CHAPTER

1

Structure and Function of Skin

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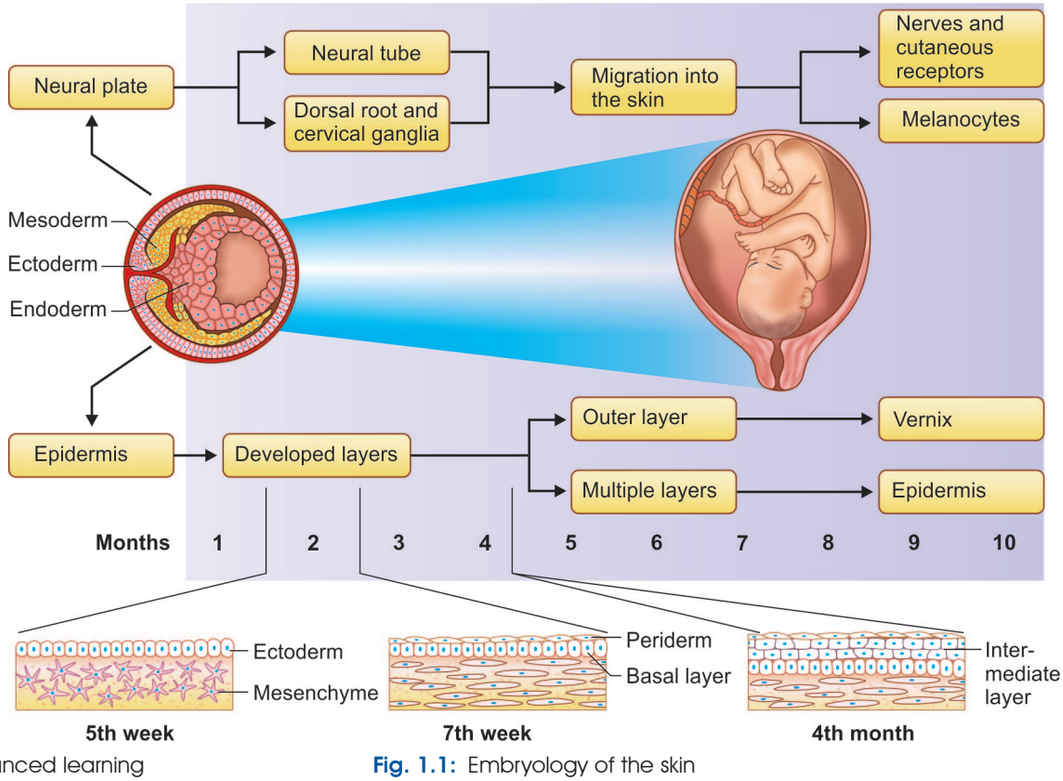
Chapter Outline

The skin is the interface between humans and their environment. It weighs an average of 4 kg and covers an area of 2 m^2. It acts as a barrier, protecting the body from harsh external conditions and preventing the loss of important body constituents, especially water.[DRa.1]

EMBRYOLOGY

The skin consists of the epidermis with layers of variously differentiated keratinocytes and an underlying dermis with adnexal structures, vessels, and nerves, as well as subcutaneous fat. The skin develops from the ectoderm and mesoderm (Fig. 1.1). Initially,



for advanced learning

Fig. 1.1: Embryology of the skin

there is a single layer of ectodermal cells, but by around 8 weeks, a flattened outer layer (periderm) appears. By birth, the complex epidermis is present. Melanocytes[Q] migrate into the skin from the neural crest, as do nerves. The dermis, with its connective tissue, derives from the mesenchyme.

The adnexal structures develop from interaction between epidermal invaginations and supporting mesenchymal structures.

STRUCTURE AND FUNCTION

The skin has three layers. The outer one is the *epidermis*, which is firmly attached to, and supported by connective tissue in the underlying *dermis*. It adheres to the dermis at the basement membrane where downward projections **(epidermal rete ridges or pegs)** interlock with upward projections of the dermis **(dermal papillae)**. This is akin to the interlocking of the hands and it gives stability to the epidermis. This interdigitation is responsible for the ridges seen most readily on the fingertips (as fingerprints). Beneath the dermis there is loose connective tissue, the *subcutis* or *hypo-dermis*, which usually contains abundant fat (Fig. 1.2).

EPIDERMIS

Keratinocytes

The epidermis is the outer layer of the skin. It is formed by **keratinocytes** which are arranged into multiple layers. The word keratinocyte literally means cells coated by keratin.[Q]

The thickness can vary from less than **0.1** mm on the eyelids to nearly **1 mm** on the palms and soles.[Q] That is why even a minor injury around eye leads to an ugly black eye!

- *Stratum basale* (*stratum germinativum—single layer*): Anchors the epidermis to the dermis and contains cuboidal cells which continuously divide, allowing for replacement of the epidermis. The basal surfaces are attached to the basement membrane zone via fine processes and hemidesmosomes,[Q] anchoring them to the lamina densa of the basement membrane. They contain housekeeping granules.[Q]
- *Stratum spinosum* (*8–10 cells*): Thickest layer of epidermis[Q] so named because connecting desmosomes[Q] appear as 'spines' under the microscope. These cells contain lamellar granules.
- *Stratum granulosum* (*2–5 cells*): This is so-called due to the presence of keratohyalin granules and Odland bodies, which contain profilaggrin and lipids, respectively.[Q] These help in completing the process of keratinization. The latter is important as its defect leads to atopic dermatitis.[Q]
- *Stratum lucidum:* An amorphous band between the stratum granulosum and stratum corneum, only seen in the palms and soles.[Q]
- *Stratum corneum* (*20–25 cells*): Remnants of keratinocytes, consisting of keratin and cell walls without nuclei. The typical 'basket weave' appearance of the horny layer in routine histological sections is artefactual. In fact, cells deep in the horny layer stick tightly together and only those at the surface flake off, this

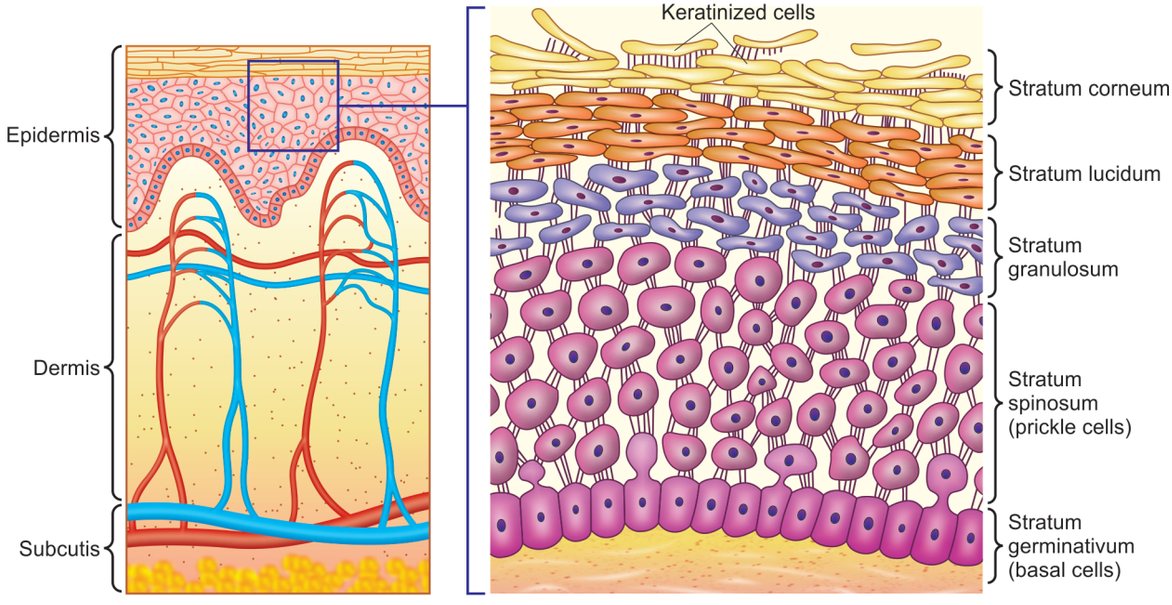


Fig. 1.2: Components of the skin

process is called desquamation.[Q] This is in part caused by the activity of cholesterol sulfatase which is deficient in X-linked recessive ichthyosis.[Q]

The stratum basale and stratum spinosum together are called stratum malpighii, which along with stratum granulosum are the living layers of skin, while stratum corneum is the dead layer.[Q]

The journey of terminal differentiation towards the dead stratum corneum takes about **30 days**[Q] and the stratum basale eventually becomes the stratum corneum, much like our own human body, but of course much faster! This process is called **keratinization**, and in this, the keratin fibrils in the cells of the horny layer align and aggregate, under the influence of filaggrin. Cysteine, found in keratins of the horny layer, allows cross-linking of fibrils to give the epidermis strength to withstand injury.

Other Epidermal Cells

Three other cells are found in the normal epidermis; also called immigrant cells (Fig. 1.3):[Q]

- *Melanocytes*, which synthesize melanin, the main photoprotective factor. (Melanocytes are derived from the neural crest.)
- *Langerhans cells*, which are the antigen-presenting cells of the skin and are part of innate immunity (800 Langerhans cells per mm^2). It also lacks desmosomes and tonofibrils, but has a lobulated nucleus. The specific granules within the cell look like a tennis racket (Birbeck granules).[Q] Topical or systemic glucocorticoids reduce the density of epidermal Langerhans cells as does ultraviolet radiation.
- *Merkel cells*, which are neuroendocrine cells, that function as mechanoreceptors and mediate touch.[Q] (Merkel cells are derived from the neural crest).

Clinical Pearl

Of these cells, the pigmented races, like in India, are hell-bent on removing the melanocyte in a bid to get fairer, but this cell still luckily bounces back! This is good for us, they serve as an effective natural sunscreen in tropical countries!

Cell Junctions

There are several types of cell junctions in the epidermis. Each plays an important pathophysiologic role:

- Desmosomes are complex structures with many proteins and hold cells together (Fig. 1.4). They are composed of transmembranous desmoglein–desmocollin pairs.[Q] There are four types of desmoglein found in the epidermis. Desmoglein (Dsg) 1 is expressed in the upper epidermis while Dsg 3 is mostly expressed in the basal epidermis

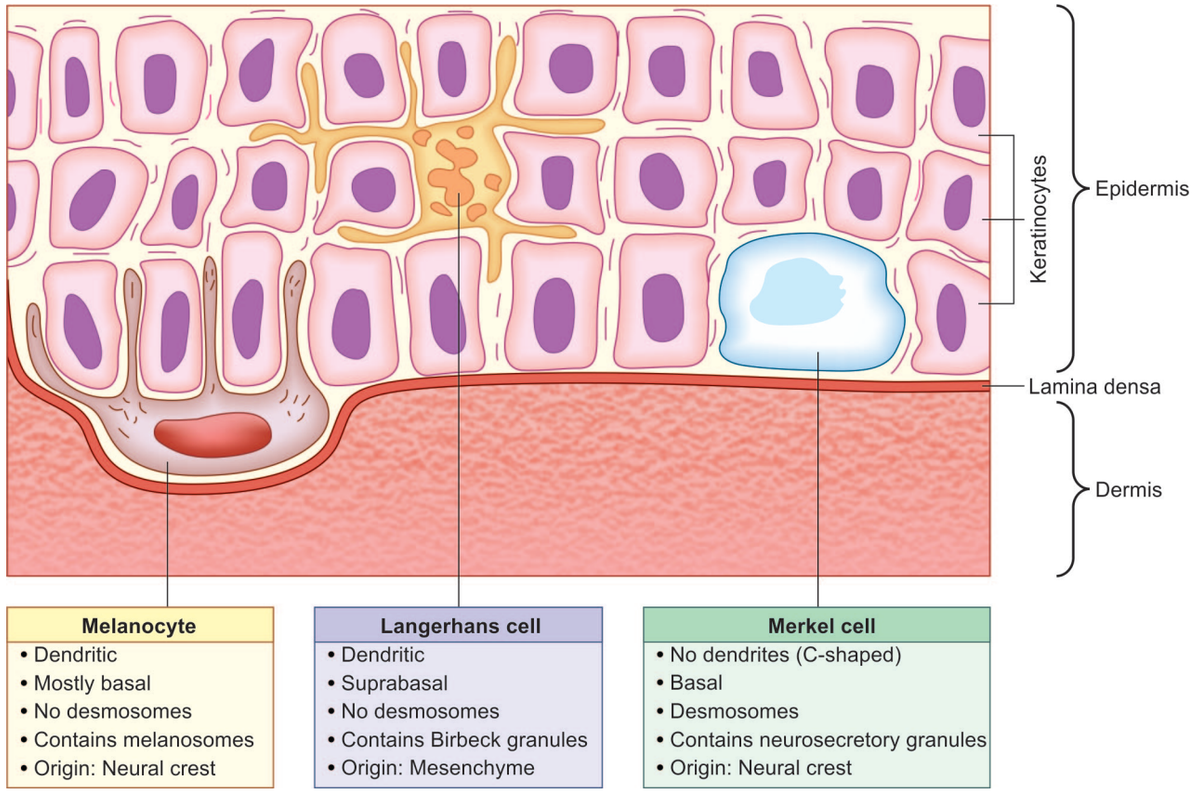


Fig. 1.3: Depiction of the three immigrant cells in the epidermis[Q]

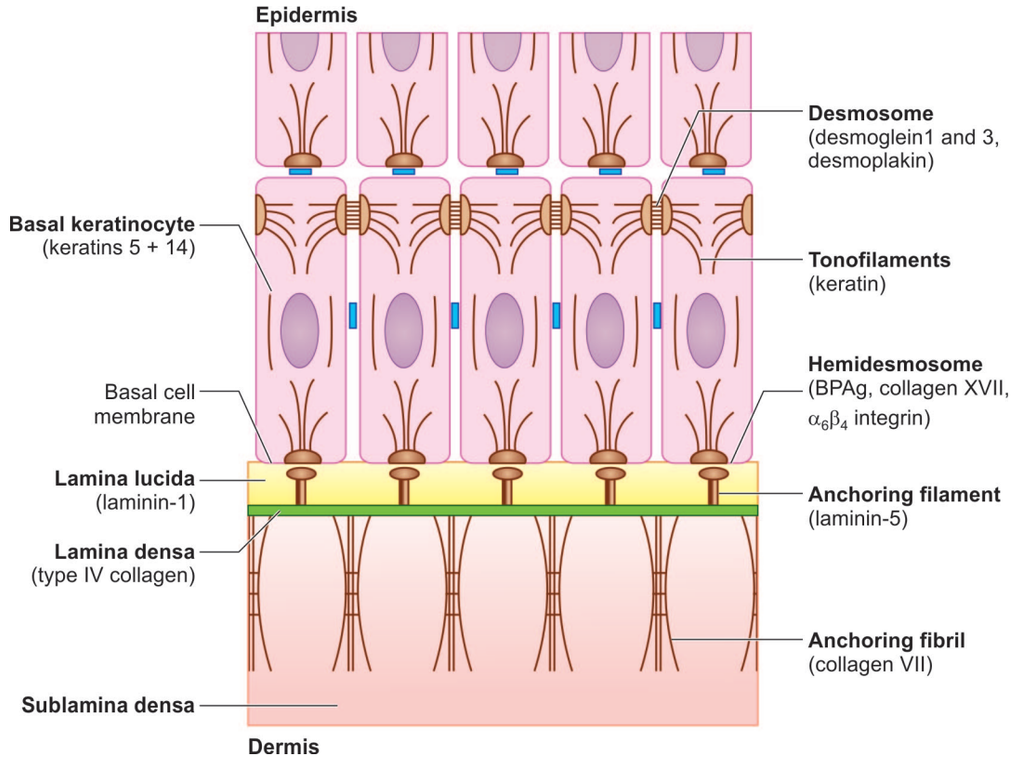


Fig. 1.4: An overview of the basement membrane zone and its components, each defective component of the BMZ is linked to a skin disorder

*('1' number top of epidermis, '3' number down in the epidermis).*Q Dsg 1 is not present in mucosal epithelium. The pemphigus group features dissolution of the epidermis due to damage by autoantibodies against the desmogleins (Dsg 1/3).Q Staphylococcal scalded skin syndrome is caused by bacterial toxins that damage desmogleins (Dsg 1).Q

- The other cell junctions are adherent, gap and tight junctions.

THE BASEMENT MEMBRANE ZONE

Different proteins interact to anchor the epidermis to the dermis. Key components of the basement membrane zone (BMZ) are hemidesmosomes, structures in the lower pole of basal cells sharing many features with desmosomes, and the basal membrane, made up of the lamina lucida and lamina densa (Fig. 1.4). The hemidesmosomes are made up of bullous pemphigoid antigens 1 (a 230 kDa plakin) and 2 (180 kDa collagen XVII) *(1 is more important than 2; 230 >180 kDa)*, plectin and $\alpha_6\beta_4$ integrin.Q The BMZ contributes the barrier function, allowing molecules to diffuse to and from the dermis.

- QDamage via mutations in proteins of the BMZ leads to epidermolysis bullosa, a family of diseases featuring easy blistering.
- Another condition affected by this zone an autoimmune bullous disease, bullous pemphigoid (BPAg 1 and 2).

DERMIS

The dermis is the major structural component of the skin. The predominant cells are fibroblasts, which are responsible for the synthesis of collagen and elastin (the main dermal fibers) (Fig. 1.5).

The dermis has two main compartments:

- Superficial or papillary dermis (1/10th of dermis)
- Deeper or reticular dermis (9/10th of dermis).

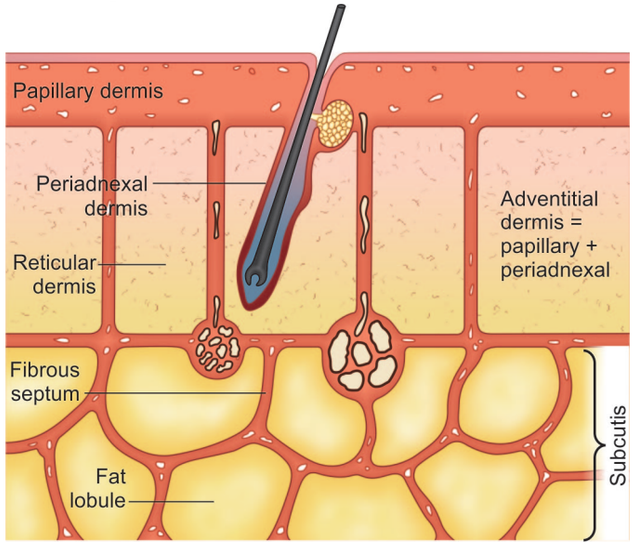


Fig. 1.5: Various components of dermis

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TABLE 1.1 Types of collagen in the skin and their defects

I	Main structural protein	
III	Blood vessels, skin	Ehlers-Danlos syndrome (joint hypermotility and skin extensibility, also blood vessel instability)
IV	Essential component of the BMZ	
VII	Anchoring fibrils in the upper dermis	Dystrophic epidermolysis bullosa,Q EB acquisita
XVII	HemidesmosomesQ	Junctional epidermolysis bullosa, bullous pemphigoid, pemphigoid gestationis

Collagen: Collagen is an ubiquitous structural protein which accounts for 70% of the dry weight of the dermis (collagen 1–70% and collagen 3–15%).Q There are some major collagens and their defects can cause certain disorders as described in Table 1.1.

Elastic fibers: Elastic fibers account for only 2–3% of the dry weight of skin and they impart a resilience and stretchability to the skin.

Abnormalities in elastin can lead to saggy skin "cutis laxa". Disorders in copper metabolism, e.g. Menkes syndromes, can affect the elastic fiber. Ultraviolet (UV) light induces changes in elastic fibers, which play a major role in cutaneous aging.

Clinical Pearl

- The use of 'fillers' in the beauty industry and various moisturizers are aimed at plumping up the dermis, but the results are temporary!
- For lighter skin type, like those who live in the hills, the intense sunlight and the damage to the dermis is the reason for early aging.

Extrafibrillary matrix: The main constituents are proteoglycans, composed of core proteins and glycosaminoglycans (GAGs), which are also known as mucopolysaccharides because of their slimy, tenacious nature.

ADNEXA

The adnexal structures include hair, nails, and glands.

Adnexal Glands

Eccrine Glands (Sweat Glands)

These are active since birth. These are widely distributed, but are most concentrated on the palms and soles. They are not found on the lips, external ear canal, clitoris, glans penis and labia minora.Q Each individual has several millions. They consist of a coiled secretory portion and a long duct coursing through the dermis to open onto the epidermis (Fig. 1.6) and work through merocrine secretion.Q

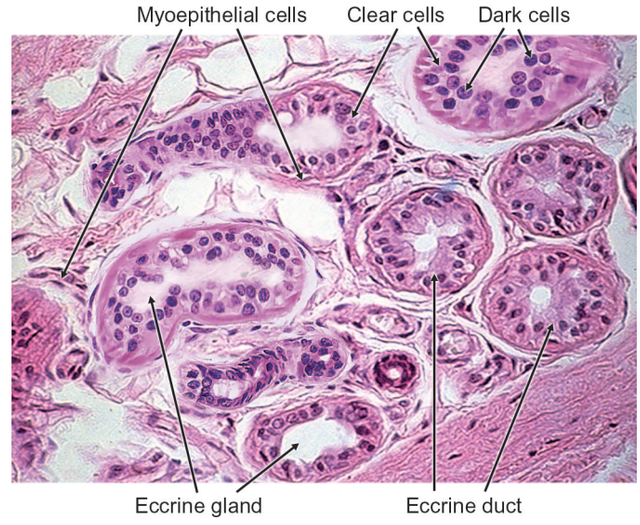

Fig. 1.6: Histology of the eccrine gland

Eccrine sweat is usually **clear** and **odorless**, so the eccrine glands are to some extent 'the skin's kidneys.'Q

Apocrine Glands

These glands are associated with hair follicles; their secretory duct empties into the upper part of the hair follicle.Q They are richest in the axillae, nipple areola complex and groin.Q They function via 'decapitation secretion',Q where the free luminal end of the cell is shed with the secretory products. Apocrine sweat is odoriferous; their function may be to produce pheromones for sexual attraction and other messaging (Fig. 1.7). Although present since birth, they develop around puberty, as they are androgen sensitive.Q

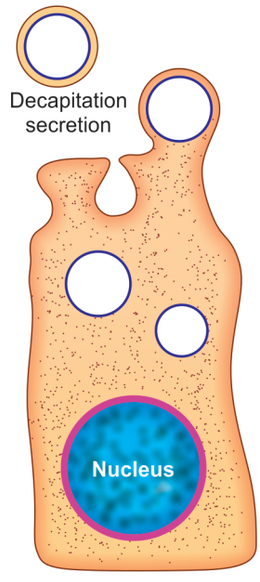

Fig. 1.7: Apocrine gland with decapitation secretion

Apoeccrine Glands

These glands are found in the axillae of adults and have overlapping features of eccrine and apocrine glands, with both types of secretory cells found in the coiled gland. They open directly on the skin surface, not via hair follicles.

Sebaceous Glands

These glands are also intimately associated with hair follicles, as their oily secretion lubricates the follicle to allow the hair shaft to grow outwards against less resistance. Sebaceous glands are very androgen sensitive. When they function to excess, the skin becomes oily and of course, they cause **acne**.

Temperature Control

Eccrine glands are intimately involved in temperature control. In a resting state, evaporative loss of water through the skin is approximately **900 mL** daily.Q This insensitive water loss provides about 20% of the cooling effect of the skin. Apocrine glands have no role in thermoregulation.Q

Core temperature: The body maintains a central temperature at 37°C. By varying skin blood flow, the heat lost by convection and radiation (dry heat loss) can be manipulated over a wide range. For example, digital blood flow can change 500-fold between warm and mid temperatures. Shunts in the digital circulation controlled by contractile glomus cells **(Sucquet-Hoyer anastomosis)**Q make this variation possible. The main control of core temperature is in the preoptic nucleus of hypothalamus.Q

Sweating: When the ambient temperature rises, less dry heat loss can occur, so sweating assumes a major role. Sweating is an active process controlled by cholinergic sympathetic fibers.Q With increased temperature and physical activity, sweat volumes of 1–4 L/hour are possible. Because the eccrine sweat is rich in electrolytes, attention must be paid to replace not only fluids but also sodium chloride and other ingredients.

When one lives in a warm climate baseline sweating increases, electrolyte concentration in sweat decreases, and thirst increases. No such adjustments are possible in cold climates. Furred and feathered animals can increase their insulation by fluffing their outer coats. 'Goose bumps' in humans are residual ineffective attempts to fluff the hairs!

THE INNERVATION

Cutaneous Innervation

The skin is the largest sensory organ; it is served by a variety of nerves, including somatic sensory nerves and autonomic sympathetic fibers (Fig. 1.8). The autonomic nerves help control vessel and sweat gland function. The sensory nerves transmit information about the periphery (skin) to the central nervous system (CNS).

Dermatomes: Sensory nerves follow a dermatomal pattern, best seen in herpes zoster.

Nerve fibers: ***C fibers*** are slow polymodal unmyelinated fibers that can sense and transmit pain, itch, touch, heat, cold, and movement. ***A fibers*** are myelinated and have a higher conduction velocity. They interact with a variety of receptors:

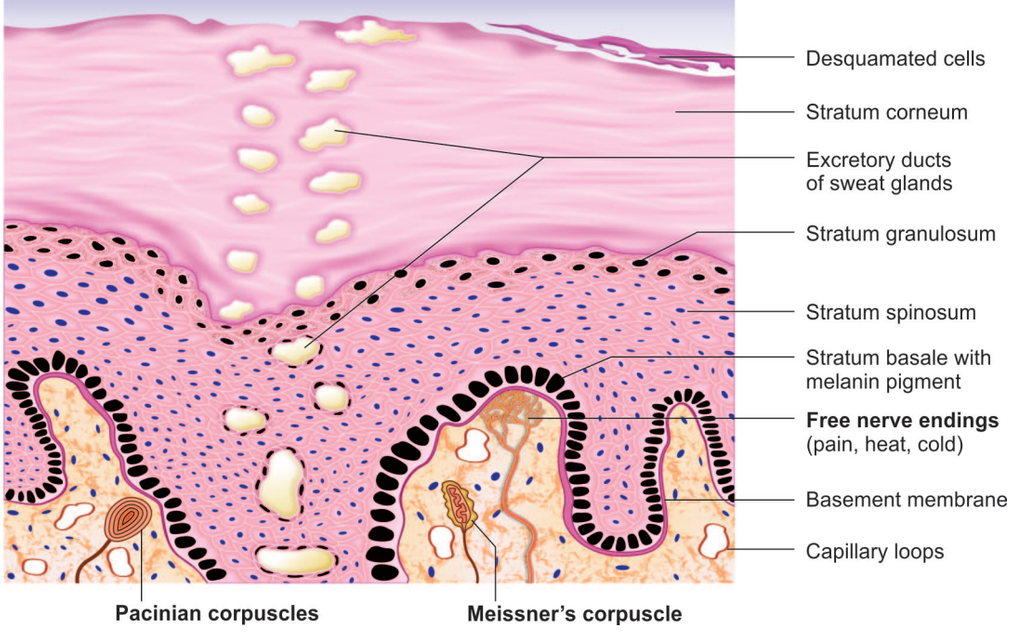

Fig. 1.8: Depiction of the various cells with a focus on skin innervation

- **Free nerve endings** are widespread, found extending into the epidermis and around hair follicles. Known as nociceptors,[Q] they sense pain, motion, touch, heat, and cold.
- **Meissner's corpuscles**—superficial mechanoreceptors, most common on the digits, sensitive to **T**ouch.[Q]
- **Pacinian corpuscles**—deep mechanoreceptors with a 'cut onion' pattern, sensitive to **P**ressure.[Q]
- **Hair disks**—complexes of Merkel cells and free nerve endings, most common on the face; they are not seen on ordinary histology but stain with cytokeratin.
- **Golgi-Mazzoni corpuscle:** SC tissue of fingers laminated structure.
- **Krause end bulb:** Encapsulated swelling of myelinated fibers, superficial dermis.

ADIPOSE TISSUE

The subcutis contains numerous connective tissue septa which carry lymphatics, blood vessels, and nerves. The network of septa keeps the lobules of fat in place and provides support. The smallest functional unit is the microlobule which is nourished by an arteriole.

The vast majority of fat is known as white fat. It serves as a site for energy storage, as well as providing thermal insulation and padding. Newborns have about **5% brown fat**, which is more rapidly metabolized producing heat directly. Brown fat is usually located on the back and along large vessels. Adults have only rudimentary deposits. Brown fat has smaller lipid droplets and is rich in mitochondria. The rapid production of heat is necessary for infants, who cannot shiver as adults do routinely when exposed to cold.

HAIR AND NAILS

Hair

Human hair plays a major role in forming one's image and also has biological functions. Scalp hairs provide ***sun protection*** as skin cancers are more common on bald scalps. The density varies from 615/cm^2 at age 25 to 425/cm^2 after 70 years of age. The eyelashes, eyebrows, and hairs in the anterior nares help to protect these orifices from airborne particles.

The first hair follicles appear in the 10th week of embryonic life,[Q] resulting from an interaction between the epithelial hair germ and the underlying hair papillae, a condensation of mesenchymal cells. Further follicular epithelial regions differentiate into the sebaceous glands, apocrine glands, and the bulge or regenerating region of the hair follicle. The hair papilla determines the size of the hair bulb and thus the hair thickness. The activity of the melanocytes within the matrix determines the hair color.

Parts of Hair

The ***infundibulum*** starts where the sebaceous duct enters the follicle. Just below this, the outer root sheath thickens at the site of attachment of the arrector pili muscle into the ***bulge region***, which contains epithelial stem cells. It also blends with the epidermis at the distal end of the follicle (isthmus) (Fig. 1.9). If the bulge region is damaged, scarring alopecia results (**scarring** also known as cicatricial).[Q]

The hair shaft consists of a medulla, cortex, and cuticle. The cortex is the main component of hair; it contains cornified hair matrix cells analogous to the stratum corneum but formed into a cylindrical mass. The outer layer of the hair shaft is the cuticle, whose overlapping shingle-like cells *interlock* with the cuticle of the inner root sheath, anchoring the hair in the follicle (Fig. 1.10).

Types of Hair

Lanugo hairs are fetal hairs and only seen in premature infants. They are long, thin, non-medullated, soft, and usually without pigment.

Vellus hairs are the normal body hairs, usually <2 cm thin, non-medullated and colorless.

Terminal hairs are long, thick, pigmented hairs with a medulla. They are present at birth on the scalp, as well as forming eyelashes and eyebrows.

Sexual hairs are specialized terminal hairs which appear during puberty as androgens influence vellus hairs in certain body areas, such as the axilla, genitalia, and beard area of men.

Hair Cycle

Hair growth occurs in repetitive cycles. The **3–6 years** period with stable hair growth and maximal follicular size, with high mitotic activity in the matrix, is known

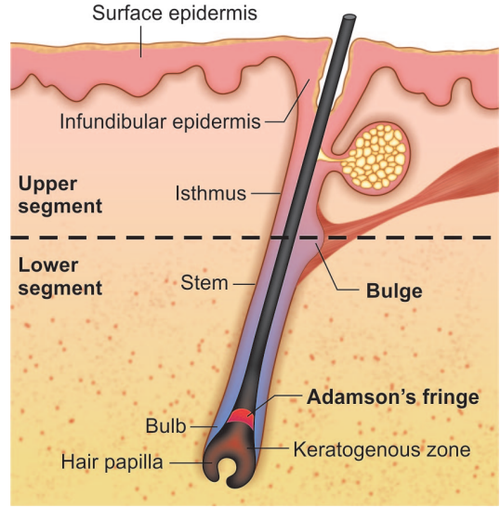

Fig. 1.9: Depiction of the components of hair

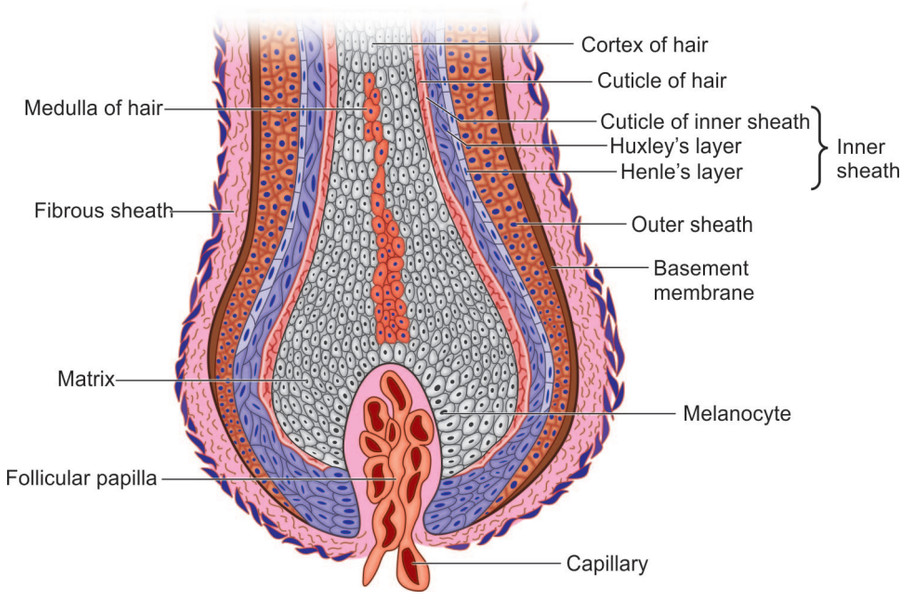

Fig. 1.10: Depiction of the various layers of the hair follicle

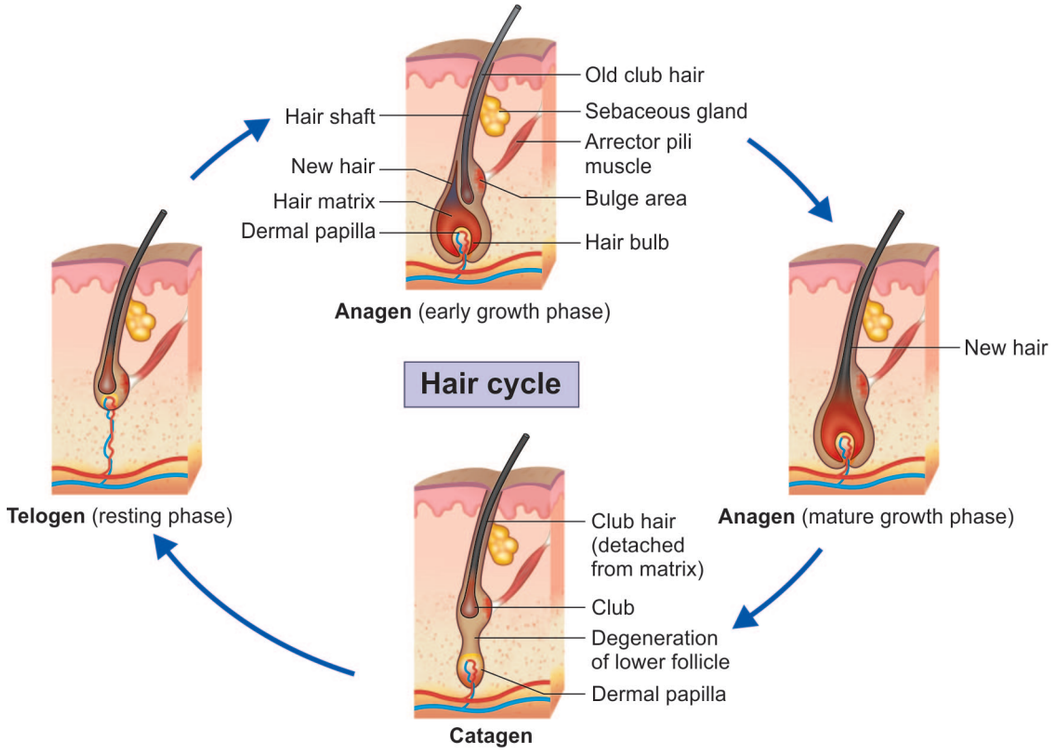

Fig. 1.11: Various phases of the hair cycle

as the **anagen** phase.Q Next, the hair follicle enters a short 2-week transitory period known as the **catagen phase**, with apoptosis of the hair bulb region and regression to about one-third of its previous length as the hair papilla condenses and moves upward and forms the club hair. After 2–4 months of the telogen or resting phase, the club hair is pushed aside by the next anagen hair developing from the interaction between the bulge region and the papilla, and then shed. Normally, more than 80% of hairs are anagen and less than 20% telogen,Q with only a fraction of a percent catagen (Fig. 1.11).

Nails

The nail unit develops between the 9th and 20th embryonal week as pocket-like invagination of the epidermis at the distal end of the digits.

Parts of Nail

It consists of the nail matrix, nail plate, nail bed and periungual skin or paronychium.

The nail stabilizes and protects the fingers and toes, serves as an important tool, and has significant cosmetic effects. In many animals and some humans, it is an effective weapon!

The **nail matrix** is the **growth zone** of the nail; it extends for 3–6 mm beneath the proximal nail fold. The proximal part of the nail fold forms the superficial third of the nail plate, while the more distal part forms the rest of the plate. The nail plate is sealed proximally by the **cuticle (eponychium)** and laterally by the nail folds.

Nail bed: Dermal tissue beneath nail plate, 2–5-cell layer thick.

At its distal end, the 0.5–1.0 mm yellow-brown **onychodermal band** marks the site where the nail plate loses its adherence to the nail bed. Distal to this attachment, the free nail appears white because of the underlying air, and covers the **hyponychium**, a thin stripe of skin without dermatoglyphics or adnexal structures. The **lunula**[Q] is a half-moon-shaped white zone covering the distal matrix at the base of the thumb nails and sometimes other nails (Fig. 1.12).

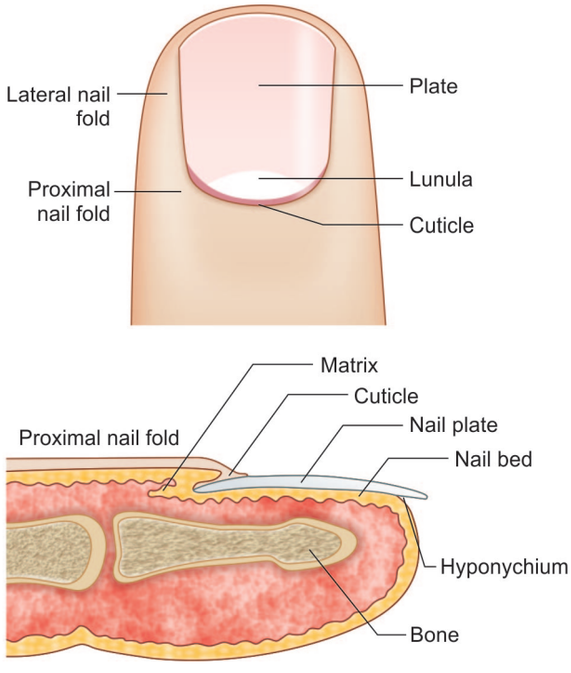

Fig. 1.12: Parts of the nail

Nails grow slowly; a finger nail requires **4–6 months** to replace itself, while a toe nail needs **12–18 months**. That is why for onychomycosis, griseofulvin, a fungistatic drug, has to be given for 12 months!

Nails grow **faster** at night than during the day, in summer than in winter, in young individuals than in the elderly, and in men than in women.

Disorders and Nail

Skin diseases may be associated with more rapid nail growth (psoriasis) or slowed nail growth (atopic dermatitis). The capillaries are visible through the transparent nail plate and cuticle. Using capillary microscopy, vessel changes can be visualized in the nail fold, helping diagnose collagen-vascular diseases such as systemic sclerosis and dermatomyositis.[Q]

Anemia (pale), methemoglobulinemia (blue-gray) and pigmented disorders (melanin deposits, melanocytic nevus, or melanoma) can be seen through the nail, as can subungual tumors such as glomus tumors.

About 10–20% of visible light, 5–10% of UVA and 1–3% of UVB pass through a normal nail plate and reach the nail bed.

IMPORTANT FUNCTIONAL CHANGES

Keratinization

The transition from the cuboidal cells of the basal layer to the scales of the stratum corneum is a complex one. The change from a **basal layer** keratinocyte to a corneocyte takes **14 days** and then the loss of this cell remnant, as scales occur after another **14 days**.[Q] Total 4 weeks (28–30 days).

The main component of the epidermis is keratins and they are arranged in a pair, one acidic and the other basic. This rule of nature that opposites attract is seen down to the molecular level! These two cytokeratins, one basic and one acidic, combine to form a keratin filament[Q] (tonofilament), a hallmark of epithelial cells.

The main events during keratinization:[Q]

1. Cell size increases, cell flattens
2. Nucleus size decreases
3. Metabolism becomes focused
4. Dehydration of the cell
5. Finally, apoptosis

TABLE 1.2 Keratin pairs in skin

Keratins 5 and 14	Basal layer[Q]
Keratins 1 and 10	Spinous layer[Q]
Keratins 6 and 16	Psoriasis
Keratins 4 and 13	Mucosa
Keratins 6a, 6b, 16, and 17	Hair and nails
Keratins 31–40 and 81–86	Hair

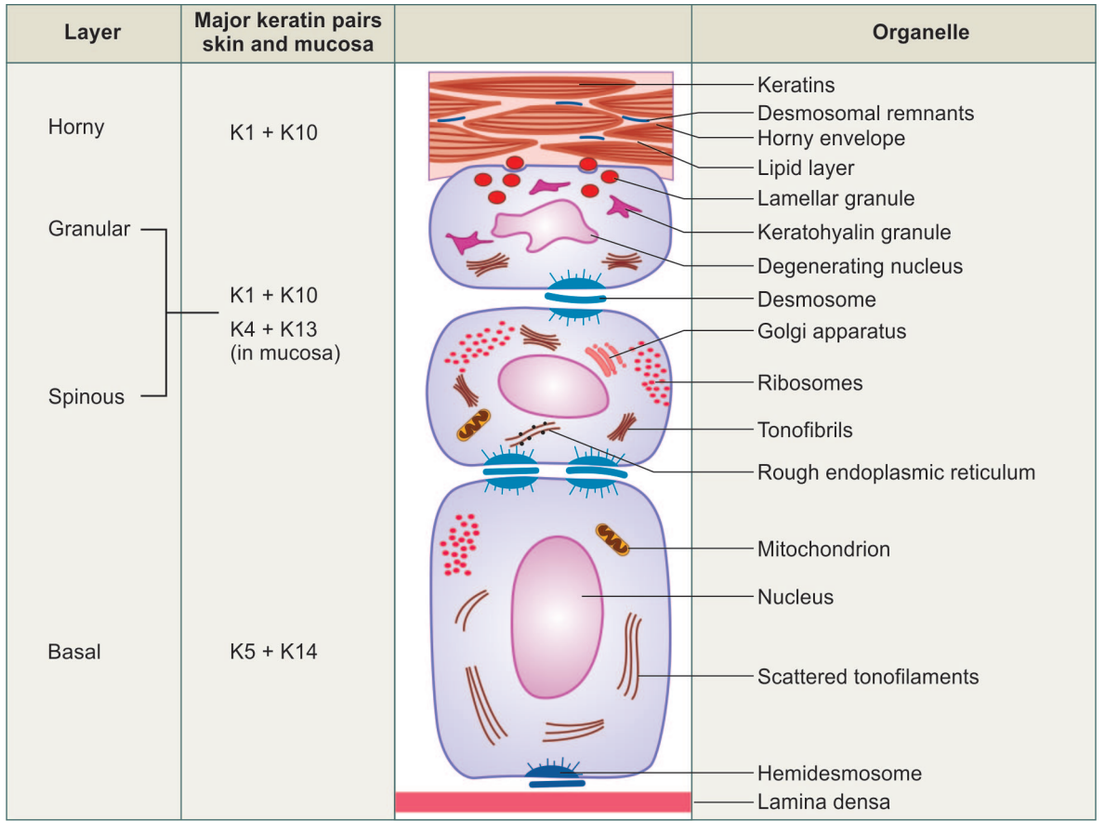

Fig. 1.13: An overview of the keratin pairs with their location in the epidermis

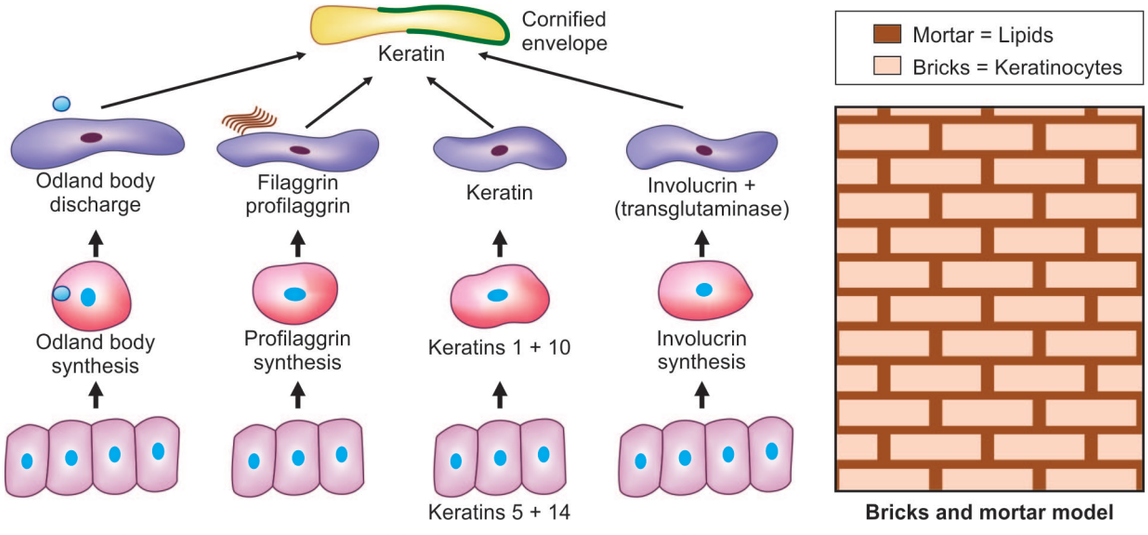

Fig. 1.14: An overview of the process of keratinization. Though the composition of the stratum corneum is akin to a brick wall, the keratinocytes (bricks) and the intercellular space (mortar) undergo metamorphosis and are dynamic

Different pairs of keratin are transcribed and expressed at different levels of the epidermis (Fig. 1.13).

They are important as any dysfunction of these pairs can lead to skin disorders (Table 1.2).

There are three important aspects of the process of keratinization—one involves keratin, second filaggrin and third Odland bodies (Fig. 1.14).

- Odland bodies (keratinosomes), which discharge epidermal lipids into the intercellular spaces of the stratum corneum.Q

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- Profilaggrin, which is synthesized by keratinocytes in the stratum spinosum; it is the precursor of filaggrin, which binds together with keratin to form keratohyalin granules.Q

Clinical correlate: Mutations in filaggrin are important in both **atopic dermatitis and ichthyosis vulgaris**.Q

- **Involucrin**, which is the main component of the cornified envelope, is linked by transglutaminase.

Melanization

Melanocytes

Melanocytes are derived from the neural crest and migrate into the epidermis.Q On light microscopy, they are dendritic cells located in the basal layer. About every 10th basal layer, cell is a melanocyte **(ratio of melanocyte to basal cells—1:10)**.Q

Melanogenesis

Melanocytes manufacture melanin, the key pigment of the skin. The synthesis of melanin is complex starting with tyrosine; the most important enzyme is tyrosinase.Q An important intermediate is DOPA (a precursor of dopamine). Two major forms of melanin are:

- **Eumelanin (brown-black)** (*EBB—eumelanin, brown, black*).
- **Pheomelanin:** It contains sulfur (red-yellow; copper) (*PC—pheomelanin; copper*).

The melanin is packaged into melanosomes in the Golgi apparatus and then transferred to keratinocytes. Melanocytes have long cell extension (dendrites) and transfer pigment to approximately 36 keratinocytes (Fig. 1.15).Q (*Epidermal melanin unit → 1:36*).

Defects in Melanogenesis (Fig. 1.16)

- **Albinism—**lack or reduced function of tyrosinase or other enzymes leading to defective production of melanin; often associated with visual problems.
- **Transfer defect—**'ash-leaf' macules of tuberous sclerosis result from abnormal transfer of melanosomes.
- **Piebaldism—**congenital absence of melanocytes because of aberrant cell migration secondary to loss of function mutations in the tyrosine kinase (Kit)Q receptor; causes white streaks of hair (poliosis) or hypopigmented patches of skin; it may be coupled with deafness **(Waardenburg syndrome)**.
- **Vitiligo—**an autoimmune disease with localized destruction of melanocytes.

Skin Color and Type

Very minor differences in melanogenesis lead to major variations in skin color. **Skin color** is determined by the *type of melanin* and by the nature of the *melanosomes*, NOT *by the number* of melanocytes.Q In black skin, the melanosomes are larger, deeply pigmented and more slowly degraded; they primarily contain eumelanin (Fig. 1.17).

Brown and black hairs have eumelanin, while blond and red hairs contain more pheomelanin. Red hair also contains trichrome melanin.

Melanin is crucial as it provides protection against ultraviolet (UV) irradiation. It functions as a free-radical scavenger and can be called the **'umbrella' of the skin.**Q Fitzpatrick identified six different skin types, based on tendency to burn or tan. Type I individuals burn always, never tan, and are at increased risk for both melanoma and other skin cancers. Indians have Type IV,

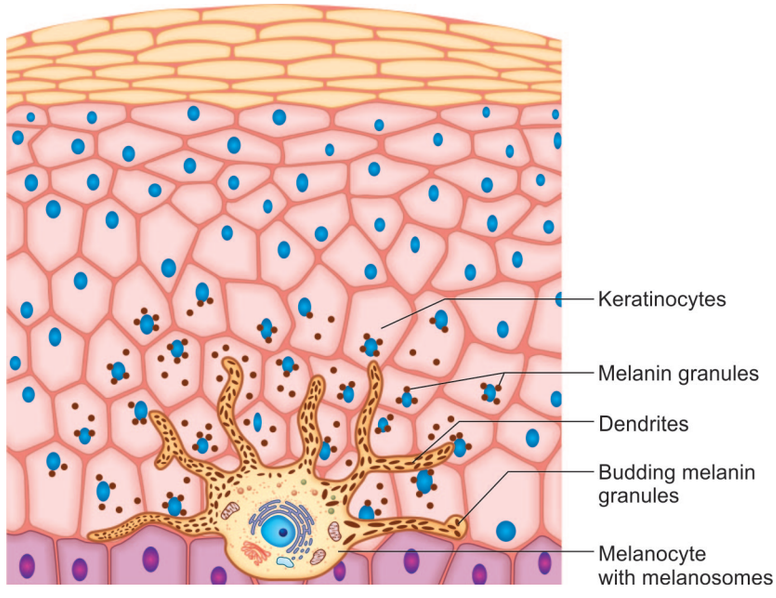


Fig. 1.15: Localization of the melanocyte and its interaction with the keratinocytes

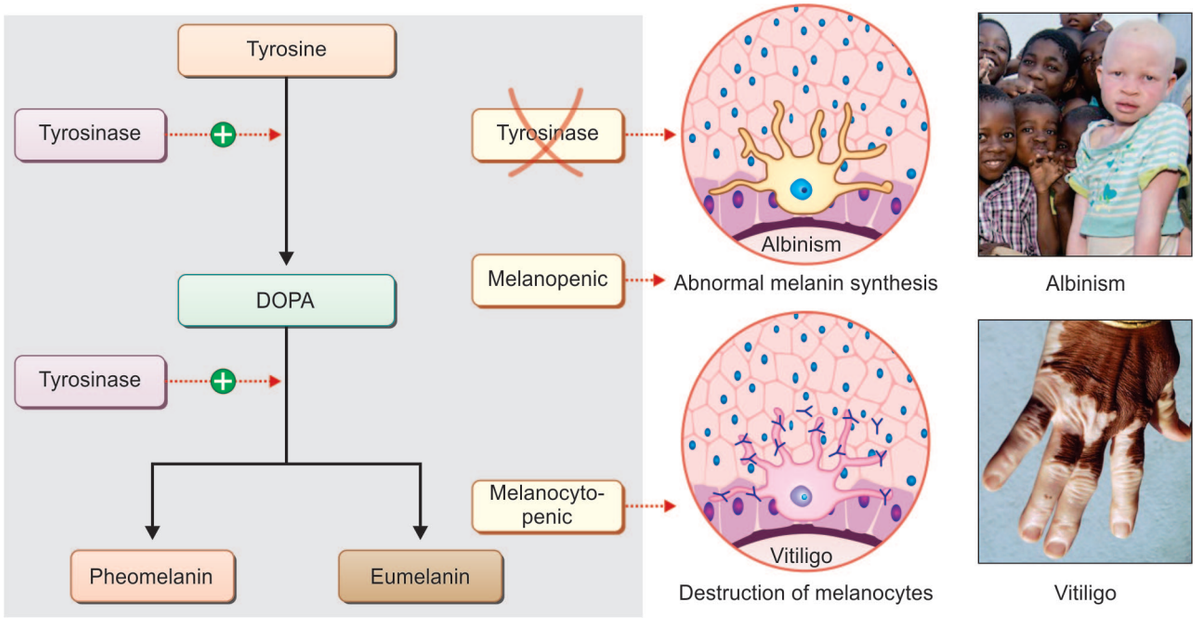
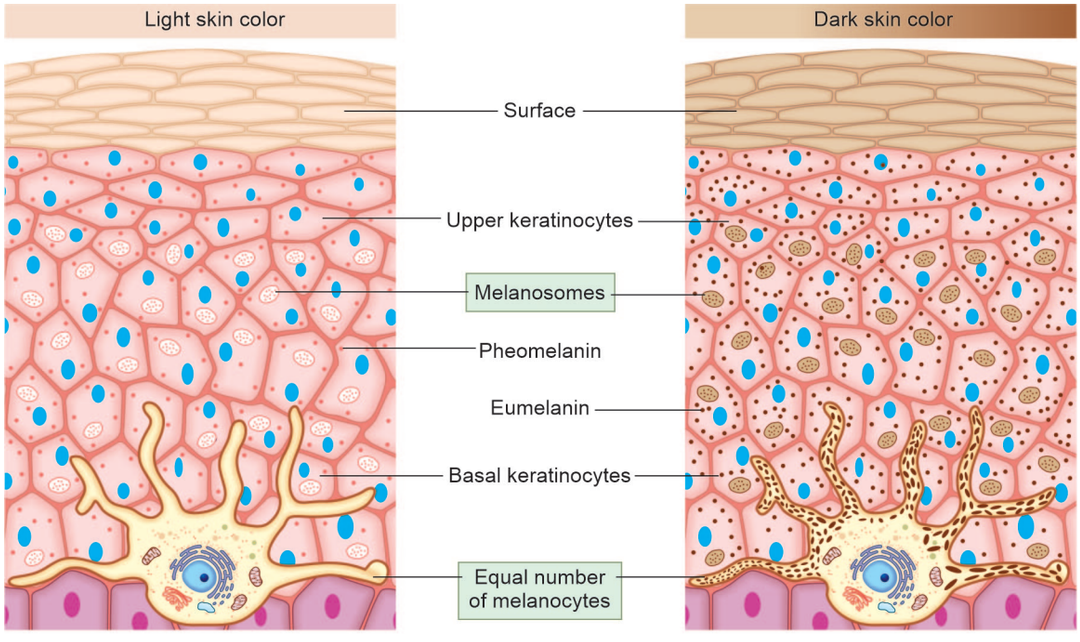


Fig. 1.16: Common defects in melanogenesis and their clinical effect



Skin types	I	II	III	IV	V	VI
Sunburn	Always	Always	Sometimes	Minimal	Rarely	Never
Tan	Never	Minimal	Gradually	Easily	Darkly	Always

Fig. 1.17: Comparison of a light skin and dark skin patient. It is the *melanosomes* content and the type of pigment that determine skin color. Indians are lucky to have this "natural" sunscreen and have Type IV skin. The sad part is that we keep trying to reduce our natural skin color to become fairer, fighting nature's protective mechanism

Clinical Pearl

Diagnosis of pigmentation disorders can be made by two observations:

Q. Hyperpigmented lesions—increased melanin or increased melanocytes? Pigment in the epidermis or dermis?

Q. Hypopigmented lesions—absent melanocytes or defects in melanin production and transfer?

but we try to use products to make our skin fairer, a mistake, as it is our protection against UV damage.

IMMUNOLOGY OF SKIN

The purpose of the immune system is to protect the body against potentially damaging influences like microbes or toxins. The first step is the mechanical barrier and biologic barriers, which prevent entry of the noxious agents into the body. When these agents penetrate the skin defense, the immune system is activated (Fig. 1.18).

There are two types of immune responses, the *inborn* or also called the *innate immunity* and when this cannot contain the outside agent, the *acquired immunity* is activated.

Innate Immunity

Some immune cells can phagocytose and destroy damaged cells or microorganisms. Cell damage appears to release alarm signals, which trigger the immune response and later also enhance the effector functions of the defense. All the cells that can be attacked by exogenous agents contribute to the innate response. In the skin, they include the keratinocyte; in the mucosa, epithelial cells, and in the liver, hepatocytes; in addition, fibroblasts and glial cells can also raise an alarm (Fig. 1.18).

a. The cells react to the stress signals by releasing a group of *alarm cytokines*, mainly interleukin-1 **(IL-1)**.
b. In the *skin*, inflammation starts with the activation of the *inflammasome*.
c. This activation leads to the transcription, processing and cleavage of **IL-1α** and **IL-1β**.
d. These activate the other interleukins (IL-6, IL-18), tumor necrosis factor-α (TNF-α) and chemokines, which attract and activate antigen-presenting cells (APCs).

Thus, the innate immune response is set into motion (Fig. 1.19).

Specific (Acquired) Immunity

a. Activated APCs carrying foreign antigen migrate to the regional lymph nodes, where they use chemokines to attract naive CD4+ helper T cells and CD8 cytotoxic T cells (Fig. 1.20).
b. The APCs present their antigens or haptens to these cells. The naive T cells that recognize the antigens on the basis of their receptor structure are then activated to 'blast' forms.
c. With the help of the cytokine **IL-2**, these activated T cells can increase by a factor of 10,000 within a few days. In the lymph nodes, activated T cells interact with B cells and signal them to start producing immunoglobulin.
d. The T cells then leave the lymph nodes and return via the bloodstream to the site of initial injury, guided by a variety of cell messengers. As part of the innate response, an inflammatory reaction is initiated, which leads to the production of adhesion molecules. These enable the activated T cells to attach to vessel walls, migrate through the walls, and move into the inflamed tissue. There they are further stimulated by antigen-carrying macrophages and monocytes, to produce a group of proinflammatory mediators.
e. Interferon-γ **(IFN-γ)** plays a central role, as it induces macrophages to produce important inflammatory mediators, cranking up the entire response process by stimulating the tissue cells to produce vast amounts of free oxygen radicals, TNF, and all the

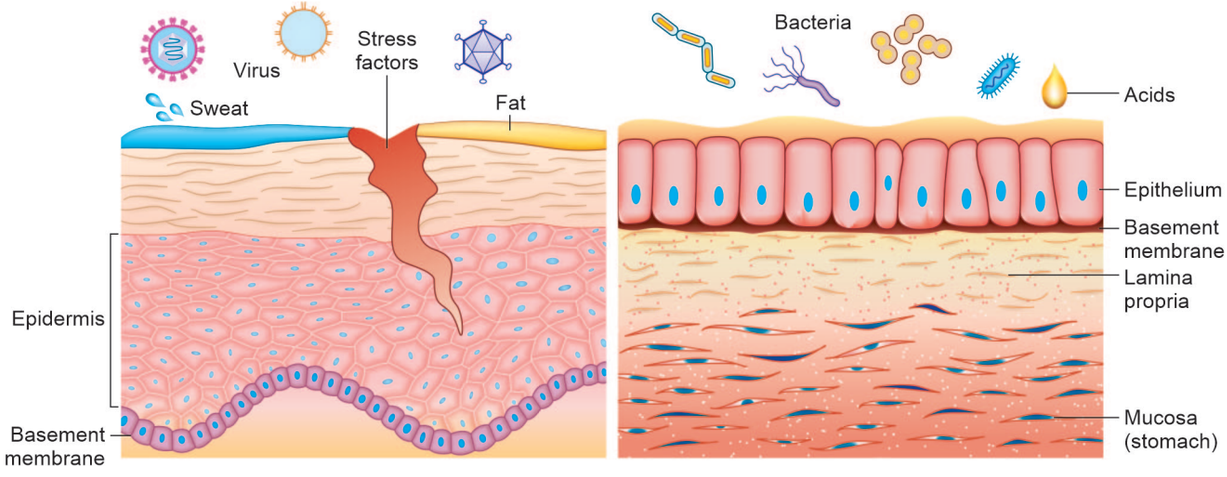


Fig. 1.18: The physical barriers that determine skin and mucosal defense

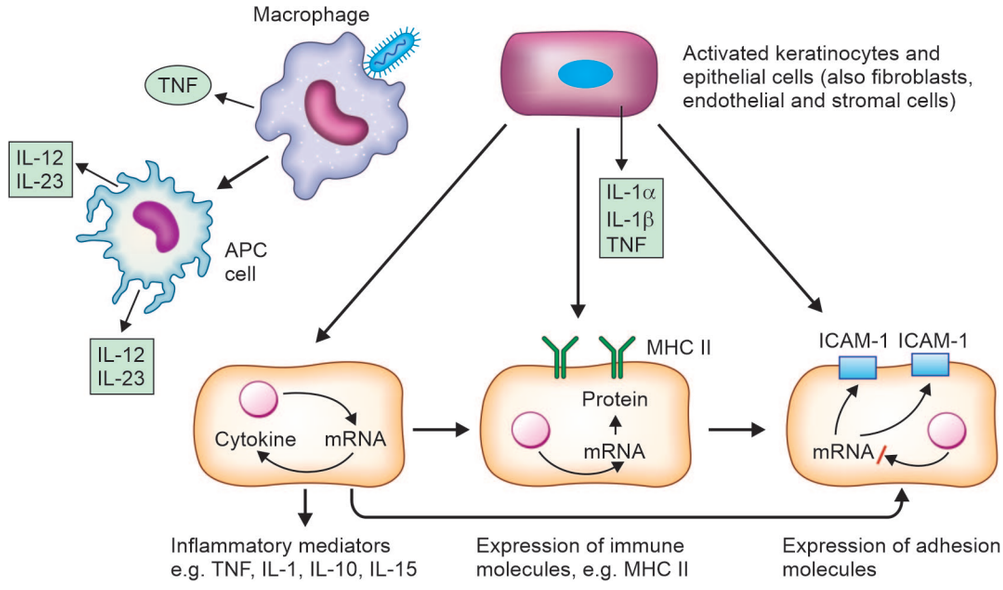


Fig. 1.19: Mechanism of activation of innate immunity

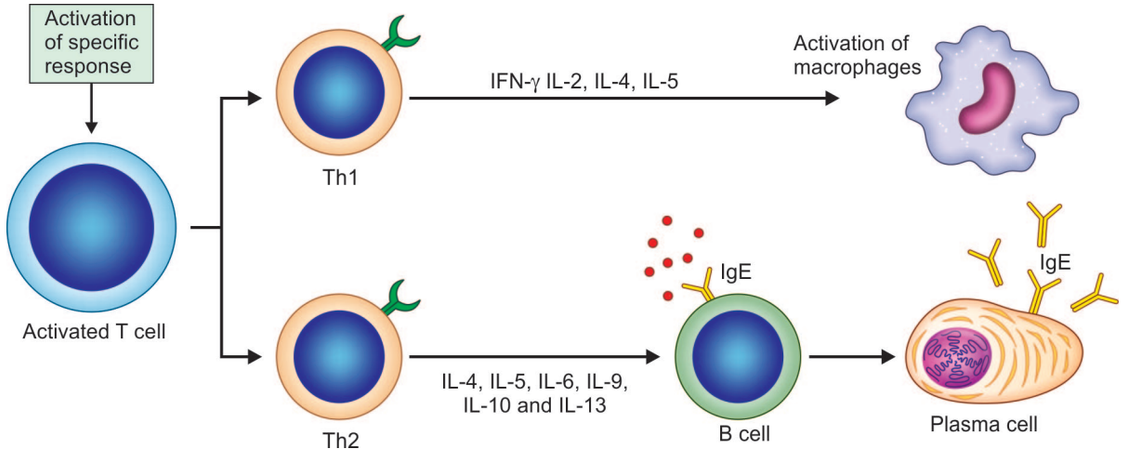


Fig. 1.20: Specific immune response and the role of Th1 and Th2 cells

other factors with which they initially signaled alarm. In contrast to the initiation phase, both the number and quantity of cytokines are now much greater.

The initially nonspecific defense mechanisms are so effectively enhanced by the appearance of immune cells specifically directed against the triggering antigen or hapten, that the process of cleaning up can begin, with the killing and phagocytosis of the invading substances. This is dominated either by lymphocytes and macrophages or neutrophils (Fig. 1.20).

T Cell Response and Activation

T cells are the binding link between the innate and specific immune responses. They are characterized by the membrane-bound T cell receptor (TCR). T cells can only be activated by APCs that present, with their MHC molecule, a peptide that fits the highly specific TCR.

There are broadly two types of cells (Fig. 1.21):

1. **CD4+ or helper T cells (Th)** can induce or suppress the inflammatory immune responses via cytokines (Th1, Th2, Th17 response) or via the T reg.
2. **CD8+ or cytotoxic T cells (Tc)** can destroy virally infected target cells.

The CD4 and CD8 molecules are membrane coreceptors that determine which MHC molecules the T cells interact with. The MHC class I molecules are expressed by almost all cells, while MHC class II molecules are only expressed by APCs.

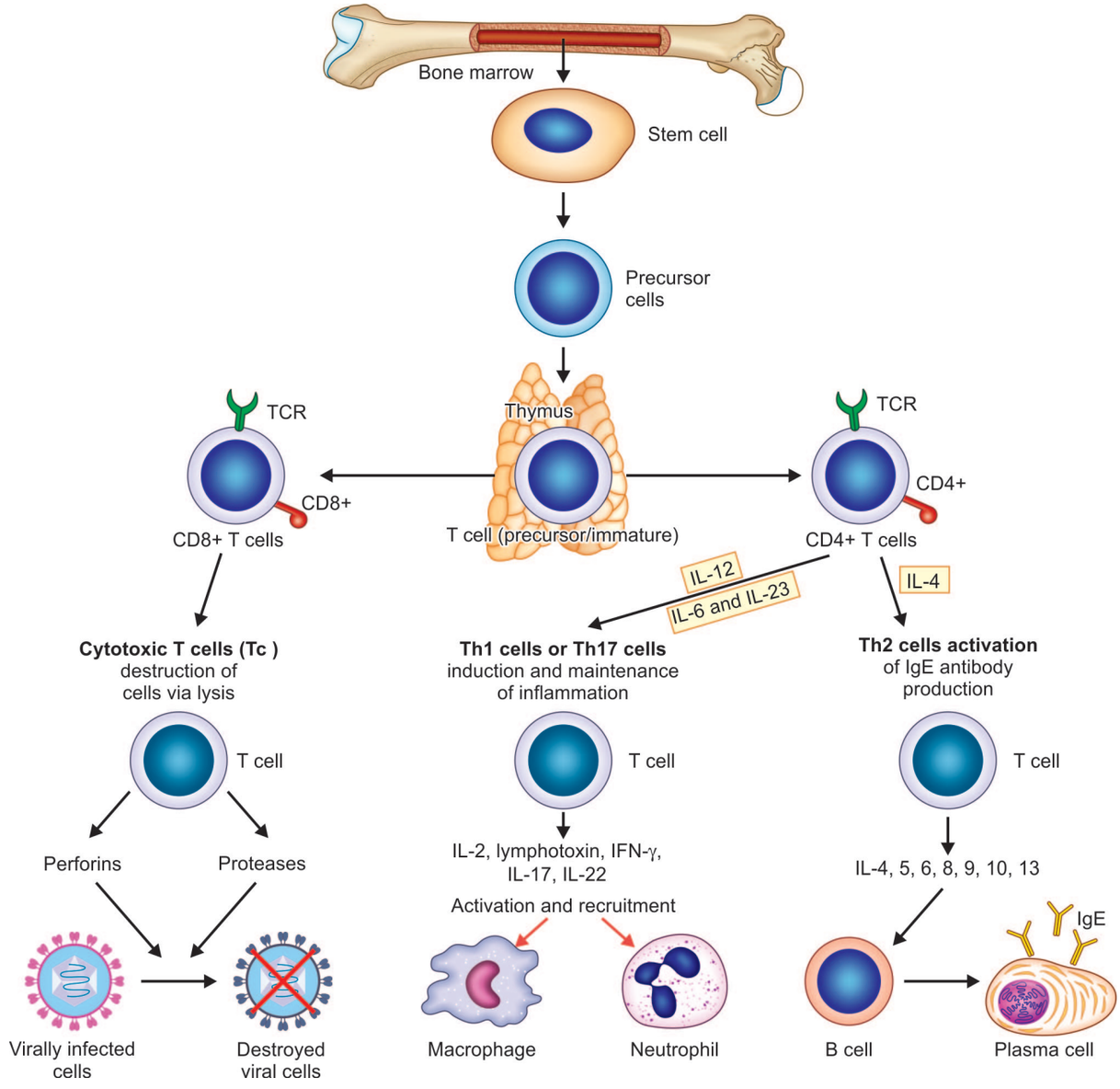


Fig. 1.21: Depiction of the T cell origin and differentiation

- **CD4+ cells** [Th] interact with **MHC class II** (HLA-DR and HLA-DQ) molecules, which primarily present *exogenous* antigens (such as allergens or haptens) to T cells.
- Cytotoxic **CD8+ cells** (Tc) interact with **MHC class I** (HLA-A and HLA-B) molecules; primarily *endogenous* antigens such as viral and tumor peptides.

The selection of those T cells that are allowed to circulate in the body, as well as the association of a TCR with a CD4 or CD8 molecule, occurs in the thymus. The average adult has around 10^{12} T cells available, with around 10^9 different TCRs, which circulate as naive T cells until they meet their specific antigen in association with an APC and are then activated. Thus the T cell repertoire is capable of recognizing 10^9 different peptides.

APC: The initiation of a specific immune response requires the stimulation of naive T cells by activated APCs in the lymph nodes. The Th cells then have the task of initiating the production of immunoglobulin by B cells in the lymph nodes, and of further activating the nonspecific effector cells, such as macrophages and monocytes, in the tissue. For this apart from TCR and MHC molecules, adhesion molecules are essential for cell affinity—they include intracellular adhesion molecule (ICAM)-1 and lymphocyte function antigen (LFA)-1. Costimulatory molecules are then required for T cell activation.

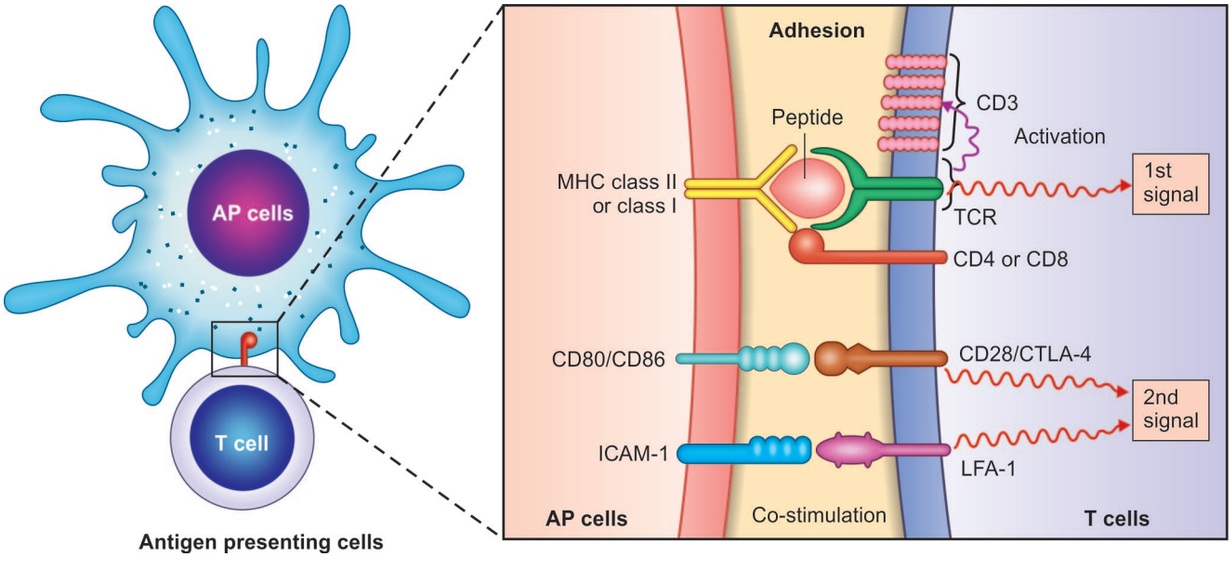


Fig. 1.22: Interaction of T cells and APC

Important representatives are CD28 and CTLA-4 on T cells, and their partners CD80 and CD86 on APCs (Fig. 1.22).

Cytokines: For adequate activation and clonal expansion of T cells, both IL-2 and IL-15 are required. In addition, cytokines direct the differentiation of T cells (Fig. 1.23A).

a. **IL-12** promotes the development of naïve Tc cells into cytotoxic Tc 1 cells, and naive Th cells into proinflammatory Th1 cells.
b. **IL-1**, **IL-6**, and **IL-23** induce IL-17-secreting Th17 cells.
c. **IL-4** induces Th cells to the Th2 cells which counterbalances the Tc, Th1 and Th17 cells.

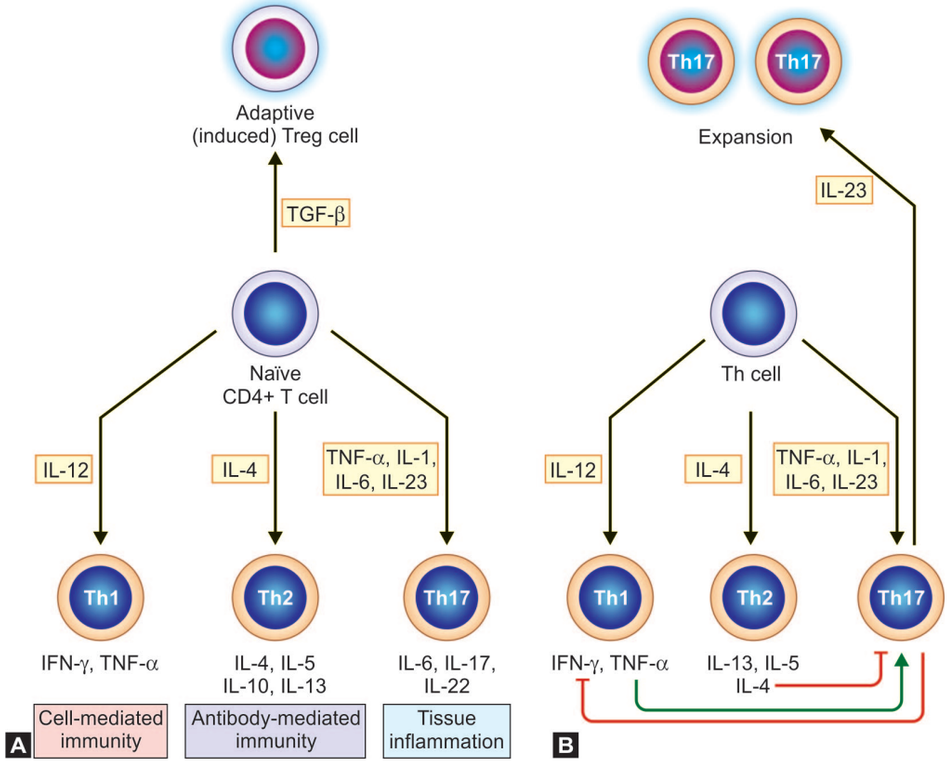


Fig. 1.23A and B: (A) Depiction of the major cytokines that determine immune response; (B) Interplay of cytokines and Th1, Th2, and Th17 cells

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d. Th2 cells induce IgE production by B cells, and activate and attract eosinophils, playing an essential role in all forms of immediate allergy.

Th17 cells: The importance of Th17 cells was recognized with the observation that both IL-17 and IL-23 play a central role in the development of autoimmune inflammatory diseases. These cells produce interleukin IL-17A and recruit neutrophils.

This cell is important both in the causation and treatment of psoriasis[Q] and multiple sclerosis. Recent data suggest that Th17 cells in coordination with the Th1 cells play a role in delayed-type hypersensitivity reactions, such as allergic contact dermatitis and many other inflammatory diseases.

During inflammation, the Th17 cells are produced with the Th1 cells but are activated by different cytokines. IL-12 is important for the differentiation of naive CD4+ T cells into a Th1 phenotype. In contrast, IL-1, IL-6, and IL-23 are required for the induction of Th17 cells, while IL-23 (a subtype of IL-12) is needed for their expansion. IFN-γ and IL-4 suppress the differentiation of Th17 cells (Fig. 1.23B). IFN-γ suppresses angiogenesis, while IL-17 stimulates it.[Q]

T regulatory cells: The most important counterbalance to the Th1,Th2 and Th17 cells are the T reg cells. These are activated CD4+ T cells which express the IL-2 receptor CD25 on their surface apart from the transcription factor FOXp3 (forkhead box p3). They keep the other cells in balance primarily by cell-cell contact. The inhibition is via soluble mediators like IL-10 and TGF-β.

Their use stems from the fact that they mediate the aggravated allergic response in conditions like asthma, a classic type I allergy, allergic alveolitis, and severe forms of allergic rhinoconjunctivitis, and can arrest the progression to asthma, the 'atopic march'.[Q] There is good evidence that hyposensitization therapy or allergen-specific immunotherapy against Type I allergies involves the induction of specific T reg cells.

B Cells and Antibody Production

B cells are responsible for Ab production. To differentiate into Ig-secreting plasma cells, B cells must be stimulated by Th cells, usually in the lymph node follicles. With their ability to present peptide antigens with MHC class II molecules, and to produce cytokines for the innate immune response, B cells also function as weak APCs in the regulation of the T cell response. They appear to suppress cell-mediated immune reactions and facilitate the differentiation of T cells into Th2 cells or regulatory (T reg) cells.

Antibodies (immunoglobulins): Antibodies are immunoglobulins that react with antigens.

- Immunoglobulin G (IgG) is responsible for long-lasting humoral immunity. It can cross the placenta, and binds complement to activate the classic complement pathway. IgG can coat neutrophils and macrophages and acts as an opsonin by cross-bridging antigen.
- IgM is the largest immunoglobulin molecule. It is the first antibody to appear after immunization or infection. Like IgG, it can fix complement but unlike IgG, it cannot cross the placenta.
- IgA is the most common immunoglobulin in secretions. It acts as a protective paint in the gastrointestinal and respiratory tracts. It does not bind complement but can activate it via the alternative pathway.
- IgE binds to Fc receptors on mast cells and basophils, where it sensitizes them to release inflammatory mediators in type I immediate hypersensitivity reactions.

Mediators of Immune System

Immune cells interact via both direct cell-cell contacts and soluble molecules known as mediators. They include a broad spectrum of different molecular classes and are a crucial component of the signaling system that leads to an effective immune response.

The ultimate effect of these mediators on the cells can be variable. IFN-α and IFN-β bind to the same receptor, but transmit in part different signals, so IFN-α is used for *immunostimulation* and IFN-β for *immunosuppression*.

Important mediators include:

- Cytokines
- Chemokines
- Soluble surface molecules.

Cytokines

The cytokines are a large family of soluble mediators which include interleukins (ILs), growth factors (GFs) and IFNs (Figs 1.21, 1.23 and 1.24).

- **Basic mediators:** Tumor necrosis factor (TNF), IL-1, and IL-6 are rapidly released by macrophages in all forms of inflammation. Blocking IL-1 or TNF inhibits many aspects of inflammation.
- **T cell:** T cell cytokines, which confusingly can also be secreted by other cells, regulate the course of the immune response via T cells. IL-2 is the most important T cell growth factor. The function of T cells is determined by the cytokine pattern.

IL-2 and IFN-γ are **Th1** cytokines that have the following effects:

a. Formation of TNF and free radicals in macrophages.
b. Convert CD8+ T cells into cytotoxic cells.
c. Drive B cells to isotype switch to produce complement-binding immunoglobulins.

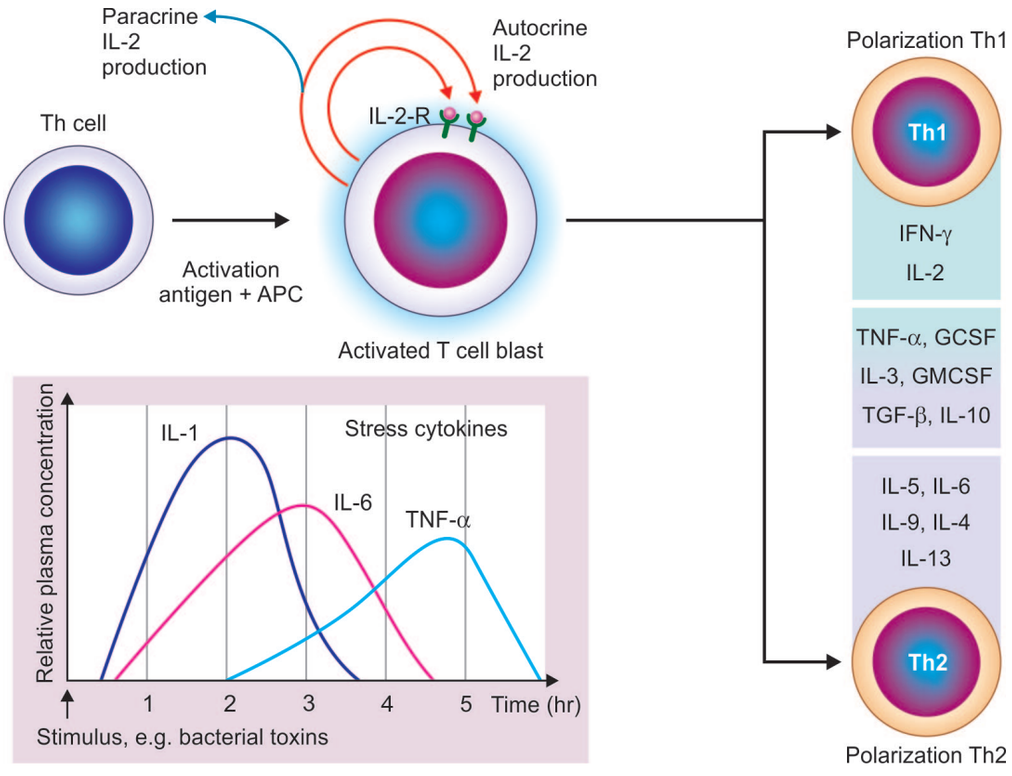

Fig. 1.24: Depiction of various cytokines and their role in Th1 and Th2 polarization and response to stress

Th1, cytokines and **IL-17**, the main cytokines of the **Th17** cells, initiate the cell-mediated or delayed-type immune response.

The **Th2 cytokines** are IL-4, IL-9, and IL-13, and have the following actions:

a. Suppress the proinflammatory properties of macrophages.
b. Drive B cells to isotype switch producing IgG4 and IgE.
c. Support immediate-type allergies or type I reactions, including airway hypersecretion and increased smooth muscle tone.

Additional important cytokines are IL-10, IL-12, and IL-23, which are secreted by APCs. **IL-10** can block immune responses, while **IL-12** and **IL-23** can induce strong delayed-type hypersensitivity reactions, **IL-31** seems to induce itch.

Chemokines

Chemokines help in migration and homing of different immune cells, in cooperation with IL-1 and TNF, which induce the expression of adhesion molecules by endothelial cells. This facilitates the attachment of immune cells to the vessel wall and then migration through the wall. The chemokines guide the successful migrants to the site of inflammation. The chemokine pattern determines the type of infiltrate. For example, eotaxin binds to chemokine receptor 3 (CCR3), thus attracting eosinophils and Th2 cells (Fig. 1.25).

Surface Molecules

In addition to the classic soluble mediators, cell surface molecules and receptors can have a similar function when they are separated.

For example, in severe inflammation, the soluble TNF receptor is released into serum and has an anti-inflammatory effect by binding to TNF.

Types of Immune Reaction

Specific immune responses enable a targeted and amplified inflammatory response. As shown above, a close and intricate interaction between the antigen and the APC is needed. This leads to certain specific kinds of response which were divided into 4 types using the original classification of Coombs and Gell.

Their basic classification is still useful:

- Type I—immediate
- Type II—cytotoxic
- Type III—immune-complex mediated
- Type IV—cell-mediated or delayed-type hypersensitivity reaction

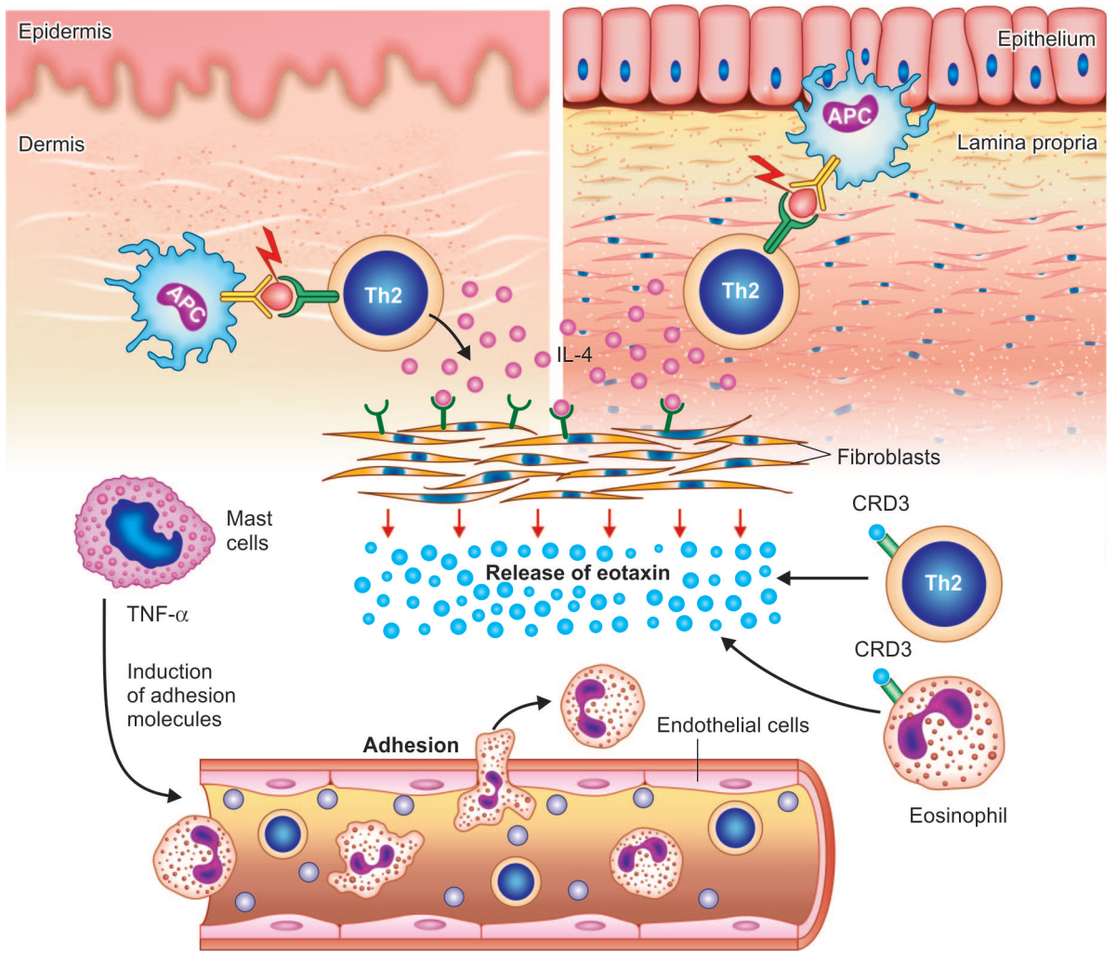

Fig. 1.25: Role of chemokines in migration and homing of inflammatory cells

Immediate Reaction (Type I)

This immune reaction is mediated by lgE antibodies. They are directed against soluble protein antigens (allergens); typical examples are pollen, animal dander, house dust mites, foods, and arthropod toxins. Allergen contact leads to linking of IgE molecules on the surface of mast cells or basophils, and triggers a cascade of events:

- Release of immediate mediators such as histamine or TNF.
- Synthesis and release of leukotrienes and prostaglandins.
- Synthesis of proallergic cytokines like IL-4 or IL-5.

These can trigger disorders like allergic rhinitis, asthma, or urticaria.

Cytotoxic Reaction (Type II)

Here, IgG antibodies react with antigens that sit on the cell surface. The antigens are medications (such as penicillin) bound to erythrocyte membranes, cell components like the Rhesus D antigen (RhD), or basement membrane components. The IgG mediates cytotoxic effects through complement and phagocytosis.

Examples of Type II reactions include medication- or RhO-mediated hemolysis, heparin-induced thrombocytopenia (HIT), glomerulonephritis, and urticaria caused by anti-Fc€-receptor antibodies.

Immune-complex Reaction (Type III)

The responsible IgG antibodies are directed against soluble antigens. Examples include:

- Injected serum
- Fragments of pathogenic microbes, e.g. in bacterial endocarditis or viral hepatitis
- Molds or components of hay or that are inhaled.

The resultant antigen–antibody complexes (immune complex) can cause local or systemic reactions. Effector mechanisms include complement binding and activation, as well as activation of granulocytes and macrophages with vessel wall and tissue damage.

Clinical examples are serum sickness or localized Arthus reaction to injected products, vasculitis affecting the skin, joints, and kidneys, persistent viral hepatitis, and allergic alveolitis (farmer's lung).Q

Delayed Reaction (Type IV)

Antigen-specific T cells mediate the delayed-type hypersensitivity or cell-mediated reaction. Triggers include metal ions (such as nickel or chromium) or low molecular weight substances such as fragrances or preservatives, which can bind to body proteins to form complete antigens. Protein antigens from mycobacteria, bacteria, yeasts, and dermatophytes can also induce delayed reactions. The allergen contact is mediated by antigen-presenting dendritic cells and monocytes macrophages, leading to stimulation of T cells. Released cytokines trigger the inflammation, with T cells returning to the site of antigen exposure.

Clinical examples include allergic contact dermatitis and dermal erythematous papules, as in a tuberculin reaction when the allergen bypasses the epidermis.