1

Structure and function of the skin

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The skin is the largest of the organs. It performs a wide variety of functions vital to maintenance of the homeostatic status of the body (Figure 1.1) and plays an active role in immune responses via the innate and acquired immune system. In addition, different regions of the skin such as the ears, eyelids, lips, prepuce, footpads and claws have specialized functions and differ structurally from the skin that covers the general body surface. A consideration of all of these topics is beyond the scope of this chapter. Attention will be concentrated on the anatomy and physiology of the unspecialized skin and its role in body defence, with the aim of providing a basis for understanding the pathogenesis of cutaneous disease.

Function	Range of activities
Barrier	Controls loss of water, electrolytes, etc. Excludes chemical, physical, biological agents
Sensation	Heat, cold, pain, itch, pressure
Temperature regulation	Insulation, variable blood flow, sweating
Haemodynamic control	Peripheral vascular changes
Secretion, excretion	Glandular function, hair and epidermal growth Percutaneous loss of gases, liquids and solutes
Synthesis	Vitamin D
Immune function	Surveillance, response

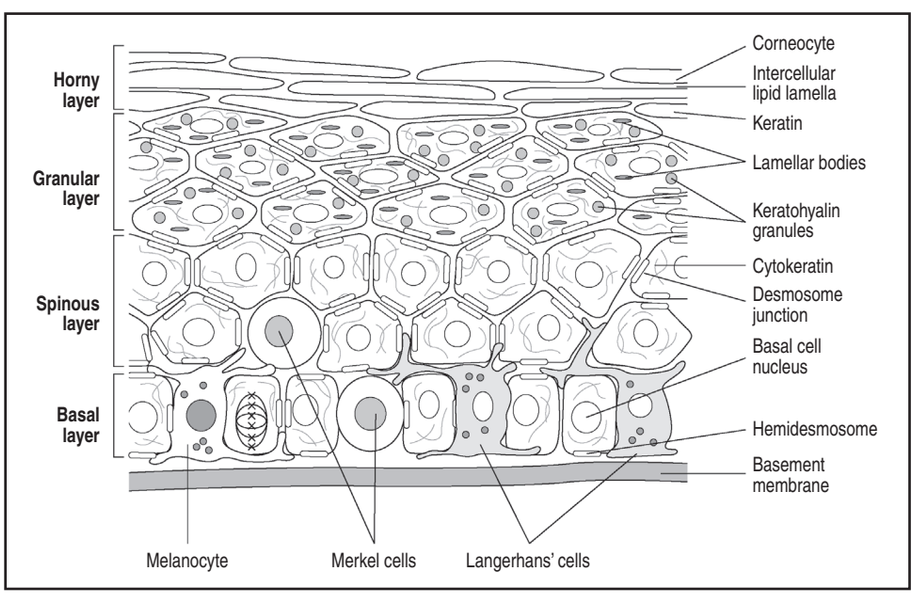
1.1 Skin activities associated with homeostasis.

The epidermis

The epidermis forms the superficial layer of the skin and is thus subjected to a wide variety of chemical, physical and biological stresses. It is not, in itself, physically strong but preserves its integrity by continually secreting protective components. These include the hair coat, the keratinized cells of the stratum corneum and the secretions of the skin glands. The epidermis rests on the basement membrane, which provides not only the firm attachment of the epidermis to the dermis but also allows the selective passage of molecules and cells between the two structures. In canine skin, the stratum corneum is 12–15 µm in thickness and is composed of 45–52 layers. The living epidermis has 3–4 layers and is 8–12 µm thick over the general body surface.

Epidermal structure and function

The epidermis is a stratified squamous epithelium and is normally composed of four layers (Figure 1.2), which are, from the inside out:



1.2 Epidermis showing the organization of the cells and their maturation into fully cornified cells. © Anita Patel.

- Basal layer (stratum basale)
- Spinous layer (stratum spinosum)
- Granular layer (stratum granulosum)
- Horny layer (stratum corneum).

Each layer is one to several cells thick, depending on the anatomical site. The keratinocyte is the principal cell of the epidermis (~85%), the remainder being resident epidermal dendritic cells, Langerhans' cells (~5–8%), melanocytes (~5%) and Merkel cells (~3–5%). Other cells such as lymphocytes, eosinophils and neutrophils may also be present in the epidermis but are not resident. The origins and functions of cells in the skin are summarized in Figure 1.3.

Basal layer

The keratinocytes of the basal layer are tightly packed columnar cells. They are daughter cells produced by mitosis of a small number of more primitive cells known as stem cells. This process is called epidermal proliferation. The daughter keratinocytes are also able to divide transiently, and migrate outwards gradually to replace the cells shed from the skin surface.

The cytoskeleton of the keratinocyte is composed of actin filaments, keratin intermediate filaments and microtubules, which provide it with structural strength. The cell's ability to produce pro- and anti-inflammatory cytokines, interferons and antimicrobial peptides, and to function as a phagocytic cell, allow it to perform an important role in inflammation and immunity.

Spinous layer

The spinous layer is largely composed of polygonal keratinocytes that undergo biochemical and structural changes as they migrate towards the surface. They are called spinous cells because in conventional histological sections they appear to have spines when examined microscopically. The spines are in fact the desmosomes, intercellular bridges that allow cell-to-cell adhesion. These are important structures, which allow firm attachment between cells and also allow communication between cells. The molecular structure of desmosomes has been defined. They are composed of transmembrane proteins (desmogleins (Dsg) 1, 2, 3 and desmocollins) and plaque proteins (plakoglobin, plakophillin, desmoplakin, desmocalmin and intermediate filament associated protein (IFAP) 300). These molecules form attachments to corresponding molecules on adjacent cells.

The structural and biochemical changes that occur as the keratinocyte migrates through the epidermis are referred to as differentiation (keratinization or cornification). This process is vital to the proper barrier function of the skin and involves the formation of keratin and the cornified envelope. The formation of intermediate keratin filaments accelerates in this layer; as the keratinocytes migrate towards the surface the filaments are aggregated into keratin bundles. The keratinocytes of the spinous layer also commence synthesis of lamellar bodies, which are important organelles that exert their function at the junction between the stratum granulosum and the stratum corneum. Both

Skin structure	Cell type	Origin	Function
Epidermis	Keratinocyte	Ectoderm	Barrier due to structure Immune response via production of cytokines and phagocytosis
	Langerhans' cell	Haemopoietic progenitor cells	Immune surveillance
	Melanocyte	Neural crest	Production of pigment, which protects from UV light, provides camouflage and allows sexual display in some species
	Merkel cell	Primitive epidermal cells	Slow adapting mechanoreceptors
Dermis	Fibroblast	Mesenchyme	Synthesis of extracellular matrix components Wound healing Production of degrading enzymes
	Dermal dendrocyte	Bone marrow	Antigen presentation Haemostasis Wound healing
	T lymphocyte	Bone marrow	Promote cell-mediated and humoral immune response Generally CD3, αβ positive
	Mast cell	Bone marrow	Involved in early immune response by releasing preformed granules and initiation of the process of inflammation
	Microvascular epithelial cell	Haemopoietic progenitor cells	Involved in immune response via the adhesion of effector cells such as neutrophils, eosinophils, basophils and monocytes

1.3 Origin and functions of the cells found in the epidermis and the dermis.

proliferation and differentiation are highly regulated by a complex chain of events controlled by growth factors, interleukins, arachidonic acid and its metabolites, vitamin D3, calcium and retinoids.

Granular layer

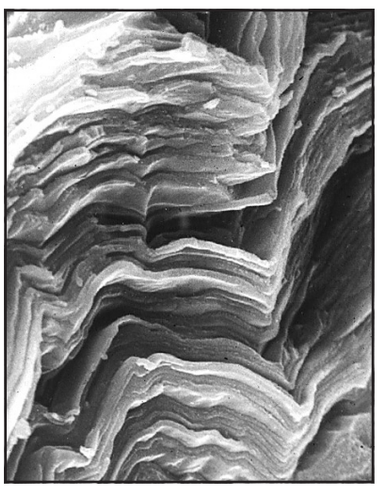
The cells of the granular layer are fusiform in shape and are characterized by the presence of keratohyalin granules. The granules contain a precursor protein, profilaggrin, which, when dephosphorylated to filaggrin, is involved in the aggregation of the keratin bundles. The lamellar bodies, which contain lipid (phospholipids, sphingolipids, fatty acids, free sterols and sterol esters) and hydrolytic enzymes (acid phosphatase glycosidases, proteases and lipase), are extruded into the intercellular spaces where they are reorganized to form the outer layer of the cornified cell envelope and the intercellular lamellae. Epidermal lipids have extremely important functions, including:

- Barrier function
- Control of epidermal permeability
- Protection of underlying tissues from chemical and biological insults
- Regulation of hydration status
- Temperature control through transepidermal water loss
- Stratum corneum water-holding capacity
- Cohesion and desquamation
- Control of epidermal proliferation and differentiation.

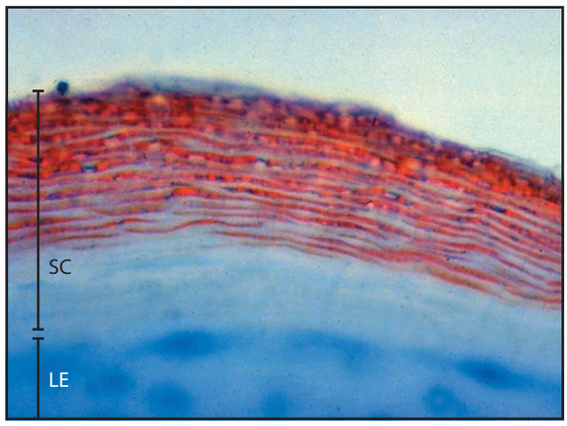
Horny layer

The horny layer is the outermost layer of the epidermis and is in direct contact with the external environment. This layer is composed of anuclear flattened polyhedral keratinocytes or corneocytes, interspersed with an extracellular matrix of lipids. These are high in free fatty acids, cholesterol, cholesteryl esters and ceramides, and form a compact lamellar structure that is a vital component of epidermal permeability (Figure 1.4). The corneocytes have undergone structural and biochemical changes and are composed mainly of aggregated keratin bundles and filaggrin, within a cornified envelope that replaces the plasma membrane. The latter comprises an inner proteinaceous portion composed of envelope proteins (e.g. involucrin, cystatin A, loricrin, trichohyalin, filaggrin), which are cross-linked by transglutaminase enzymes to form the insoluble envelope. The outer lipid portion of the cornified cell envelope is a continuous layer of hydroxyceramide that is covalently bonded to the inner portion of the cornified envelope.

The cells of the stratum corneum are shed continually from the skin surface by a process called desquamation. In the looser outer layer of the corneum, the intercellular spaces are permeated by sweat and sebum (Figure 1.5). The shedding of cells by healthy skin is in equilibrium with the processes of proliferation and differentiation. All three processes are influenced by the epidermal lipids. The interaction between the lipid portion of the cornified cell envelope and the intercellular lamellae is important for normal cohesion and the function of the epidermal permeability barrier. The structure of the stratum corneum can be likened to a brick and mortar structure, in which the keratins and the inner portion of the cornified envelope form the 'bricks' and the lipid forms the 'mortar' that holds the corneocytes together and provides a hydrophobic barrier.



1.4 Scanning electron mircrograph of frozen hydrated canine stratum corneum, showing the compact layered arrangement of the squames. (Courtesy of IS Mason and DH Lloyd)



1.5 Frozen section of bovine skin after treatment with an alkaline buffer, swelling the stratum corneum. Red-staining lipid (Sudan IV stain) can be seen in the distal intercellular layers of the corneum. The stratum corneum is somewhat thinner in dogs and cats. LE = living epidermis; SC = stratum corneum.

Resident and transient cells

The protective functions of skin are enhanced further by the resident and transient cells found within the epidermis (see Figure 1.3).

Langerhans' cells: These are antigen-presenting cells that are capable of phagocytosing and presenting processed native antigen to naïve T lymphocytes, which can mount a primary immune response, and also to memory T cells. By performing this task, the Langerhans' cells protect an individual from superficial infections. They are also thought to play a role in preventing cancer by responding to new tumour antigens.

Melanocytes: These are melanin-producing dendritic cells found mainly in the basal layer. Mammalian melanocytes produce two main types of melanin: eumelanin (black) and phaeomelanin (yellow to reddish-brown). Melanins absorb ultraviolet light but also serve as free radical scavengers, bind to drugs and provide camouflage, thus protecting the individual in several ways.

Merkel cells: The Merkel cells are slow-adapting type 1 mechanoreceptors that are located in the basal layer or just below it. They occur mainly in the tylotrich pads and the hair epithelium and are able to respond to tactile stimuli.

Hair and its associated structures

Hair is a characteristic of mammals and protects the individual in several ways. It provides physical, microbial and chemical barriers and aids in camouflage and in signalling between animals. The length and density of the hair coat provides thermal insulation, while colour and glossiness play thermoregulatory roles. Specialized tactile hairs (sinus and tylotrich hairs) have been modified structurally to be able to perceive sensory stimuli.

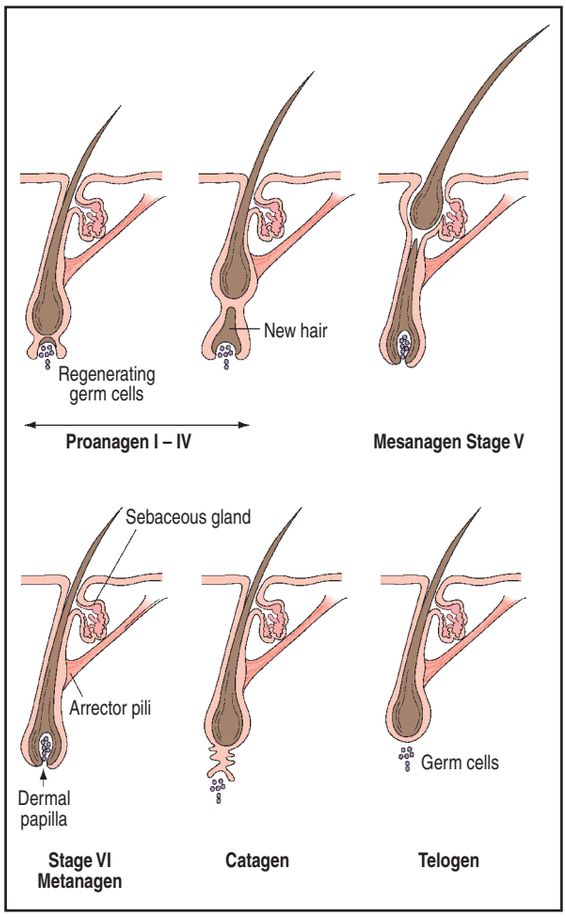
The hair follicle and hair cycle

Hair is formed by the hair follicle in a growth cycle (Figure 1.6) that is controlled by both internal and external factors (Figure 1.7). Hair follicles are formed during embryonic development by complex interactions between the mesenchymal and ectodermal cells. Their task is to produce hair in clearly defined growth cycles, to replace hair lost by moulting or pathological conditions. The hair of cats and dogs is replaced in a mosaic pattern with peaks in the spring and autumn, and replacement is influenced by the photoperiod, temperature and nutritional status. Other replacement patterns include seasonal and wave patterns.

Anatomically the hair follicle is divided into three segments: the infundibulum, the isthmus and the inferior segment (Figures 1.8 and 1.9). Each primary follicle is associated with an arrector pili muscle, a sweat gland and a sebaceous gland, which jointly form the hair follicle unit. Grouped follicles, as found in dogs and cats, are referred to as compound follicles, in which a primary hair is associated with several smaller secondary hairs, all of which leave the epidermis through the same opening. The ratio of primary to secondary hairs determines the different types of hair coat seen in different species and breeds of mammal. Compound hair follicles are grouped into follicular units that usually comprise three compound follicles.

Hairs

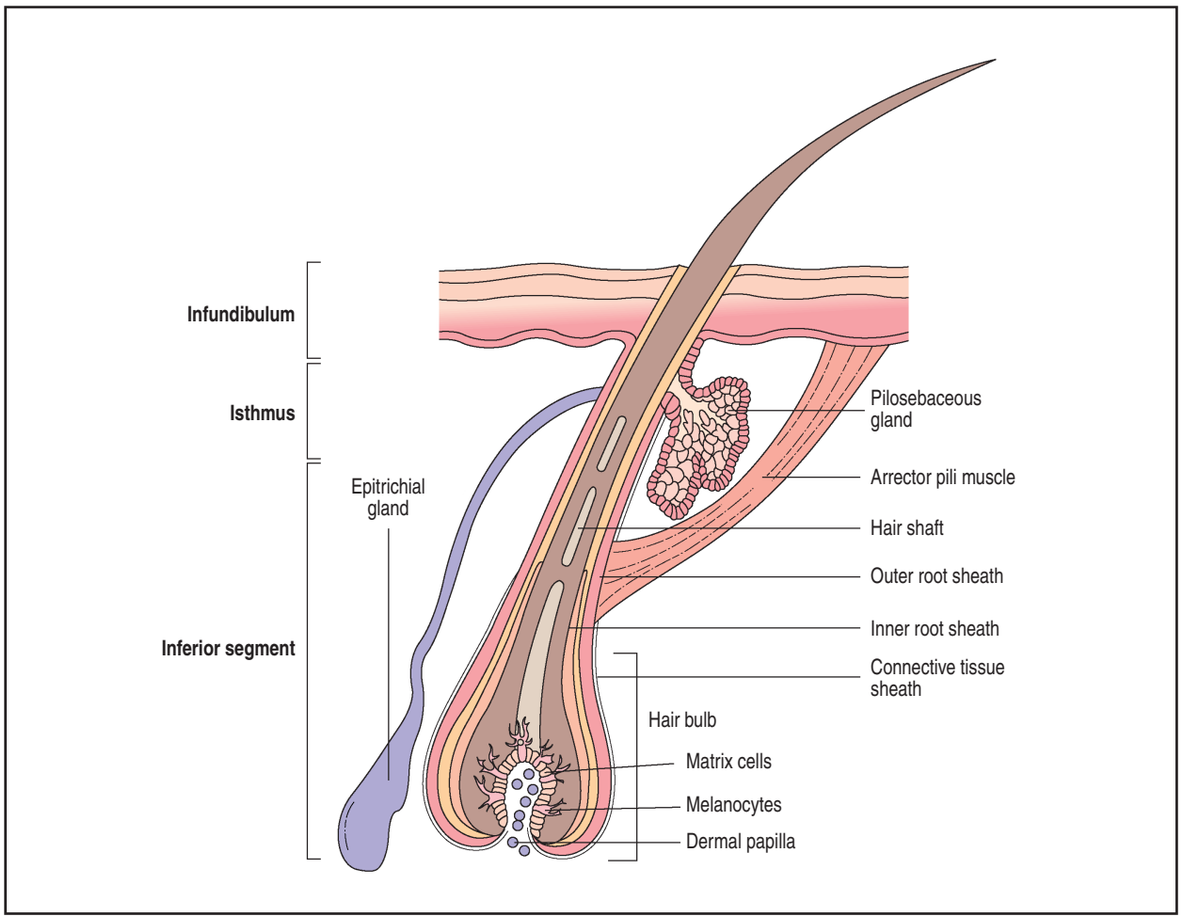
Figure 1.10 shows the surface ultrastructure of a canine hair. Sinus hairs, known as vibrissae or whiskers, are found on the face and throat of domestic animals and in the cat on the palmar carpal pad. These are stiff hairs that are associated



1.6 The hair growth cycle. Anagen, the active growth phase, is divided into six stages: proanagen, stages I–IV; mesanagen, stage V; and metanagen, stage VI. During these stages the hair follicle undergoes differentiation, rapid growth and hair elongation. Telogen represents the resting phase of the hair follicle, and catagen is the transitional period between the growth and resting phases. © Anita Patel.

Factor	Effect on hair growth
Intrinsic	
Cytokines	Either inhibit or stimulate hair growth
Adhesion molecules	Found in dermal papilla during anagen
Oncogenes and tumour suppressor genes	Influence mRNA synthesis and control cell death (apoptosis)
Extrinsic	
Environmental (photoperiod and temperature)	Stimulates or inhibits
Hormonal (melatonin, prolactin, sex hormones, glucocorticoids, growth hormone)	Varying effect on the hair cycle (i.e. hair growth and differentiation) depending on body location
Nutrition	
General health status	
Genetics	

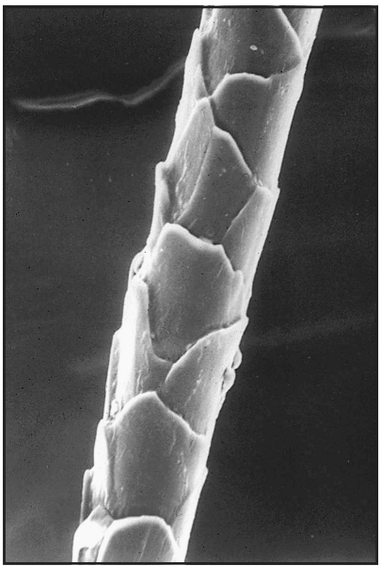
1.7 Intrinsic and extrinsic factors that control the hair cycle.



1.8 The hair follicle and its associated structures. © Anita Patel.

Structure	Characteristic	Function
Dermal papilla	Dermal fibrocytes embedded in extracellular matrix and containing nervous and vascular supplies	Induces follicular development Nourishes hair matrix
Hair matrix	Proliferative epithelial cells. Melanocytes visible and active during anagen	Produce inner and outer root sheaths and hair shaft Produce and transfer pigment to hair shaft
Hair shaft: Medulla Cortex Cuticle	 Consists of cuboidal cells absent in secondary hairs Pigment-containing cornified cells Outermost overlapping cornified cells	 Insulation Bulk and strength of hair, hair colour Protects the cortex, provides glossiness or reflexivity
Inner root sheath (IRS): Cuticle Huxley's layer Henley's layer	 Flat overlapping cells interlocking with hair cuticle 1–3 nucleated cells containing trichohyalin granules Single layer of non-nucleated cells also containing trichohyalin	Protects and supports the growing hair
Outer root sheath (ORS)	Covered by IRS below the isthmus. Cells contain glycogen vacuoles. Does not undergo keratinization At isthmus undergoes tricholemmal keratinization In infundibulum undergoes normal keratinization and is characterized by keratohyaline granules	
Basement membrane zone	Surrounds ORS, composed of a fibrous tissue and glassy membrane	

1.9 Hair follicle structural components and their functions.



1.10 Scanning electron micrograph of a normal canine hair. The surface is tiled with cells of the cuticle, which point away from the base of the hair.

Location	Specialized gland	Type	Species
Skin	Atrichial/epitrichial Free and pilosebaceous	Sweat Sebaceous	Dog, cat Dog, cat
Eyelids	Moll's gland Meibomian (tarsal) Glands of Zeis (cilia)	Sweat Sebaceous Sebaceous	Dog, cat Dog, cat Dog, cat
Ears	Ceruminous	Sweat	Dog, cat
Perineum	Hepatoid (circumanal) Anal sac gland	Sebaceous Combined	Dog Dog, cat
Tail	Tail gland	Sebaceous	Dog, cat
Prepuce	Preputial glands	Sweat	Dog, cat
Footpads	Atrichial	Sweat	Dog, cat

1.11 Occurrence and distribution of cutaneous exocrine glands in mammalian skin.

with a blood-lined endothelial sinus in close association with Pacinian corpuscles. They act as slow-adapting mechanoreceptors. Tylotrich hairs are large stout single hairs that have a neurovascular complex at the level of the sebaceous gland and are scattered throughout the skin surface in close association with the tylotrich pads. They act as rapidly adapting mechanoreceptors.

Sebaceous glands

The sebaceous glands are simple alveolar glands with ducts that open directly on to the skin surface or into the infundibulum. The former are referred to as free sebaceous glands and the latter as pilosebaceous glands. Their density and size depend on their anatomical site. They are most abundant around mucocutaneous junctions, interdigital spaces, on the dorsal neck, rump and tail, and on the chin. They are absent from the nasal planum and footpads. Figure 1.11 lists the types and location of exocrine glands.

Sebum has both protective and behavioural roles. Combined with sweat it forms a waxy emulsion that provides a protective barrier against pathogenic organisms. Sebum is rich in wax esters and, by coating the surface of the skin and hair, controls wetting and provides the animal with a glossy coat that may assist in the reflection of heat. Specialized sebaceous glands are able to produce pheromones and thus play a role in behaviour. In recent years, the sebaceous gland has been used to modulate the distribution of topical medicaments such as flea control products.

Sebaceous lipids are synthesized actively by the sebaceous glands and secreted as products of cell death (holocrine). However, studies have suggested that the passage of ionic components into sebum results from paracellular transport. Sebum is stored in the sebaceous glands, which are controlled by both endocrine and non-endocrine factors. In general, androgens stimulate glandular activity by increasing the mitotic rate and sebum output. Oestrogens and glucocorticoids tend to have the opposite effect.

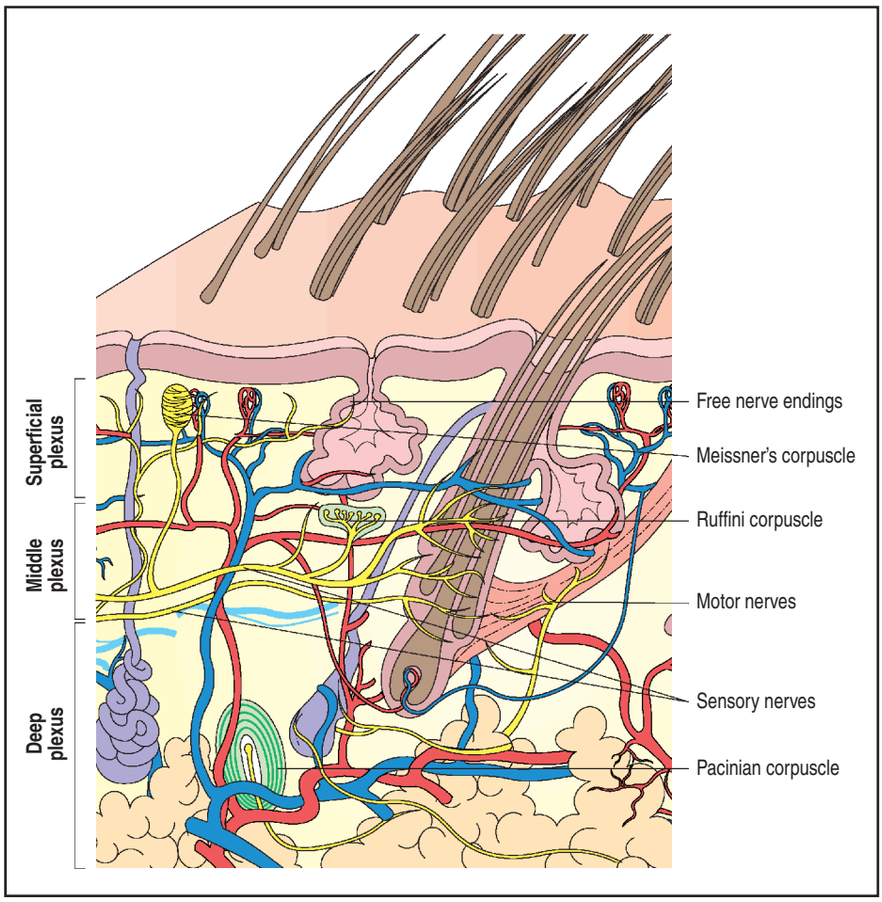
Sweat glands

The sweat glands are simple or coiled tubular glands of the skin. Those with a duct that opens into the infundibulum are referred to as epitrichial (formerly apocrine) glands, while those that have ducts opening directly on to the skin surface are known as atrichial (formerly eccrine) glands (Figure 1.12). In some species, specialized sweat glands are involved in scent production.

While sweat does not have a universal function, it protects the skin and its specialized structures, such as the eyelids and footpads, from frictional damage, maintains skin pliability and provides microbial defence through the presence of immunoglobulins, cytokines, the iron-binding protein transferrin and inorganic ions such as sodium chloride. Sweat does not play a significant role in thermoregulation in cats and dogs.

Sweat secretion varies with species, and several different modes have been described. They include cell death, paracellular transport, exocytosis, microapocrine blebbing and transcellular ion and water transport.

It has been postulated that sympathetic nerves control sweat gland activity in some species, such as the dog and cat. It is thought that the production of adrenaline (epinephrine) and noradrenaline (norepinephrine) by adrenergic and cholinergic sympathetic nerve endings on the cutaneous blood vessels, or dopamine released by mast cells, transfers neurotransmitter substances such as adrenaline and noradrenaline to the gland. In the footpads of cats and dogs, it has been suggested that sweating is controlled directly by acetylcholine and catecholamines produced by sympathetic nerve endings located next to the fibrocyte sheaths of the glands.

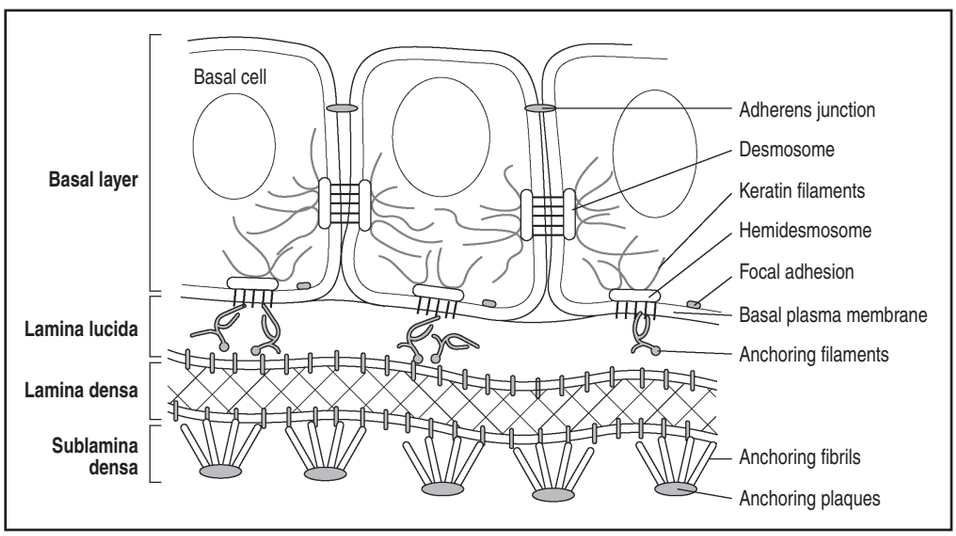


1.12 Components of mammalian skin, including epidermal structures (compound hair follicle and adnexal structures, free sebaceous gland, atrichial sweat gland), blood supply, nerves and associated mechanoreceptors. © Anita Patel.

The dermoepidermal junction

The dermoepidermal junction (DEJ) is the interface between the epidermis and the dermis. It is composed of the plasma membrane on the basal aspect of the basal cell and the basement membrane. The latter is subdivided ultrastructurally into the lamina lucida, lamina densa and sublamina densa (Figure 1.13).

The basal keratinocytes are attached firmly to anchoring filament proteins found in the lamina lucida, mainly by hemidesmosomes. These cell–substrate attachments are composed of plaque proteins (bullous pemphigoid antigen type 1) and transmembrane proteins (bullous pemphigoid antigen type 2 and $\alpha 6\beta 4$ integrin). Focal adhesions are located along the basal aspect of cultured keratinocytes and are thought to mediate adhesion during cell migration.



1.13 Structural components of the dermoepidermal junction. © Anita Patel.

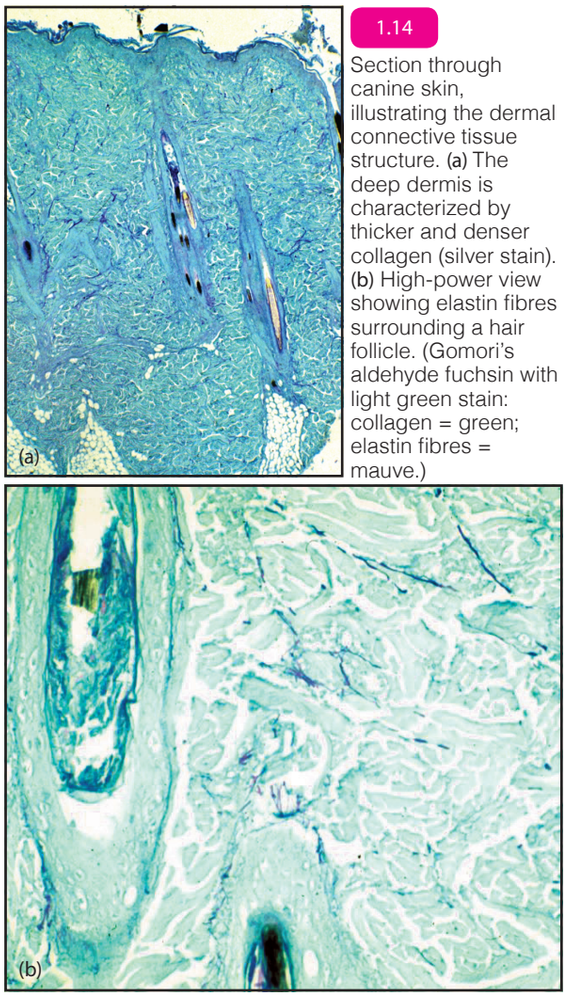
The lamina densa is composed of collagen IV, laminin, nidogen and perlecan, forming a tight network that acts as a filter to restrict the passage of molecules from the dermis to the epidermis and *vice versa*, but allows the movement of immune cells between the two layers. The sublamina densa is located below the lamina densa and is formed by anchoring fibrils, composed of collagen VII, which insert on to anchoring plaques in the superficial dermis. This intricate network of molecules provides the overall basis of the firm attachment between the dermis and the epidermis.

The dermis

The dermis is the major structural component of the skin. It provides a matrix of supporting structures and secretions that maintain and interact with the epidermis and its adnexa. These include the connective tissue, blood and lymphatic vessels, nerves and receptors, and cellular components. It is an important thermoregulatory and sensory structure and also contributes significantly to body water storage.

Connective tissue

The dermal connective tissue matrix consists mainly of collagen and elastic fibres organized in a coherent pattern, principally bundles of collagen bordered by the elastic fibres (Figure 1.14). The non-fibrous component consists of the proteoglycan ground substance and certain glycoproteins. The superficial dermis is composed of fine, irregularly distributed, loose collagen fibres and a network of fine elastin fibres. Deeper in the dermis the collagen is thicker and more dense and the fibres tend to run parallel to the skin surface; the elastin fibres are also thicker but less numerous.



1.14 Section through canine skin, illustrating the dermal connective tissue structure. (a) The deep dermis is characterized by thicker and denser collagen (silver stain). (b) High-power view showing elastin fibres surrounding a hair follicle. (Gomori's aldehyde fuchsin with light green stain: collagen = green; elastin fibres = mauve.)

Collagen

Collagen is the major extracellular protein of the dermis and forms about 80% of the extracellular matrix. The fibres provide strength and elasticity but are also involved in cell migration, adhesion and chemotaxis. They are secreted by the skin fibroblasts. The fibres are very resistant to animal proteases but are broken down by collagenases that are secreted chiefly by fibroblasts. The collagenases are neutral metalloendoproteases that require calcium as an activator and zinc as the intrinsic metal ion; they are uniquely able to break down the native collagen triple helix.

Collagen turnover in the dermis is slow. It is controlled by dermal cellular components, particularly fibroblasts, but also inflammatory cells (macrophages, neutrophils, eosinophils, keratinocytes) which are able to respond to particular demands such as skin damage and wound healing. Hydroxyproline, an amino acid that is an abundant and vital component of collagen, is released during collagen breakdown. Urinary hydroxyproline levels can be used as an indicator of this *in vivo*.

In mature individuals, the majority of dermal collagen is formed by types I (87%) and III (10%), which align into relatively large fibrils. Types IV, V and VII are found in basement membranes. Type V collagen represents about 3% of dermal collagen and is found in nearly all connective tissues.

Elastic fibres

Elastic fibres form a network throughout the dermis and are also present in the sheaths of hair follicles and in the walls of blood and lymphatic vessels (see Figure 1.14). They are composed of two components, elastin and microfibrillar protein. The elastin is amorphous and, in fully mature elastic fibres, forms the core, surrounded by an envelope of microfibrils. Microfibrillar material in the absence of elastin is called oxytalan. When small amounts of elastin are present it is called elaunin.

Elastin is a covalently cross-linked polypeptide with a very characteristic amino acid composition (rich in valine and alanine, low in cystine, and with no histidine or methionine). Like collagen, it possesses much glycine and also contains hydroxyproline. It is synthesized by fibroblasts and smooth muscle cells. Its metabolic turnover is slow but continuous. Degradation is mediated by a variety of elastases including some calcium-dependent metalloenzymes. The microfibrils are composed of type VI collagen and fibrillin.

Glycosaminoglycans and proteoglycans

These substances are secreted by fibroblasts. They were originally called mucopolysaccharides (viscous polysaccharides), but the term glycosaminoglycan was introduced subsequently (glycan = polysaccharide; glycosamino = containing hexosamines). However, the polysaccharides are normally linked to protein and are thus called proteoglycans.

The glycosaminoglycans and proteoglycans form the ground substance, a viscous sol–gel that encompasses and supports the other dermal components. The ground substance is composed chiefly of hyaluronic acid and dermatan sulphate, with heparin, chondroitin 4 and chondroitin 6 sulphates. Its degradation and turnover is not well understood, but half-lives of 2–5 days and 7–14 days have been demonstrated for dermal hyaluronic acid and chondroitin sulphate, respectively. Hyaluronidase has been demonstrated in skin wounds and also in normal rat skin.

The ground substance appears to be involved in salt and water balance and can bind over 100 times its weight of water. It may also play a part in promoting growth, differentiation and cellular migration.

Blood and lymphatic vessels

Blood supply

The skin has a well developed vascular supply, in keeping with its role in thermoregulation and haemodynamics; blood flow through the skin substantially exceeds that required merely to supply oxygen and metabolites. The cutaneous arteries (see Figures 1.12 and 1.15) ascend from the subcutaneous region and branch to form three networks. These are located:

- At the base of the dermis, supplying the hair papillae and sweat glands
- At the level of the follicular isthmus, supplying the sebaceous glands, arrector pili muscles and the mid-portion of the hair follicle
- Just below the epidermis (superficial plexus), giving rise to the superficial capillary network that supplies the epidermis, which is itself avascular.

1.15 A section of bovine skin stained with haematoxylin following arterial perfusion with Indian ink. Note that the thin, superficial epidermal tissue is avascular.

The veins that drain the skin run parallel to the arteries. Arteriovenous anastomoses, which enable the capillary beds to be bypassed and are associated with thermoregulation, are concentrated in the deeper parts of the dermis and are particularly common in the extremities. They vary in form from the complex glomus to simple coiled structures. Control of blood flow in the capillaries is regulated by the contractile, fusiform pericytes that are aligned parallel to them.

Lymphatic drainage

The lymph vessels provide drainage for tissue fluid from the dermis. This fluid is collected in lymphatic capillary networks in the more superficial layers of the dermis, associated with components of the hair follicle units. The lymph vessels also provide a channel by which cellular traffic can flow to the lymph nodes. They differ from blood vessels in being flatter and wider, with thinner and flatter endothelial cells and no contractile components.

Nerves

The general pattern of nerve distribution is similar to that of the blood vessels because they generally travel alongside one another (see Figure 1.12). A plexus of nerves is present beneath the epidermis, and free nerve endings also penetrate the epidermis itself. In addition, nerve networks are associated with the hair follicle, sweat and sebaceous glands, and the arrector pili muscles. Encapsulated nerve endings are found in mechanoreceptors (Figure 1.16) such as the Pacinian corpuscles which are found deep in the dermis.

Receptor	Sensory end organ	Function
Mechanoreceptors (corpuscular)	Pacinian corpuscle	Pressure and vibrations
	Merkel cells	Slow-adapting changes in pressure
	Meissner's corpuscle	Rapidly adapting pressure and velocity changes
	Ruffini's end bulb	Skin movement
Nociceptors	Free nerve endings	Itch and pain
Thermoreceptors	Free nerve endings	Warm and cold

1.16 Sensory nerve endings and organs, and their functions.

Cellular components

A variety of cells are present in the normal dermis (see Figure 1.3), in addition to those of the glandular, muscular, nervous and vascular tissues. These cells are capable of performing a wide variety of different tasks and can interact with the dermal matrix and the other cellular components of the epidermis and dermis, both by direct contact and by means of soluble mediators.

Fibroblasts

These are mesenchymal cells responsible for the synthesis and degradation of both fibrous and non-fibrous connective tissue matrix proteins. They are quite active and are capable of secreting multiple matrix components simultaneously. Attachment of fibroblasts to the fibrous matrix is mediated via fibronectin on the cell surface; collagen and fibronectin have complementary binding sites. Fibroblasts produce collagenase and gelatinase, which degrade collagen. They migrate along the fibre bundles. Fibroblasts are also able to secrete a variety of cytokines and influence proliferative activity in the epidermis.

Mast cells

Mast cells are found throughout the dermis (rarely in the epidermis), and are associated particularly with the superficial vascular plexus and the epidermal adnexa. They contain abundant darkly staining secretory and lysosomal cytoplasmic granules. The secretory granules contain a predominance of histamine and heparin. The lysosomal granules contain acid hydrolases that are capable of degrading glycosaminoglycans, proteoglycans and glycolipids. The secretory granules also contain enzymes with this function. The cell surfaces possess microvilli and a coating of fibronectin, which may assist in attachment to the connective tissue matrix. Skin mast cells belong to the connective tissue mast cell group and differ from mucosal mast cells in both morphology and staining reaction.

Mast cells are important mediators of immediate hypersensitivity reactions. In dog skin three subtypes are recognized, which contain tryptase (T), chymase (C) or both tryptase and chymase (TC). The TC mast cells constitute about 60% of the mast cell population in normal canine skin.

Dendritic cells

These include melanocytes and antigen-presenting dendritic cells that are often present in the perivascular spaces of the superficial dermal blood vessels. The latter are differentiated from Langerhans' cells because they are positive for CD4 and CD90 (Thy-1) antigens.

The skin as an immune organ

The skin immune system (SIS) is formed of resident and transient cells that play an active role in both innate and adaptive immune responses. The functions of the resident and transient cells are described in Figure 1.3. In addition to the secretion of cytokines and antigen presentation, many of these cells also secrete antimicrobial peptides (AMPs). These are short peptides, formed generally of 12–50 amino acids, which have antimicrobial and immunomodulatory properties (Figure 1.17). Genes that express AMPs have been demonstrated recently in normal canine skin, and there is growing recognition of their importance in the defence against infections.

Conclusion

The skin is adapted in its structure and function to provide physical, chemical and mechanical barriers. Defects in certain structural components or in immunological activity can either cause or predispose individuals to certain skin diseases (Figure 1.18). Knowledge of the basic structure and functions of the skin provides a better understanding of pathomechanisms and aids decision-making in the management of skin diseases.

Activity	Mode of action
Bactericidal and bacteriostatic	Disrupt cell membranes by pore formation Intracellular penetration and binding, leading to disruption of the cell membrane and inhibiting DNA, RNA and protein synthesis
Immunomodulatory	Clearance of infection Chemokine production Inhibition of liposaccharide-induced pro-inflammatory cytokine production Promotion of wound healing Modulate responses of dendritic cells and adaptive immune responses

1.17 Functions of antimicrobial peptides.

Skin	Layer	Structural components	Disease
Epidermis	Horny	Intercellular lipid (ceramides)	Atopic dermatitis
		Intercellular lipids, cornified envelope and keratin or desmosomal components	Non-epidermolytic and epidermolytic ichthyosis
	Granular and spinous	Intercellular proteins including desmoglein 1 and desmocollin	Pemphigus foliaceus and pemphigus erythematosus
	Basal	Desmoglein 3	Pemphigus vulgaris
	All	Loss of epidermal cohesion due to weak desmosomal attachments	Canine Darier's disease

1.18 Structural defects (genetic or acquired) that result in, or predispose individuals to, certain skin diseases. (continues)

Skin	Layer	Structural components	Disease
Dermoepidermal junction	Basal	Collage VXII (bullous pemphigoid antigen)	Bullous pemphigoid
	Basement membrane zone	Laminin 332 (laminin 5) and other proteins	Mucous membrane pemphigoid Junctional epidermolysis bullosa
		Collagen VII	Acquired and dystrophic epidermolysis bullosa
Dermis	Collagen	Defects in collagen synthesis and bundle formation	Ehlers–Danlos syndrome

1.18 (continued) Structural defects (genetic or acquired) that result in, or predispose individuals to, certain skin diseases.

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