

C. Dermis

a. Structure of the dermis

The dermis is the structure beneath the epidermis, and the two are separated by the basal membrane (Fig. 1.3). The dermis is approximately 15 to 40 times as thick as the epidermis. It consists of three layers.

Papillary layer: The dermal area that projects into the intervals between the epidermal ridges. The fiber components are thin and richly supplied with capillaries, sensory nerve endings and cytoplasm.

Subpapillary layer: The area underlying the epidermis, containing the same components as the papillary layer.

Reticular dermis: Accounts for the largest part of the dermis and has dense connective tissue comprising fiber components. The

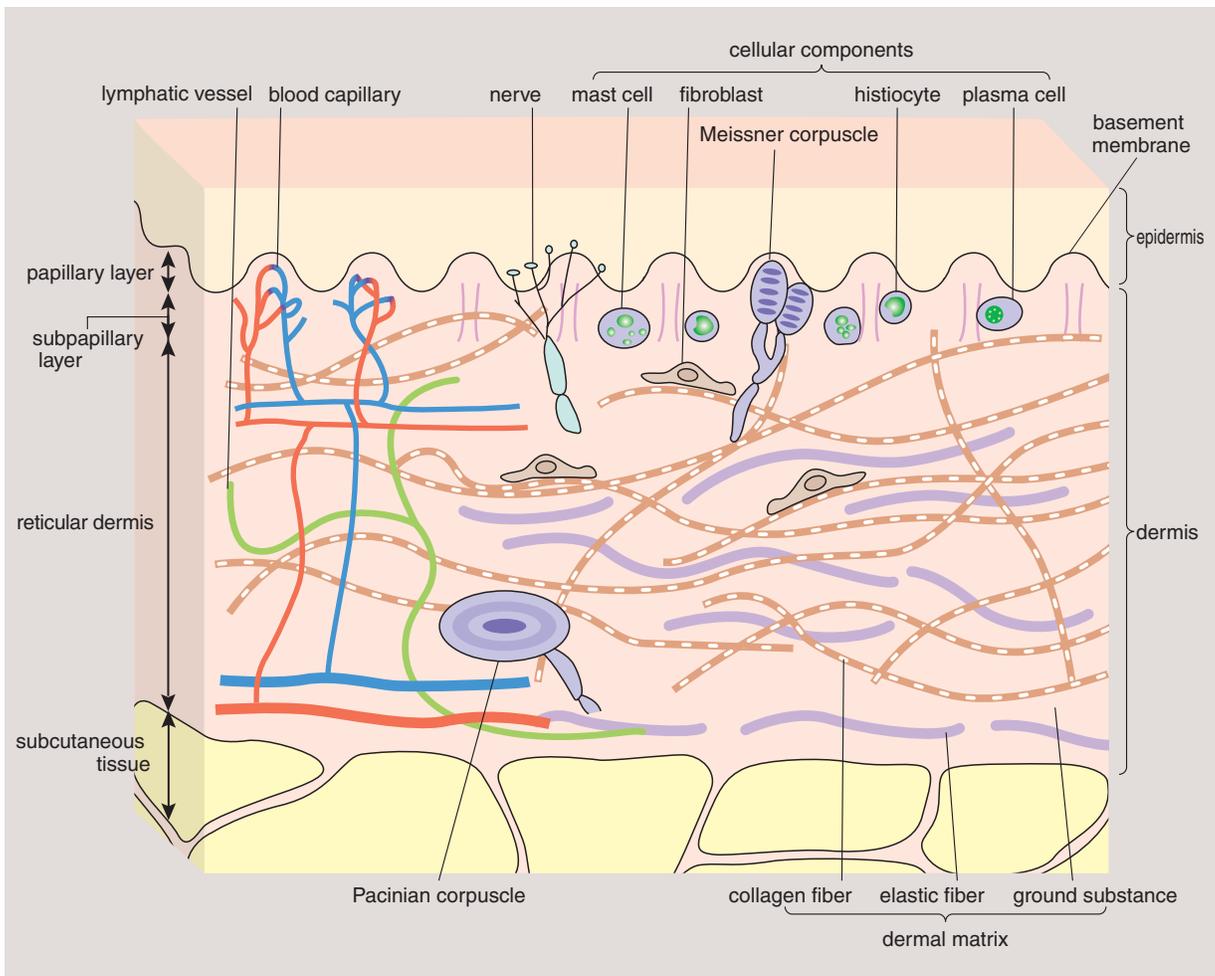


Fig. 1.22 Structure of the dermis.

lower part comes into contact with the subcutaneous fatty tissue. There are blood vessels and nerves in some parts.

The components of the dermis comprise the fibrous tissue and the dermal matrix formed by cells in the interstitial components (**Fig. 1.22**). The major components mainly consist of collagen fibers (mainly types I and III), with smaller amounts of elastic fibers, reticular fibers and matrix. This matrix generally comprises the extra-cellular matrix and ground substance made up of proteoglycans and gelatin. Fibroblasts, macrophages, mast cells, plasma cells, vascular channels and nerves are common cellular components.

b. Interstitial components

1. Collagen fibers ★

Collagen fibers account for 70% of the weight of dry dermis (**Fig. 1.23**) and appear white to the naked eye. The collagen fibrous component is poorly extensible; however, it is extremely tough and especially resistant to tension parallel to the fibers. This characteristic is important in maintaining the dynamic strength of skin.

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

In light microscopy, the proteinaceous collagen fibers stain well in eosin solution; they stain red in Van Gieson and blue after Mallory staining. The fibril is observed by electron microscopy as being very long, 100 nm to 500 nm in diameter with cross striations that repeat at intervals of 60 nm to 70 nm (**Figs. 1.23** and **1.24**). Fibrils become collagen fibers by aggregating with glycoproteins. A thick collagen bundle can reach 2 μm to 15 μm in diameter.

Collagen fiber molecules are produced in the rough endoplasmic reticulum of fibroblasts. Helical procollagens with three α -chains are secreted and the molecular ends are cut by procollagen peptidase to become tropocollagens. The molecules are cross-linked to each other with a regular gap that forms the striped collagen fiber (**Fig. 1.23b**).

Twenty subtypes of collagen molecules with α -chains of different molecular structures are known to exist (**Table 1.2**); however, type I collagen accounts for 80% of the collagen fibers that make up the dermis. Reticular fibers, which distribute in the perivascular regions as thin argyrophilic fibers and do not form thick fiber bundles, are type III collagen, and these account for about 15% of all fibers. Most of the remainder is thought to be type V collagen. Types IV, VII and XVII are mainly found in the basal membranes, associated with epidermal keratinocytes.

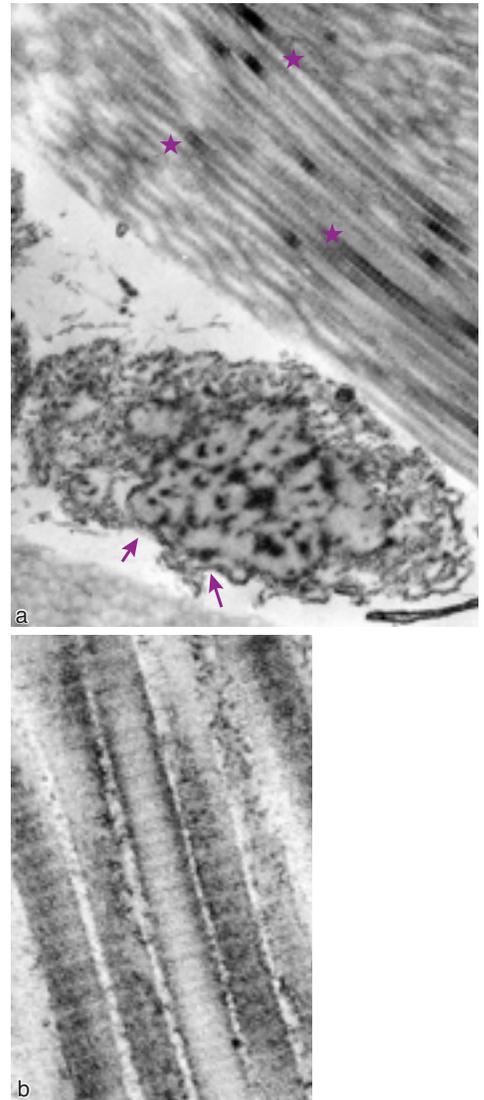


Fig. 1.23 Histopathology of the dermis.
a: Collagen fibers (stars) and elastic fibers (arrows). b: High-power magnification of collagen fibers. Stripes approximately 60 nm to 70 nm in width are seen.

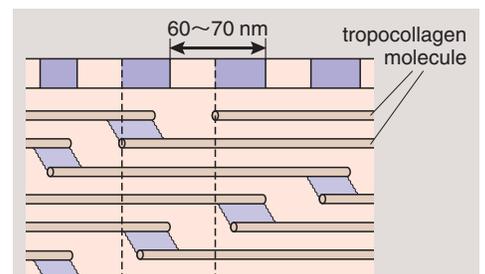


Fig. 1.24 Stripes of collagen fibers.
Fine fibrils (tropocollagens) have cross-links, giving the fibers a striped appearance.

Table 1.2 Types of collagen fibers.

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

FACIT: fibril associated collagen with interrupted triple helix

2. Elastic fibers ★

The elastic fiber is not as tough as the collagen fiber; however, it is extremely elastic and found abundantly in the dermis of the scalp, face and the extensible organs such as arteries and tendons.

In the dermis, the deeper the elastic fiber, the thicker it is. In the reticular layers, elastic fibers are scattered among collagen bundles running parallel to the skin surface. The closer the elastic fiber is to the papillary layer, the thinner it is and the more perpendicular it is to the skin surface. It forms an arch shape in the papillary layer from which thin fibers are produced that perpendicularly reach the lamina densa. Elastic fibers are also connected to the lamina densa of glands, sweat ducts, smooth muscle, nerves and blood vessels.

Elastic fibers are 1 μm to 3 μm in diameter. They cannot be differentiated from collagen fibers by HE staining. Elastic fibers stain dark blue to black in Weigert resorcin fuchsin, red-violet in aldehyde fuchsin, and brownish black in orcein. In elastic fibers, the characteristic striped pattern of collagen fibers is not observed by electron microscopy (**Fig. 1.23**). A skeletal fiber is 10 nm to 15 nm in diameter and its main content is fibrillin. The homogeneous substances are highly elastic structural proteins called elastins.

3. Ground substance, Matrix ★

Ground substance, a gelatinous amorphous substance of sugar and proteins, is observed in between fibers and between cells in the dermis.

The components of ground substance are principally proteoglycans and glycoproteins whose molecular weight is 150,000 to 250,000 and whose sugar content is 2% to 15%. The molecules stabilize the fibers to give flexibility to the skin. Fibronectin, one kind of glycoprotein, contains a domain that connects fibrin, heparin and collagen; and binds integrin receptors on the cell surface are involved in cell proliferation, differentiation and wound healing. Besides these components, blood and lymph-derived tissue fluid forms the remainder of the ground substance that is involved in the transport of substances essential to cellular activities and metabolism.

Proteoglycans are a massive molecules with a molecular weight of 10^5 to 10^6 or more and a composition of multiple glycosaminoglycans (mucopolysaccharides) connecting with backbone proteins. Glycosamine, mostly produced by fibroblasts in the dermis, is rich in hyaluronic acids, which are associated with moisture retention.

Abnormality in elastic fibers or collagen fibers



If elastic fibers are decreased, lost or denatured, dermatolysis or senile cutis rhomboidalis nuchae may occur. If fibrillin molecules are congenitally abnormal, Marfan syndrome results (Chapter 18). Abnormalities in collagens, which are components of collagen fibers, may lead to Ehlers-Danlos syndrome, which causes skin fragility.

c. Cellular components

1. Fibroblast ★

Fibroblast differentiates from the mesenchymal cells and produces collagen fibers, elastic fibers, and glycosaminoglycans. Fibroblasts appear as thin spindle-shaped cells sparse in collagen fibers (**Fig. 1.25**).

By electron microscopy, multiple Golgi apparatus and granular endoplasmic reticuli are seen in the fibroblast. When collagen fibers are produced and the dermis matures, fibroblasts stop their activities and become fibrocytes. At this point, the cell nuclei shrink and have fewer endoplasmic reticuli. Adrenal cortex hormones and thyroid hormones are involved in this process.

2. Histiocyte ★

The histiocyte, a kind of macrophage, is broadly distributed in the connective tissue and intermingles with fibroblasts on the outside of endocapillary cells (**Fig. 1.26**). A small circular nucleus and a large spindle- or star-shaped cell structure is seen in a histiocyte by light microscopy; furthermore, concave nuclei and the formation of pseudopodial protrusions are observed by electron microscopy. Histiocytes contain Golgi apparatus, smooth and rough endoplasmic reticuli, and lysosomes. Lysosomes contain hydrolases and active acid phosphatases. The histiocyte releases collagenase and lysosomal enzymes containing elastase to digest the interstitium. It is involved in organ repair. The histiocyte degrades and phagocytoses mainly foreign substances and presents them as antigens to T cells (Chapter 3).

3. Mast cell ★

The mast cell is found in the dermis around capillaries and in the periphery of subcutaneous tissues. The shape is roundish or spindle, and the diameter is 10 μm (**Fig. 1.27**). Mast cells produce and maintain various vasodilatory and hyperlucent chemical mediators. Mast cell granules stain red-violet in toluidine blue and methylene blue, and present with 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.

A mast cell intracytoplasmic granule appears as a circular structure with a diameter of 0.3 μm to 0.5 μm under electron microscopy. Multiple mast cell granules are 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. 1.28**, Chapter 3). The main components of the released substances are histamines and heparins, followed by

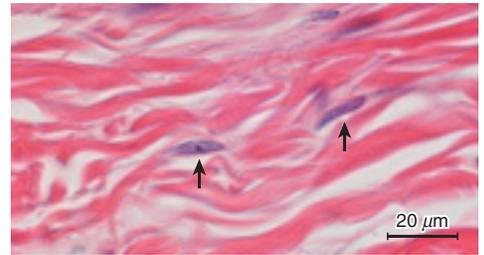


Fig. 1.25 Fibroblasts (arrows).

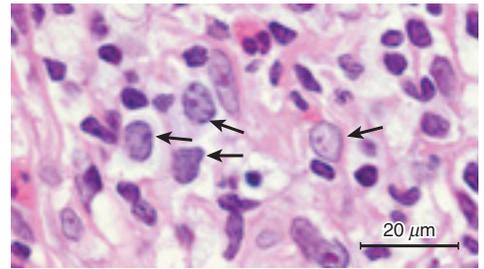


Fig. 1.26 Histiocytes (arrows)

Histiocyte, Monocyte, Macrophage

MEMO

Large phagocytic cells in the living body are called macrophages. There are two kinds.

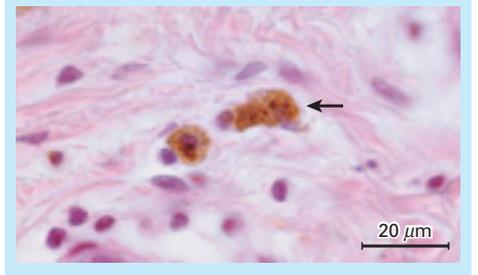
- Free macrophages: e.g., monocytes in the blood, migrating macrophages in granuloma
- Fixed macrophages: e.g., histiocytes in the dermis and subcutaneous tissues, Kupffer cells

Histiocytes and monocytes are kinds of macrophages.

Melanophages

MEMO

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.



Histiocytes, the key to pathological diagnosis

MEMO

Epithelioid cells, Touton giant cells, xanthoma cells and foreign-body giant cells in an epithelioid cell granuloma are histiocytes that pathologically present in an atypical form.

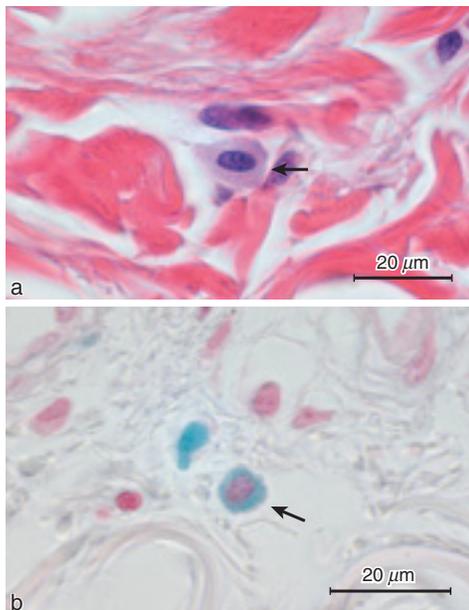


Fig. 1.27 Mast cells.
a: Hematoxylin and eosin staining. b: Metachromasia is seen by toluidine blue staining.

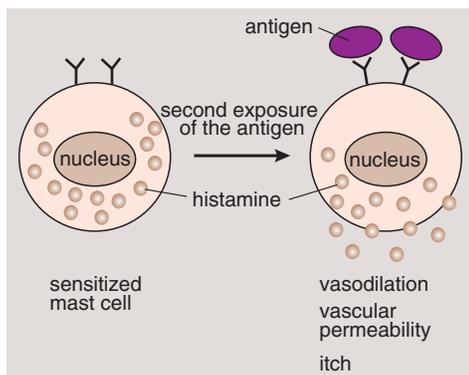


Fig. 1.28 Sensitization by mast cells.

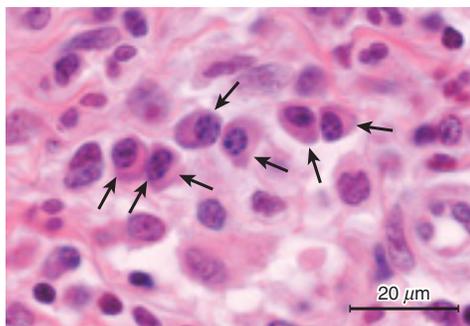


Fig. 1.29 Plasma cells (arrows).

various 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 produce and release inflammatory substances such as prostaglandins, leukotrienes and platelet-activating factors.

4. Plasma cell ★

The plasma cell is a differentiated B cell that has been stimulated by an antigen. It produces antibodies and is involved in humoral immunity. The shape of the plasma cell varies from circular to pear-shaped, and the diameter ranges from 8 μm to 14 μm , which is twice as large as a leukocyte. It has a wheel-shaped nucleus with peripheral chromatin (**Fig. 1.29**).

5. Dermal dendrocyte

The dermal dendrocyte is found in the dermal upper layer (in and between the papillary layer and the reticular layer). It is thought to be an immunocompetent cell (Chapter 3), and it is characterized by containing clotting factor XIIIa.

d. Vascular channels and nerves

1. Blood vessels ★★

Multiple branches of arteries distributed in skin (**Figs. 1.30** and **1.31**) are connected with each other in the dermal deep layer to form a horizontal network (subcutaneous plexus). With numerous branches ascending from the subcutaneous plexuses, the arteries form a second network in the papillary lower layer (sub-papillary plexus). The arterioles ascend through the papillary layer, forming capillary loops in the dermal papillaries before moving to venules that connect to each other to form two kinds of plexuses, whereby the blood flows into the cutaneous veins (**Fig. 1.30**). There are also characteristic plexuses in the periphery of the cutaneous appendages. The peripheral regions of the eccrine glands are particularly rich in vascular networks, which control blood flow volume and body temperature by perspiration. Moreover, hair follicles in the anagen (growth) stage are also richly supplied with blood vessels, present in the surrounding dermal tissue.

There is another apparatus that circulates the blood directly from arteries to blood vessels: This is the arteriovenous anastomosis, which is controlled by sympathetic nerves. The arteriovenous anastomosis controls the peripheral blood flow and is involved in body temperature regulation. Glomus apparatuses, which have spherical anastomotic branches, are seen everywhere in the skin. They are particularly well developed in the fingers, at apical ends of the toes, and below the nails. Many layers of

