39 and Fig. 1.40). Dermal stem cells reside in the hair bulge. Sebaceous glands are seen above the bulge area and apocrine glands open farther above. The base of the hair root during the anagen (growth) stage bulges out and is called the hair bulb. It contains a group of cells that form the hair papilla. The hair follicle has a funnel-shaped appearance (hair infundibulum). The hair follicle is surrounded by two layers: an epithelial inner layer and a connective tissue outer layer. The epithelial inner layer consists of an inner and an outer root sheath. The connective tissue component is called the connective tissue sheath.

Connective tissue sheath

The connective tissue sheath (CTS) covers the external aspect of the hair follicle and is in contact with the dermis. Collagen fibers are arranged concentrically within the CTS but are oriented longitudinally outside the CTS. Elastic fibers can be found among these collagen fibers.

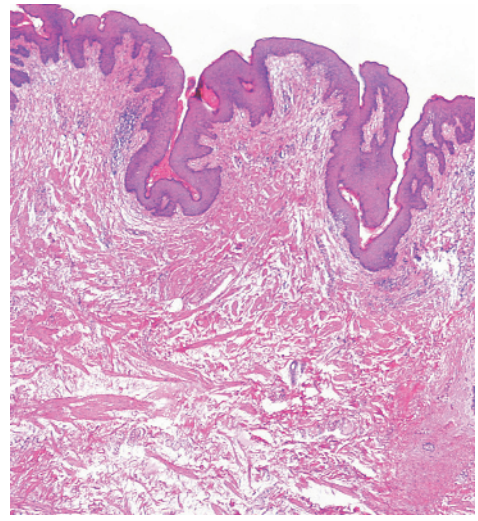


Fig. 1.38 **Tunica dartos.**

MEMO 1–14 Unusual keratinization of the outer root sheath

When cells in the outer root sheath denucleate and keratinize without passing through the granular layer or becoming flat, it is called trichilemmal keratinization.

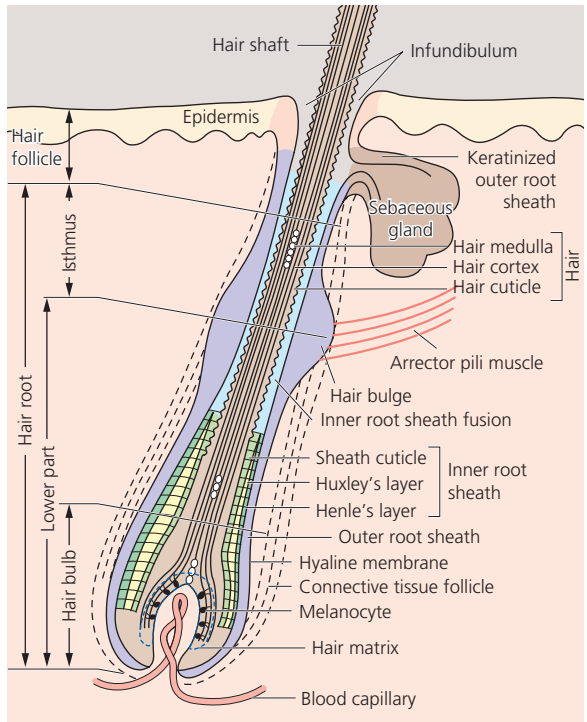


Fig. 1.39 **Longitudinal section of the hair follicle.**

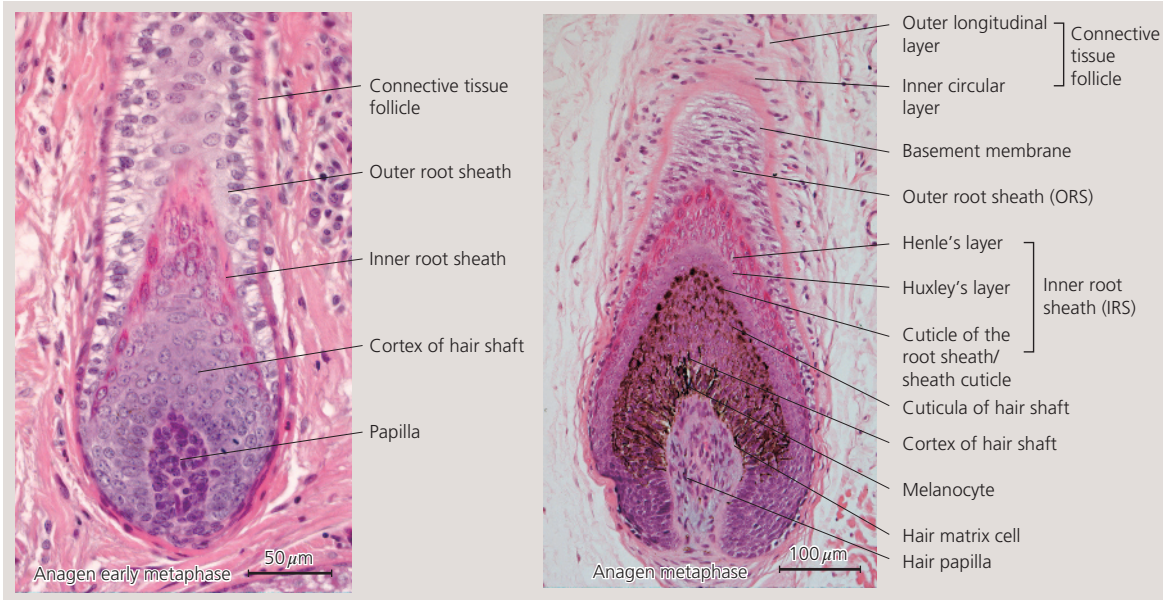


Fig. 1.40-1 **Longitudinal cross-section of the structure of the hair follicle (hematoxylin and eosin staining).**

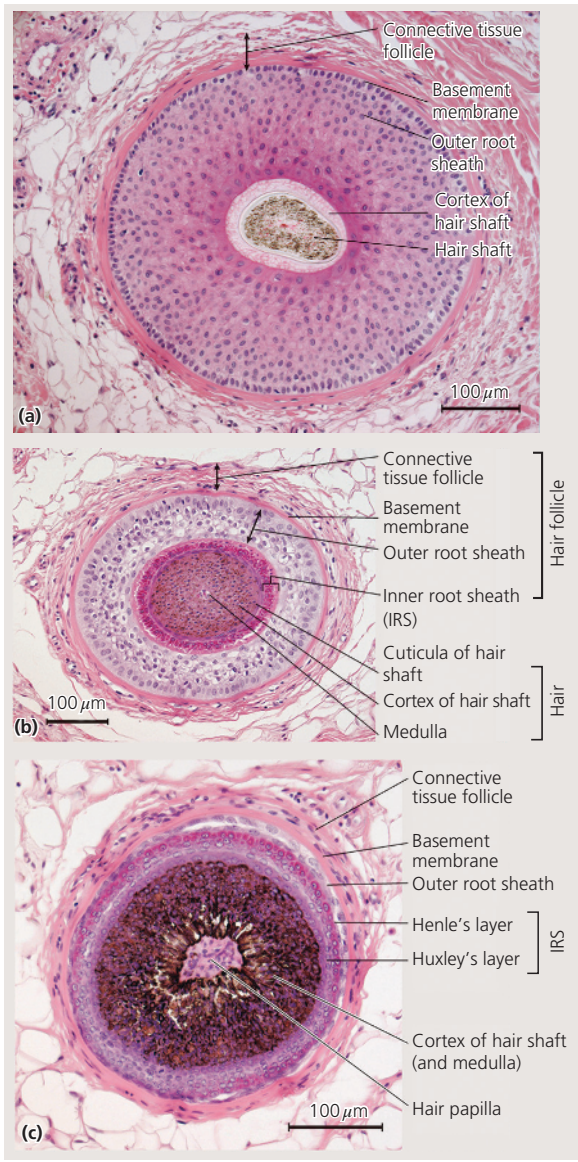


Fig. 1.40-2 Cross-section of the structure of the hair follicle (hematoxylin and eosin staining). a: Hair follicular isthmus. b: Lower part of a hair follicle. c: Hair bulb. (See Fig. 1.39 for the longitudinal positions.)

Outer root sheath

The outer root sheath (ORS) is the outermost part of the hair infundibulum (the innermost two layers). A keratinized structure, it contains keratinocytes that have light cytoplasm without keratohyalin granules. The outer aspect of the ORS is separated from the CTS

by a basement membrane. The inner aspect of the ORS is connected by desmosomes with the Henle's layer, which is the outermost layer of the inner root sheath.

Inner root sheath

The inner root sheath (IRS), found within the ORS, consists of capsular layers, Huxley's layer (consisting of a double layer of cells), and Henle's layer (containing a single layer of cells). The capsular cuticles anchor and entangle with each other, and their apical tips function as hooks to stabilize the hair. Henle's layer is connected with the ORS by desmosomes.

Keratinization occurs in the IRS close to the interfollicular epidermis. By hematoxylin and eosin staining, eosinophilic trichohyalin granules are seen in the IRS, especially within the Henle's and Huxley's layers. The process of keratinization terminates at the level of the opening of the sebaceous gland and is followed by exfoliation.

Hair bulb

The hair bulb is the bulge of the hair follicle, with a dermal hair papilla at its center. The dermal hair papilla is surrounded and covered by a hemi-spherical structure known as the hair matrix layer, where hair and inner root sheath cells grow and extend upward. The outer root sheath forms the outermost layer of the hair bulb. Melanocytes that provide hairs with melanin are also found in the hair matrix.

Hair shaft

The hair shaft consists of a three-layered structure of medulla (inner layer), cortex (middle layer), and cuticle (outer layer, also called the cuticula).

Tonofilaments are aligned in the direction of the cortical axis, and a pattern similar to that observed for keratin by electron microscopy is seen at the tips of the tonofilaments. Keratinization occurs in the cortex; however, unlike in the epidermis and inner root sheath, keratohyalin and trichohyalin granules are not seen. In addition, the keratins produced in the hair cortex are rich in cysteines, glycines, and tyrosines. The hair keratins are generally known as hard keratins, and they also can be seen at other sites, such as the nails.

Within the hair shaft cuticle, the cortex is covered in a scale-like pattern of flattened cells that are attached to the capsular cuticles of the inner root sheath. This connection becomes the outermost layer of the hair

shaft, protecting that shaft. Excessive physical damage to hair, for example from overbrushing and excessive use of hair dyes and other chemicals, may damage the hair cuticles, resulting in loss of the natural glow of the hair.

Hair color differs according to the size and number of melanosomes. Dark hair contains large and/or numerous melanosomes; red hair contains large amounts of pheomelanins.

Hair cycle

The hair cycle can be subdivided into the anagen (growth), catagen (transition), and telogen (rest) phases (Fig. 1.41). About 85% of scalp hairs are in the anagen phase, which generally lasts for several years after the emergence of the hair. This is followed by a slowing of the growth rate during the catagen phase, which lasts between 2 and 3 weeks. About 1–2% of scalp hairs are in the catagen phase and grow 0.3–0.5 mm in length per day. The hair then stops growing and remains in the telogen phase for several months. Approximately 15% of scalp hairs are in this phase. As new hairs are produced, hair within the same follicle in the telogen phase falls out. About 100 hairs are lost per day. As hair follicles transition from the anagen to the catagen phase, they begin to contract and cell division stops. The cells in the hair follicle also lose their ability to divide in the telogen phase, and they ascend to the elevated part of the hair. The hair root then has a stick-like appearance and is called a club hair. In the telogen phase, macrophages phagocytose melanin pigments and cell fragments in the hair papilla. During the anagen phase, cell division begins at the surface of the hair follicle.

The part of the hair below the hair bulge contains stem cells, and expands and contracts during the hair cycle. The human hair cycle differs for each hair; however, the overall number of hairs remains roughly constant.

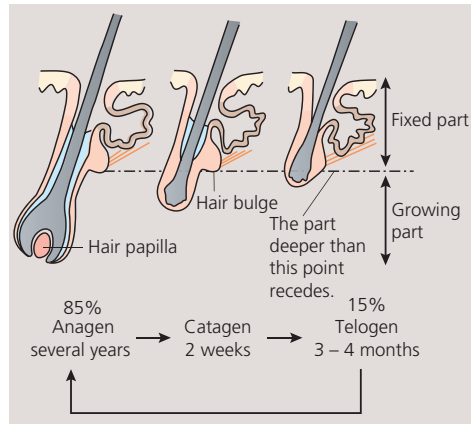


Fig. 1.41 **Hair cycle.**

Arrector pili muscle

The arrector pili muscle consists of a strand of smooth muscle that connects at the level of the hair bulge. It contracts in response to cold and to emotional factors such as fear and surprise, and that contraction pulls the hair upwards, causing "goose bumps." Goose bumps may accompany shivering that occurs to raise the body temperature. The arrector pili muscle is controlled by adrenergic sympathetic nerves.

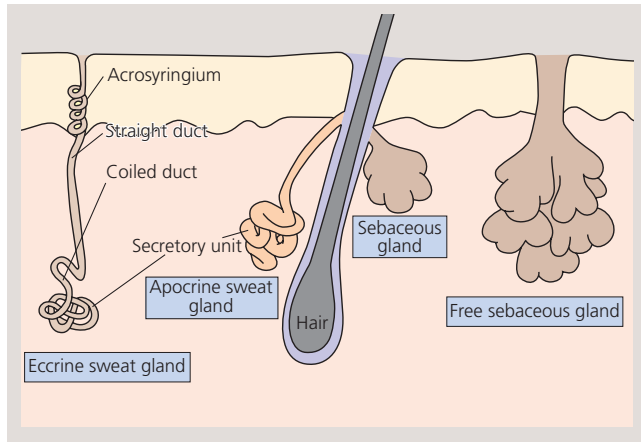


Fig. 1.42 **Sebaceous and sweat glands.**

Sebaceous glands

Sebum is produced by the sebaceous glands (Fig. 1.42) and is emulsified on the skin surface to form fatty acids, wax esters, and triglycerides that coat the skin surface. This coat is acidic, with a pH ranging from 4 to 6, and it has bactericidal properties (acid mantle). Sebum and sebaceous glands prevent invasion and infection by pathogens and toxic substances. Additionally, the sebaceous glands control water loss from the skin and help maintain moisture in the horny cell layers.

The sebaceous glands are widely distributed throughout the skin, except in the palms and soles and some mucous membranes. Mostly associated with hair follicles, they release sebum in the infundibular portion of the hair follicle. Sites at which there is a high density of sebaceous glands are called seborrheic zones. These are seen in the scalp, face (the T zone, which includes the forehead, regions of the glabella, and the nasolabial groove), sternal regions, armpits, navel, and external genitalia. The seborrheic zone is very densely distributed with sebaceous glands (400–900/cm^2). These glands are called free sebaceous glands because they are not attached to hair follicles. Meibomian glands, found in the eyelids, are a type of free sebaceous gland.

The sebaceous gland is composed of sebaceous lobules and a duct that carries sebum to the hair follicle. Sebocytes produced by cell division migrate into the lobules during maturation and acquire fat droplets. As they migrate towards the center of the gland, the cells rupture, releasing sebum in a process called holocrine secretion (Fig. 1.43).

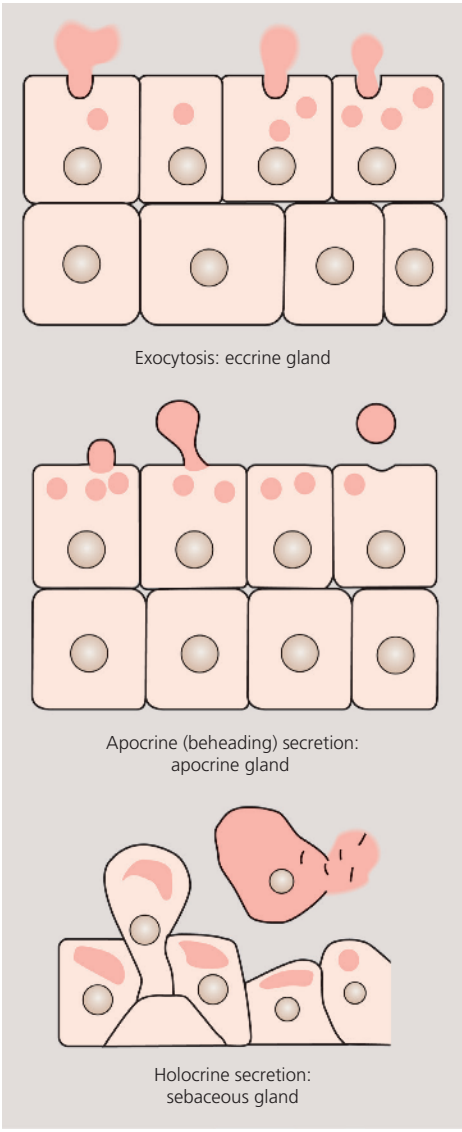


Fig. 1.43 **Types of secretion.**

The amount of sebum secretion changes with age. Large amounts of sebum are produced in newborn infants. Production begins to increase again from puberty. The secretion of sebum peaks in women in their second and third decades of life and in men in their third and fourth decades of life, decreasing thereafter. The amount of sebum secretion is controlled predominantly by sex hormones: testosterone in men and adrenal androgens in women. Hormones derived from the mother are thought to influence sebum secretion in the newborn.

Sweat glands

There are two main types of sweat glands in humans: eccrine glands, which are distributed throughout most of the body, and apocrine glands, which are found at specific sites of the body. Both are hair follicle-associated glands consisting of a secretory part and a sweat duct. The secretory parts are coiled and extend in the deep dermal layer and subcutaneous tissue (see Fig. 1.42).

Eccrine sweat glands

Eccrine sweat glands are found over the entire body, especially in the palms, soles, and armpits, at a density ranging from 130 to 600/cm^2. Approximately 3 million eccrine glands are found in the human body. Perspiration is enhanced by thermal stimulation, which is associated with body temperature control, and may also be stimulated by mental strain or gustatory stimulus (gustatory sweating). The total amount of perspiration in a day is controlled by acetylcholines and averages 700–900 mL in adults.

The secretory portion of the eccrine gland consists of two cell types within a single layer. These cells are surrounded by flat myoepithelial cells (Fig. 1.44a). Cells on the basal layer side contain few subcellular organelles and large amounts of glycogen. Since these cells secrete large amounts of serous sweat by eccrine secretion (see Fig. 1.43), they are also called serous cells. Cells on the luminal side secrete mucus. The myoepithelial cell is a smooth muscle cell that pushes the accumulated sweat out of the lumen into the sweat ducts by contraction.

The eccrine secretory unit consists of a proximal coiled portion found in the deep dermis and subcutaneous fat, and eccrine ducts that ascend perpendicularly in the dermis (straight ducts). In the epidermis,

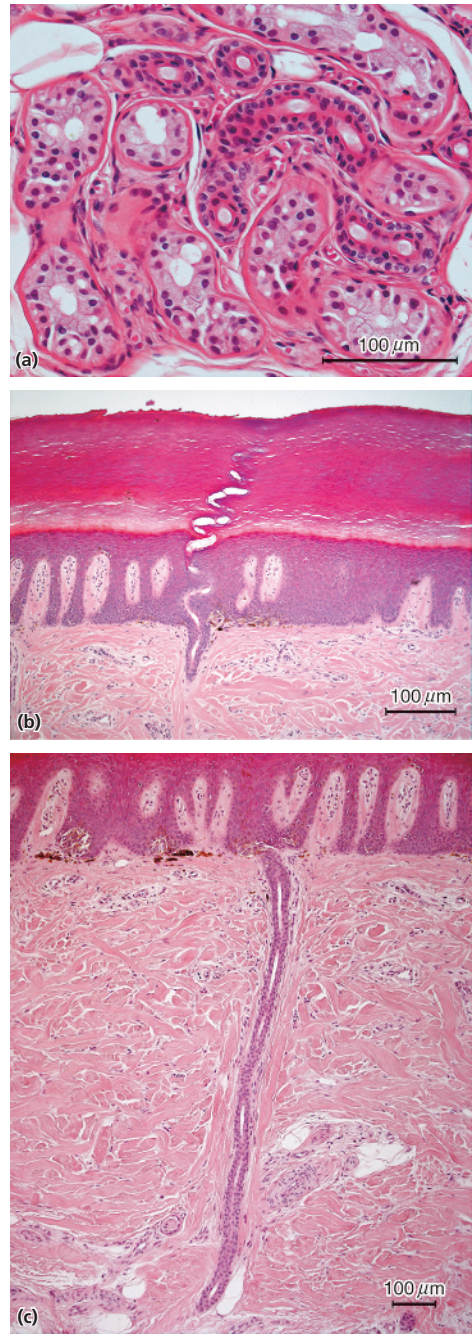


Fig. 1.44 Eccrine sweat gland. a: Cross-section. b: Longitudinal section of the duct in the epidermis. c: Longitudinal section of the duct in the dermis.

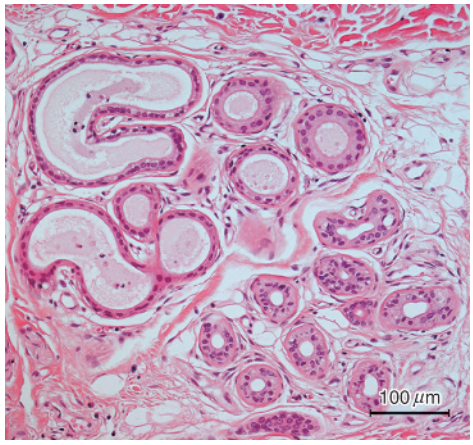


Fig. 1.45 **Apocrine sweat gland.**

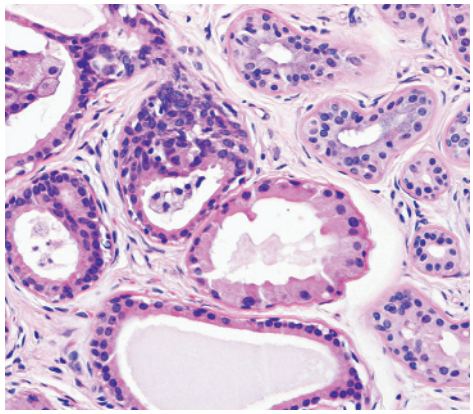


Fig. 1.46 **Apocrine (beheading) secretion of the sweat gland.**

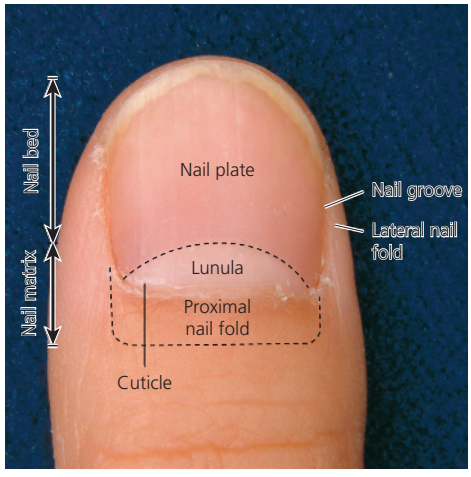


Fig. 1.47 **Anatomy of the nail.**

the duct becomes coiled again like a corkscrew and opens onto the skin surface (see Figs 1.42 and 1.44). The sweat duct contains two cell layers, consisting of intraluminal cells and peripheral cells, but it lacks myoepithelial cells. The sweat that is produced in secretory areas (known as precursor sweat) is slightly hypertonic; therefore, sodium ions and chlorine ions are reabsorbed by intraluminal cells in the coiled ducts, and hypotonic sweat is finally secreted.

Apocrine sweat glands

Apocrine sweat glands, which are fewer than eccrine glands, are degenerated pheromone-producing mammary glands found at specific sites such as the armpits, external ear canals, areola mammae, external genitals, and anus. They are always associated with hair follicles and enlarge during puberty through hormonal stimulation. Mammary glands and Moll's glands of the eyelids are modified apocrine glands. Apocrine glands produce small amounts of viscous and odorless sweat. However, the breakdown of several sweat components such as glycoproteins and fat by commensal skin bacteria produces odor.

The secretory portion of the apocrine gland is larger than that of the eccrine gland. Secretory cells are aligned as a single-layer epithelium surrounded by myoepithelial cells (Fig. 1.45). Sweat is secreted in a process called apocrine or decapitation secretion, during which the luminal surface of the cells bulges, blebs, and separates from the cell (apocrine secretion; Fig. 1.46) (see Fig. 1.43).

The sweat ducts do not open to the skin surface directly, but into the upper parts of the sebaceous glands (see Fig. 1.42).

Nails

The nail apparatus consists of the nail plate, nail matrix, nail folds, and nail bed. Each of these parts is made up of several more detailed structures (Fig. 1.47). The nail differentiates from the primitive epidermis around the third month of fetal development. Recent studies have shown that the nail has characteristics of both the dermis and the hair. The fingernail grows 0.1 mm per day, and it takes about 6 months to regrow an entire nail plate. The growth of nails is slower in the elderly, whose nails tend to be thick and brownish. Nails are important in protecting the digits and in assisting subtle sensation in the fingertips.

Nail plate

The nail plate, which can vary in size, shape, and thickness, is usually a rectangular plate of tightly organized keratinized cells (onychocytes) that rests on the dorsal tip of the digits. It is a three-layered structure of dorsal, intermediate, and ventral parts. In the proximal area, the nail plate is covered by the proximal nail fold, where the nail matrix is found. Proliferating cells within the nail matrix become keratinized to form the nail plate. Keratohyalin granules are not involved in this keratinization process. An opaque white half-moon shape (lunula) may appear at the root of the nail plate as a result of inadequate keratinization.

Nail matrix

Keratinocytes are produced in the nail matrix. The cells that differentiate and proliferate in the nail matrix extend and keratinize to form the nail plate; however, the ventral aspect of the nail plate is thought to originate from the nail bed.

Nail fold

The two edges of skin that border the nail plate and the nail bed are called the nail folds. The cuticle is the keratinized layer of skin that extends to partly cover the nail plate.

Nail bed

The nail bed is found at the base of the nail plate. It has the same components as the epidermis, except that it lacks the granular layer. It is continuously keratinized to connect with the nail plate.

MEMO 1–15 Bleeding in the cuticle



Hemorrhagic puncta in the cuticle may be seen in collagen diseases (e.g., systemic lupus erythematosus, dermatomyositis, scleroderma). It is thought to result from angiitis occurring in the microvessels.

Immunology of the skin

Basics of immunology

Immune system

Immunity is crucial in protecting the human body from invasion by pathogenic microorganisms. One of the main functions of the skin is to physically prevent such invasion. However, the human body can tolerate microorganisms known as commensals that are present on the skin surface, in the intestines, and in the mucous membranes. Disruption of the relationship between the human body and its commensals can result in invasion by these organisms, triggering the activation of immune mechanisms.

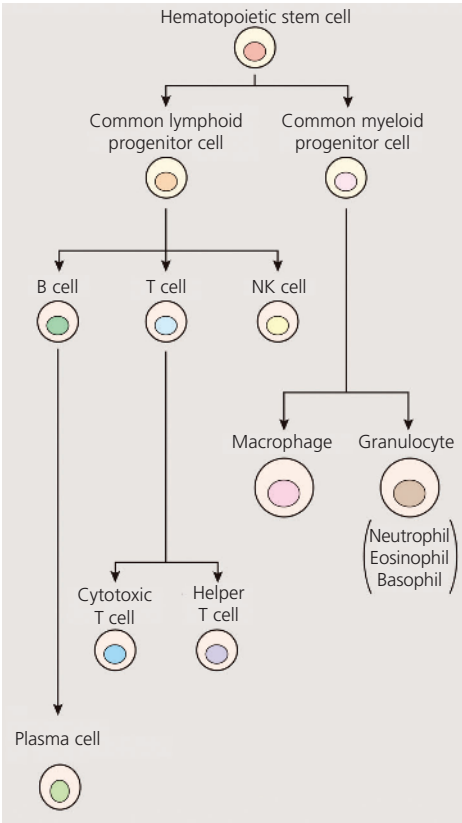


Fig. 1.48 Myelogenous cells composing the immune system.

The immune system performs the following functions.

- Distinguishing between "self" and "non-self."
- Excluding "non-self."
- Remembering what has invaded (immunological memory).

These functions are performed by immunocompetent cells such as lymphocytes and antigen-presenting cells, both of which are derived from the bone marrow (Fig. 1.48).

Reaction pattern

Foreign substances (or antigens) including bacteria, viruses, transplanted tissue, and certain proteins are distinguished as "non-self" by the immune system. The major histocompatibility complex (MHC) plays a critical role in identifying whether an antigen is self or non-self. In humans, the MHC is called HLA (human leukocyte antigen) because it was first discovered in leukocytes. HLA is categorized as class I (HLA-A, -B, -C) or class II (HLA-DP, -DQ, -DR) (Fig. 1.49). Each of us is characterized by a different HLA pattern. However, certain individuals have specific HLA patterns that increase their susceptibility to certain immunological disorders (Table 1.3).

Exogenous antigens that are recognized as non-self undergo phagocytosis by histiocytes (macrophages) or dendritic cells, such as cutaneous Langerhans cells. These cells, also known as antigen-presenting cells, process the antigen into short peptides that are then displayed on the surface nestled within a MHC class II molecule. The information of the antigen is conveyed by the combination of a T cell receptor (TCR) and MHC, resulting in immune activation and reaction (Fig. 1.50).

MEMO 1–16 Acquired and natural immunity

The antigen-specific immune system that acts through the MHC molecules confers what is called adaptive immunity, because the system reacts and adapts to various foreign objects. Innate immunity is conferred by a system that recognizes certain molecular structures of invading microorganisms and activates neutrophils, macrophages, NK cells, and complements at the initial stages of microbial invasion. The lipopolysaccharides on the surface of bacteria, for example, join with TLR4 molecules on the surface of macrophages and trigger the acquired immune system while phagocytosing and excluding the invading bacteria. Innate immunity quickly responds to bacteria whose invasion is identified for the first time by the immune system; however, the system's ability to exclude invading bacteria is low.

Serum immune reaction

Antibodies

Antibodies are immunoglobulins produced by B lymphocytes. They are able to react against infectious agents or pathogenic proteins (antigens), inhibiting infections and neutralizing protein toxicity. B lymphocytes secrete a number of specific antibodies corresponding to the antigens they have previously encountered. There are five classes of immunoglobulins, namely IgG, IgM, IgA, IgD, and IgE, in descending order of concentration (Table 1.4). IgG, produced during infection, accounts for 75% of immunoglobulins and plays a central role in the humoral immune reaction (Fig. 1.51). IgM production occurs at the very early stage of infection and precedes the production of IgG. It strongly activates the complement system (see next section). IgA is seen abundantly in exocrine secretions, such as mucus, where it prevents invasion by pathogens. IgE elicits an immune response by binding to IgE receptors (FcεR) found on mast cells, basophils, and eosinophils. It plays an important role in type I allergy. In recent years, overproduction of IgE and interleukin (IL)-4 in atopic dermatitis has been attracting attention.

Complement system

The complement system consists of a number of proteins present in serum. It forms part of the innate immune system. The components of the complement

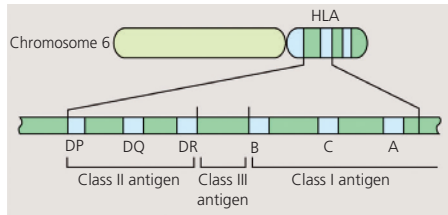


Fig. 1.49 HLA (human leukocyte antigen) genes on the short arm of chromosome 6. Genetic recombination causes the HLA pattern to differ for each individual.

Table 1.3 Association between HLA complex and skin diseases.

Disorder	Associated HLA in ethnic Japanese	Associated HLA in Caucasians	Indirect reference
Behçet's disease	B51	B51	Chapter 11
Systemic lupus erythematosus	A11, B40, DR2, DRW9	B8, DR2, DR3	Chapter 12
Neonatal lupus erythematosus	DW12		Chapter 12
Sjögren syndrome		DR3, DW3	Chapter 12
Rheumatoid arthritis	DR4	DR4	Chapter 12
Pemphigus vulgaris	A10, DR4	A10, B13	Chapter 14
Herpes gestationis		A1,B8,DR3	Chapter 14
Epidermolysis bullosa acquisita		B8	Chapter 14
Dermatitis herpetiformis (Duhring)		B8, DW3	Chapter 14
Psoriasis vulgaris	Cw6	Cw6	Chapter 15
Pustular psoriasis		B27	Chapter 15

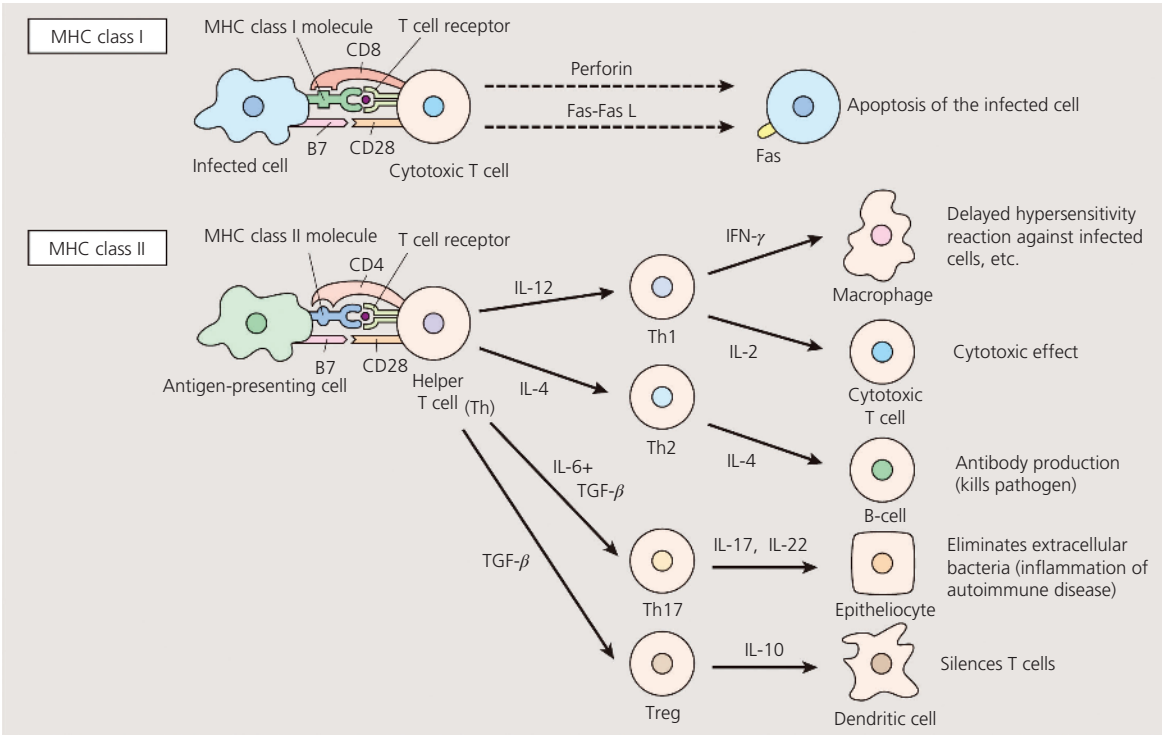
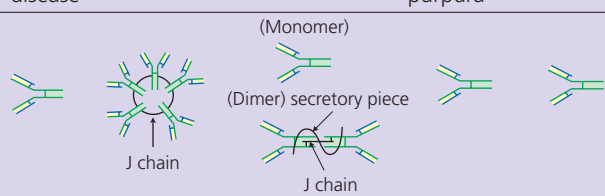


Fig. 1.50 Immune reactions classified by MHC class. Each class of MHC presents antigen information to a different type of T cell.

Table 1.4 Basic characteristics of immunoglobulins.

	IgG	IgM	IgA (secretory)	IgD	IgE
Molecular weight (kDa)	146	970	160	184	188
Serum concentration	870–1700 mg/dl	Male: 33–190 mg/dl Female: 46–260 mg/dl	110–410 mg/dl	<11.5 mg/dl	<170 IU/ml
Half-life in blood (days)	21	10	6	3	2
Antigen type of heavy chain	γ	μ	α	δ	ε
Transport across the placenta	**(+)**	**(–)**	**(–)**	**(–)**	**(–)**
Disorder with high value	Collagen disease	Schnitzler syndrome	Henoch-Schonlein purpura	Behçet's disease	Atopic dermatitis
Basic structure					

system can be classified into nine types (C1–C9) and further subclassified. In the classical pathway, C1 reacts to IgG or IgM antibodies, followed by a cascade of complement activation that causes destruction of the pathogens and infected cells. In the alternative pathway, the reaction is evoked mostly by bacterial components, which directly activate C3, factor B, and factor D. A third pathway, the lectin pathway, has also been described. This pathway involves lectin, an acute-phase protein that binds to mannose residues on the microbial surface and induces the activation of the complement system by activating mannan-binding lectin-associated serine proteases 1 and 2 (MASP-1 and MASP-2).

Immunocompetent cells

Immunocompetent cells in general

T cells

T cells play a key role in cell-mediated immunity and express T cell receptors on the cell surface. These receptors allow the T cells to recognize the antigenic information associated with MHC molecules (see Fig. 1.50). T cells are produced in the bone marrow and develop in the thymus. They are classified into CD4-positive helper T cells (helper T lymphocyte; Th) and CD8-positive cytotoxic T lymphocytes (Tc).

Th expresses the cell surface marker CD4, which allows it to adhere to MHC class II molecules. Therefore, Th reacts with antigen-presenting cells and B lymphocytes, both of which contain MHC class II molecules. Th can be differentiated into the two subtypes of Th1 and Th2, depending on the surrounding cytokine environment (see Fig. 1.50). Th1 secretes cytokines such as IL-2 and IFN-γ, which are involved primarily in histiocyte (macrophage) activation as well as induction of cellular immunity by evoking various inflammatory reactions. Th2 secretes IL-4 and IL-5, activates antibody production in B cells and inactivates foreign substances (humoral immunity). Th1 is involved mostly in type IV allergy, while Th2 is involved in type I allergy (atopic diseases).

In recent years, an IL-17-producing T cell has been found; this is called Th17. Th17 activates neutrophils through epidermal cells or fibroblasts, plays a role in eliminating bacteria and fungi from cells and is thought to engage in tissue remodeling. Th17 is strongly involved in maintaining inflammation in chronic inflammatory disorders such as psoriasis and Crohn's

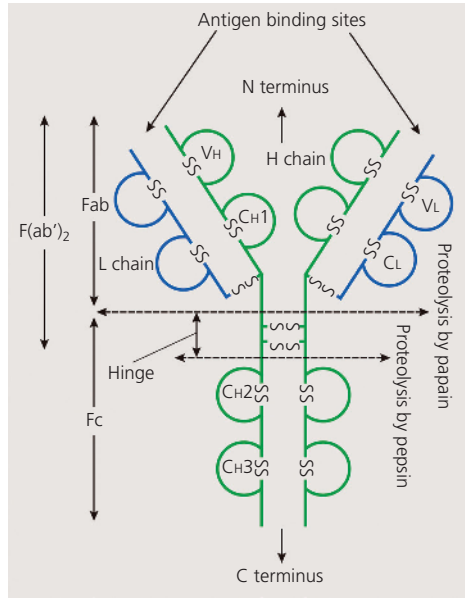


Fig. 1.51 Basic structure of human immunoglobulin (IgG). Fab, fragment antigen binding. Fc, crystallizable fragment. VL, variable light chain. CL, constant light chain. VH, variable heavy chain. CH, constant heavy chain.

disease and in autoimmune diseases including rheumatoid arthritis.

Tc expresses the CD8 molecule, which enables it to associate with MHC class I molecules and initiate cytotoxic immunity (see Fig. 1.50); in this way, non-self cells and virus-infected cells are destroyed. Tc is important in transplantation immunity, tumor immunity, and viral infections.

Recently, the presence of another T cell subtype, the regulatory T cell (Treg), has been identified. Treg is thought to be involved in immunological tolerance, including the suppression of autoimmune disease onset.

B cells

B cells are derived from hematopoietic stem cells in the bone marrow, after which they migrate to the spleen and undergo maturation. Upon activation in lymph nodes, spleen tissue and peripheral lymphoid tissue, B cells differentiate into antibody-forming cells (plasma cells). B cells express part of the ingested pathogen on the cell surface in association with MHC class II molecules. The antigen can then be detected by T lymphocytes, which in turn activate the production of antigen-specific antibodies by B cells. B cells can also be activated in a T cell-independent manner. Some B cells also differentiate into memory B cells and are able to produce specific antibodies upon reinfection.

Histiocytes (macrophages)

Histiocytes (macrophages) are bone marrow-derived cells that are induced mainly by IFN-γ. Strongly phagocytic histiocytes degrade phagocytosed antigen proteins into small peptides and present the antigenic information to T cells via MHC class II molecules (see Fig. 1.50). During inflammation, there is a proliferation of histiocytes that then migrate to the inflammatory loci. During this process, they secrete various cytokines (IL-1β, IL-6, IL-8, IFN-α) and induce phagocytosis of the pathogen, resulting in damage to the infected cells. Histiocytes may also fuse to form giant cells. They are the main cells involved in granuloma formation during chronic inflammation (see Chapter 2).

Mast cells

Mast cells play a central role in type I allergy. They contain high-affinity IgE receptors (FcεRI) and considerable amounts of histamine. When bound with IgE and further cross-linked by IgE-specific antigens, mast

cells degranulate and release various cytokines (IL-3, IL-4, IL-5), which lead to dermal edema such as that seen in urticaria. Mastocytosis is caused by the malignant proliferation of mast cells.

Eosinophils

Eosinophils have both phagocytic and cytotoxic functions. They are associated with atopic diseases (type I allergy), autoimmune blistering diseases, and parasitic infections. They are morphologically characterized by multiple eosinophilic granules, and they contain cytotoxic proteins such as major basic protein (MBP) and eosinophil cationic protein (ECP) (Fig. 1.52). They are activated by IL-3, IL-5, and GMCSF. They are hardly ever found in normal skin.

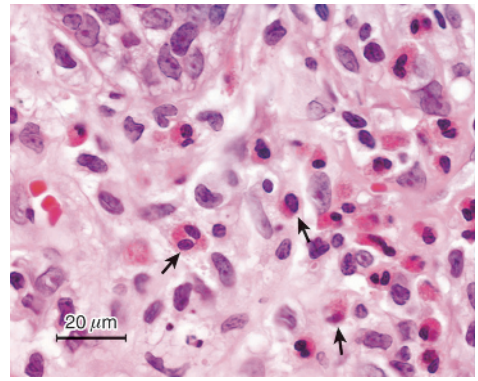


Fig. 1.52 Eosinophils. The cytoplasm is eosinophilic (red in hematoxylin-eosin staining). Note the multiple nuclei.

Neutrophils

Neutrophils are phagocytic cells that play a crucial role in fighting bacterial infections (Fig. 1.53). They strongly phagocytose bacteria bound with IgG or C3b (opsonized bacteria) through myeloperoxidase in the granules. They are hardly ever found in normal skin. In certain skin diseases, such as psoriasis vulgaris and Sweet's disease, neutrophilic infiltration can be intense, resulting in the formation of pustules.

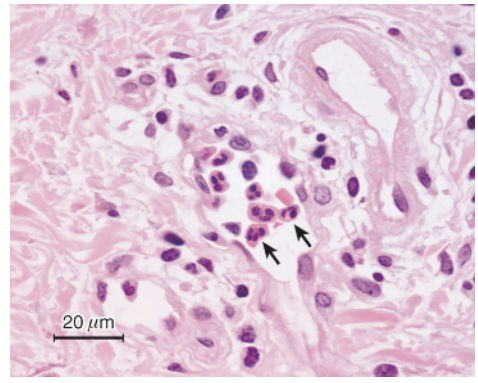


Fig. 1.53 Neutrophils. In skin, the cytoplasm of neutrophils is less eosinophilic than that of eosinophils. A neutrophil has a multi-segmented nucleus.

Basophils

Like eosinophils and neutrophils, basophils are granular leukocytes that have chemical mediators such as histamines and leukotrienes in the granules and express FcεRI on the cell surface. They are involved in type I allergy and mediate functions similar to those of mast cells.

Immunocompetent cells specific to skin

Langerhans cells

Langerhans cells are bone marrow-derived antigen-presenting cells that appear as dendritic cells. They contain the characteristic racket-shaped Birbeck granules in their cytoplasm (Fig. 1.54 and Fig. 1.55). They adhere to the epidermal keratinocytes by means of E-cadherin and guard against foreign antigens. When presenting an antigen to T cells, Langerhans cells detach from the epidermis and migrate to the regional lymph nodes via lymphatic vessels (Fig. 1.56). Human Langerhans cells express MHC class II molecules, CD1a, and S-100 proteins on their cell surface; the presence of these molecular markers is useful for the identification of Langerhans cells.

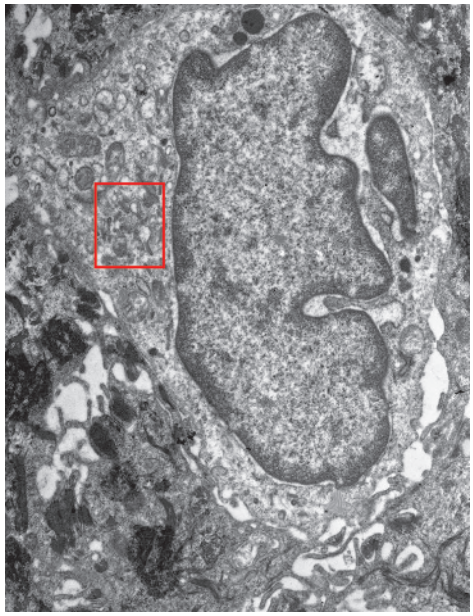


Fig. 1.54 Langerhans cell electron micrograph. A high-power magnification of the part in the red square is shown in Fig. 1.55.

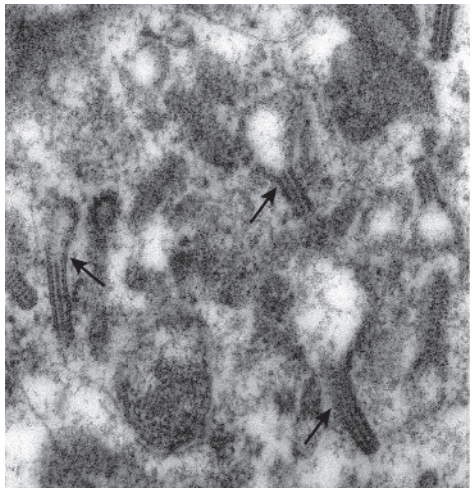


Fig. 1.55 Birbeck granules (arrows). A high-power magnification of the part in the red square in Fig. 1.54. In cross-section, Birbeck granules look like tennis rackets.

When Langerhans cells are stimulated by antigens, they express CD80 and CD86 by the functions of granulocyte macrophage-colony stimulating factor (GMCSF) and tumor necrosis factor-α (TNF-α) secreted by keratinocytes. They produce and secrete various cytokines (IL-1β, IL-6, TNF-α) to activate immune mechanisms.

Langerhans cells are not found in cutaneous lesions of graft-versus-host disease (GVHD). Ultraviolet rays, UVB in particular, suppress the numbers and functions of Langerhans cells, which is thought to be one of the mechanisms by which ultraviolet therapy works.

Keratinocytes

Keratinocytes, in addition to their role in cornification, play a crucial part in skin immunity. They produce and secrete various cytokines to stimulate immunocompetent cells (Table 1.5). IL-1α is particularly abundant in keratinocytes. When keratinocytes are destroyed by inflammation or injury, IL-1α, IL-3, IL-6, and GMCSF are released to activate lymphocytes, histiocytes, and vascular endothelial cells.

Dermal dendrocytes

Dermal dendrocytes are bone marrow-derived antigen-presenting cells found in the upper dermal layers. Since dermal dendrocytes are characterized by the cell surface expression of factor XIIIa, they are considered to be Langerhans-related cells in the dermis. They increase in number in inflammatory diseases and Kaposi's sarcoma.

Allergic reactions

The skin is a major organ where immune/allergic reactions occur. A number of skin diseases occur as a result of heightened immunological response. Such disorders, known as allergic or hypersensitivity disorders, are generally classified into the four categories established by Coombs & Gell (Table 1.6).

Type I allergy

Type I allergy is mainly mediated by mast cells. It is also called an immediate hypersensitivity reaction, since it manifests 5–15 min after an antigen (allergen) is presented. Mast cells with IgE on the surface react to a specific antigen, causing massive degranulation and the release of chemical mediators such as histamines

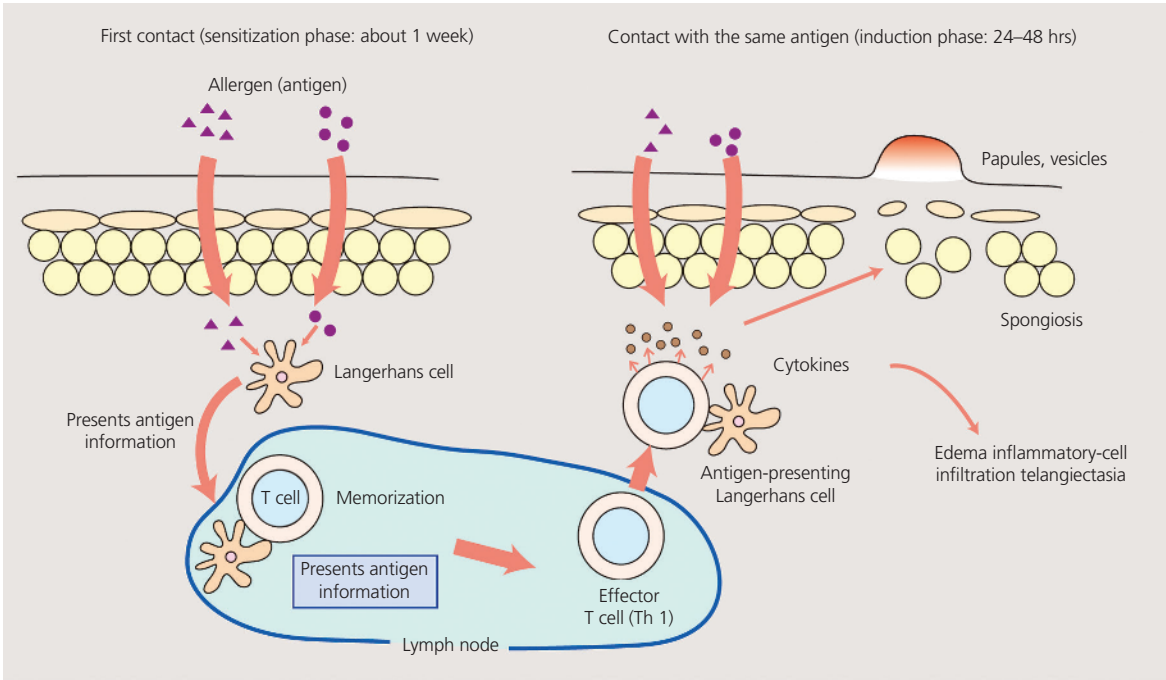


Fig. 1.56 Mechanism of allergic contact dermatitis.

and leukotrienes (see Chapter 8). These inflammatory mediators enhance vascular permeability to produce edema; in addition, they induce migration of eosinophils to evoke inflammation. The typical clinical features are nasal discharge and congestion, pruritus, conjunctivitis, and bronchial asthma. There may also be a sharp drop in systemic blood pressure due to rapid vascular dilatation. In serious cases, the patient may develop anaphylactic shock, which requires immediate treatment with epinephrine and antihistamines. In the majority of type I allergy cases, the symptoms subside within several hours.

Typical skin diseases caused by type I allergy are urticaria and certain types of drug eruptions (e.g., urticarial reaction). In atopic eczema, other factors such as filaggrin gene mutation may be involved. Additionally, allergic rhinitis (hay fever), bronchial asthma, allergic conjunctivitis, and atopic eczema are common diseases mediated by type I allergy.

Type II allergy

In type II allergy, antibodies are directed against endogenous cell surface antigens that have previously activated the complement system and cytotoxic T cells,

MEMO 1–17 Th1/Th2 balance

Th1 is involved in cytotoxic immunity, including apoptosis; Th2 is involved in humoral immunity, including type I allergy. Th1 and Th2 release mutually inhibitive cytokines that are thought to maintain a Th1/Th2 balance. In recent years, various allergic disorders and malignant tumors have been explained by the concept of Th1/Th2 imbalance. For example, atopic dermatitis and type I allergy are thought to be caused by a Th2-dominated immune reaction, whereas organ-specific autoimmune diseases and arterial sclerosis are thought to result from a principally Th1-mediated immune reaction.

Table 1.5 Main cytokins secreted by keratinocytes.

Classification, cytokines	Main functions
Multifunctional cytokines	
Interleukin (IL) IL-1α IL-3 IL-6 IL-7 IL-12 IL-15 IL-18 TNF-α MIF	Induction of secondary cytokines Modulation of adhesion molecules Modulation of activation and migration of T cells, B cells and macrophages Activation of endothelial cells and fibroblasts Modulation of activation and migration of Langerhans cells (IL-1α, TNF-α) Induction of fever and acute inflammatory proteins
Chemotactic factor: associated with leukocyte migration	
IL-8	Activation and migration of T cells and neutrophils
Colony stimulating factor: associated with leukocyte proliferation	
GM-CSF	Activation of granulocytes, macrophages, T cells and Langerhans cells
G-CSF	Proliferation of granulocytes
M-CSF	Proliferation of macrophages
Growth factor: associated with local cutaneous reactions	
TGF-α	Proliferation of keratinocytes
b-FGF, PDGF	Proliferation of fibroblasts and endothelial cells
Suppression factor: modulates immunity	
TGF-β	Suppression of keratinocytes and endothelial cells
IL-10	Suppression of immunity through Th1 cells

IL: interleukin, TNF: tumor necrosis factor, MIF: macrophage migration inhibitory factor, GM-CSF: granulocyte macrophage colony-stimulating factor, G-CSF: granulocyte colony-stimulating factor, M-CSF: macrophage colony-stimulating factor, TGF: tumor growth factor, b-FGF: basis fibroblast growth, PDGF: platelet derived growth factor

MEMO 1–18 Clinical symptoms resulting from abnormalities of the complement system

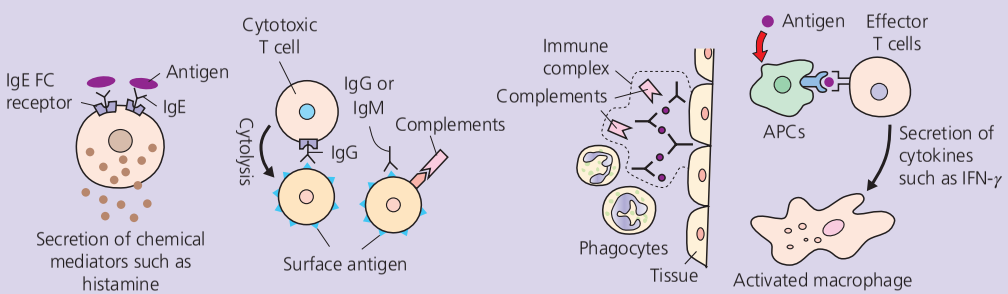
Several skin diseases, such as SLE, Raynaud's phenomenon, and angioneurotic edema, may be caused by congenital abnormalities and deficiencies in components of the complement system.

leading to cellular injury. Type II allergy is involved in the pathogenesis of cutaneous diseases such as autoimmune blistering diseases, e.g., bullous pemphigoid. In the case of bullous pemphigoid, autoantibodies bind to type XVII collagen, a component of hemidesmosomes in the basal cells, resulting in basal cell injury and blisters (see Chapter 14).

A drug may function as a hapten (MEMO, see Chapter 1) and bind to epidermal cells or blood cells to cause type II allergy. Drug-induced hemolytic anemia, thrombocytopenic purpura, and toxic epidermal necrolysis (TEN) occur by this mechanism.

Blood group incompatibility from transfusion, autoimmune hemolytic anemia, and Goodpasture's syndrome are other type II hypersensitivity disorders.

Table 1.6 Classification of allergy.

Coombs classification	Type I	Type II	Type III	Type IV
Type of reaction	Anaphylaxis (immediate hypersensitivity)	Cytolytic reaction (cytotoxic hypersensitivity	Immune complex reaction	Cellular immunity (delayed hypersensitivity)
Associated antibodies	IgE	IgG, IgM	IgG, IgM	-
Associated immune cells	Histiocytes, basophils, mast cells	Cytotoxic T cells, macrophages	Multinclear leukocytes, macrophages	Sensitized T cells, macrophages
Complement	Unneeded	Needed	Needed	Unneeded
Target tissues/ cells	Skin, lung, intestines	Skin, erythrocytes, leukocytes, platelets	Skin, vessel, joint, kidney, lung	Skin, lung, thyroid gland central nervous system, etc.
Disorders	Urticaria, drug eruption, asthma, pollinosis, anaphylaxis	Bullous pemphigoid, haemolytic anemia, idiopathic thrombocytopenic purpura, TEN, transfusion incompatibility	Cutaneous small-vessel vasculitis, serum sickness, glomerulonephritis	Allergic contact dermatitis, erythema induratum, GVHD
Illustration of reaction				

MEMO 1–19 Hapten

Phagocytic cells engulf antigens that contain proteins of 10,000 molecular weight or greater (complete antigen) and carry the antigenic information to the lymphocytes. Non-proteinaceous substances of low molecular weight (e.g., carbohydrates, fats, organic compounds, metallic molecules) cannot be antigens by themselves and are referred to as haptens or incomplete antigens. Haptens can elicit an immune response when they are attached to a carrier molecule such as a protein. An example of a hapten is the drug hydralazine, which can produce drug-induced SLE in certain individuals.

MEMO 1–20 Type V allergic reactions

Type V is similar to type II, in that the antigen is produced in reaction to proteins on the surface of the cells. However, in type V, a functional increase or decrease occurs in the cell when the antigen binds with the cell receptor. Graves' disease is an example of type V allergy.

Type III allergy

Type III allergy occurs when circulating antigen-antibody complexes (immune complexes) deposit in the blood vessels and other organs, such as the kidneys and joints. An infection or a drug may induce immune complex deposition in cutaneous blood vessels, resulting in fibrinoid degeneration and neutrophilic infiltration; this is called cutaneous small vessel vasculitis (see Chapter 11).

Serum sickness disease, glomerular nephritis, and lupus nephritis are other type III allergies.

Type IV allergy

Type IV allergy is an inflammation caused by a reaction between an antigen and the corresponding T cells (Th1 in particular). There are two stages in type IV allergy: a sensitization phase and an effector phase. After the initial invasion, the antigen is engulfed by antigen-presenting cells to activate T cells in the regional lymph nodes. At this time, memory T cells along with effector T cells are produced in order to enable them to respond promptly to any future exposure to the same antigen (sensitization). If future exposure occurs, memory T cells are activated by the antigen-presenting cells, inducing inflammation that peaks around 48 h after the antigenic challenge (effector phase). Since it takes a long time for the inflammation to occur, type IV allergy is also called delayed hypersensitivity (see Fig. 1.56).

Diseases caused by type IV allergy include allergic contact dermatitis and GVHD.