Histology of Skin
Attacks and Defenses

Learning Objectives

Given a histological image of skin, students should be able to identify and list the functions of epidermis, dermis and hypodermis.

Given a histological image of skin, students should be able to distinguish the structure and functions the four layers of the epidermis.

Given a histological image of a skin, students should be able to identify melanocytes and Langerhans cells.

Given a histological image of skin, students should be able to distinguish and list the functions of eccrine, apocrine and sebaceous glands.

Introduction

The skin is the largest organ of the body and has five primary functions:

- Protection
- Homeostasis of Body Temperature
- Sensation
- Metabolism
- Sexual Attraction

This reading will focus on the structure and composition of skin and its role in protecting the body from desiccation, mechanical forces and ultraviolet (UV) light.

Layers of the Skin

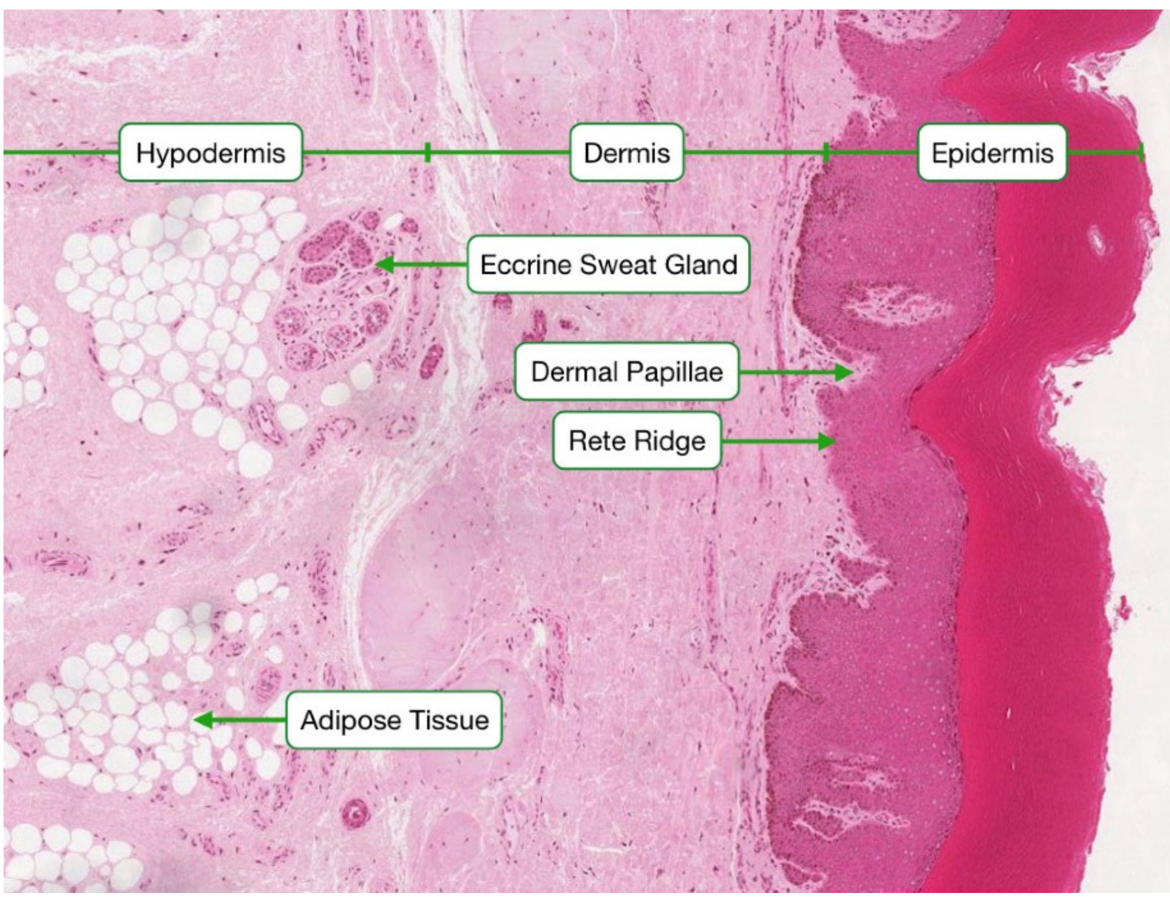
Skin comprises three layers: epidermis, dermis and hypodermis. The epidermis is most superficial and interacts with the external environment. It is a self-regenerating, stratified squamous epithelium that produces a protective layer of keratin. Keratin generates a barrier that protection against desiccation and penetration of foreign microorganisms and chemicals. The thickness of the epidermis will vary depending on the its location and the amount of mechanical force that impacts that location. For example, the thickest epidermis is usually found in the palms of the hand and soles of the feet.

Underneath the epidermis is the dermis, a layer rich in collagen. The collagen provides mechanical support by resisting tension in multiple directions. The dermis also contains blood vessels, nerves and sensory receptors.

Note the rete ridges that are down growths of the epidermis into the dermal layer. These generate a stronger connection between the epidermis and dermis and help the skin resist shearing forces. In between rete ridges are dermal papilla, which contain sensory receptors called Meissner's Corpuscles.

The deepest layer is the hypodermis that is largely composed of adipose tissue but also has large blood vessels and sensory receptors. Adipose tissue provides metabolic support and creates an insulating layer to prevent loss of heat.

Note the presence of eccrine sweat glands near the border between the dermis and hypodermis. Eccrine sweat glands are found throughout the skin and help reduce core body temperature through evaporation of fluid on surface of the epidermis.



Skin comprises three distinct histological layers: epidermis, dermis and hypodermis.

Epidermis

The epidermis is a stratified squamous epithelium that contains layers of cells called keratinocytes. Kertinocytes in different layers are in different stages of development. All keratinocytes derive from stem cells in the deepest layer, the stratum basale, and undergo structural and functional changes as they migrate upward toward the surface of the epidermis. These changes ultimately lead to apoptosis of the keratinocytes and the formation of keratin on the surface of the epidermis.

The epidermis is divided into four layers based on the structural appearances of keratinocytes in each layer. Changes in gene expression and activity of various biochemical pathways lead to the structural changes in keratinocytes. The layers from deepest to most superficial are stratum basale, stratum spinosum, stratum granulosum and stratum corneum.

The stratum basale is a row of cuboidal to columnar cells resting on the basement membrane that separates the epidermis from the dermis. Stem cells in this layer give rise to transit amplifying cells that rapidly divide to replace all of the cells in the stratum basale that have migrated into more superficial layers of the epidermis. The precise location of the stem cells in basal layer is still unclear. Some studies support the conclusion that epidermal stem cells are found at the peaks of the dermal ridges, whereas other studies find stem cells throughout the stratum basale, In either case, epidermal stems cells divide to produce another stem cell and/or a cell that will differentiate into a keratinocyte. As keratinocytes develop, they migrate upward in the epidermis.

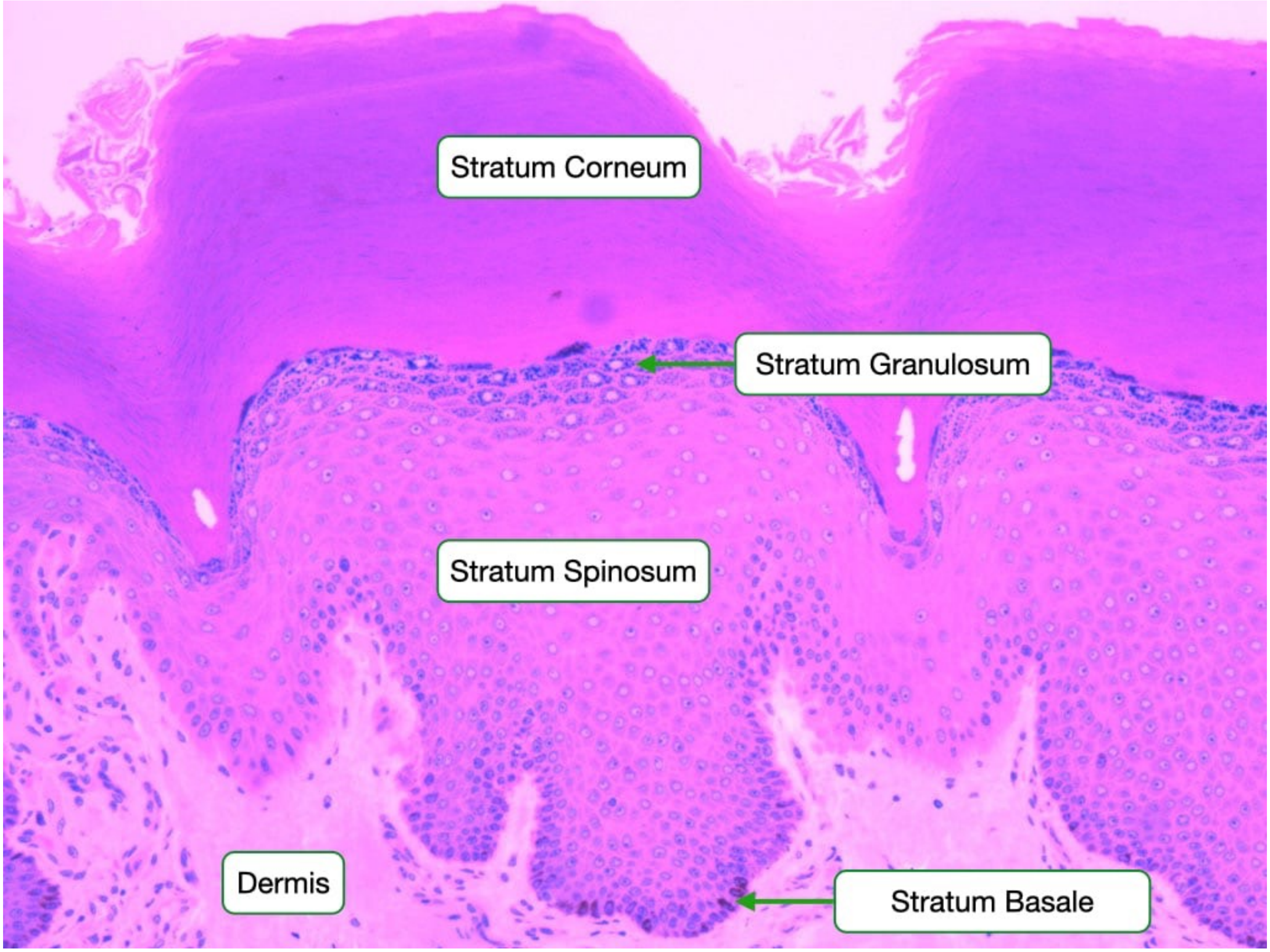
After forming in the basal cell layer, keratinocytes migrate upwards into the stratum spinosum. Keratinocytes in all layers are linked to each other via desmosomes which connect intracellularly to intermediate filaments. The proteins that compose intermediate filaments in keratinocytes are collectively called cytokeratin. Keratinocytes change their expression patterns of cytokeratin genes as they migrate from the stratum basale toward the surface of the epidermis. For example, keratinocytes in the basal layer express keratins KRT5 and KRT14 where as keratinocytes in more superficial layers express keratins KRT1 and KRT10. Mutations in all four keratin genes can lead to fragility of skin and various skin-blistering diseases.

Recall that desmosomes in adjacent cells are linked via integral membrane proteins from a large family of genes called cadherins. In skin, desmosomes primarily contain a type of cadherin called desmoglein. Keratinocytes express four different types of desmoglein (Dsg 1 - 4). Each desmosome can contain a mix of different desmogleins.

The stratum granulosum is the third defined layer in the epidermis. Here, the keratinocytes have become squamous and contain granules of keratohyaline. The contents of the granules bundle cytokeratin that will eventually form the keratin sheets seen on the surface of the epidermis.

In addition, cells in this layer release lipids into the extracellular space that will form a layer of lipids between the keratin sheets to prevent desiccation.

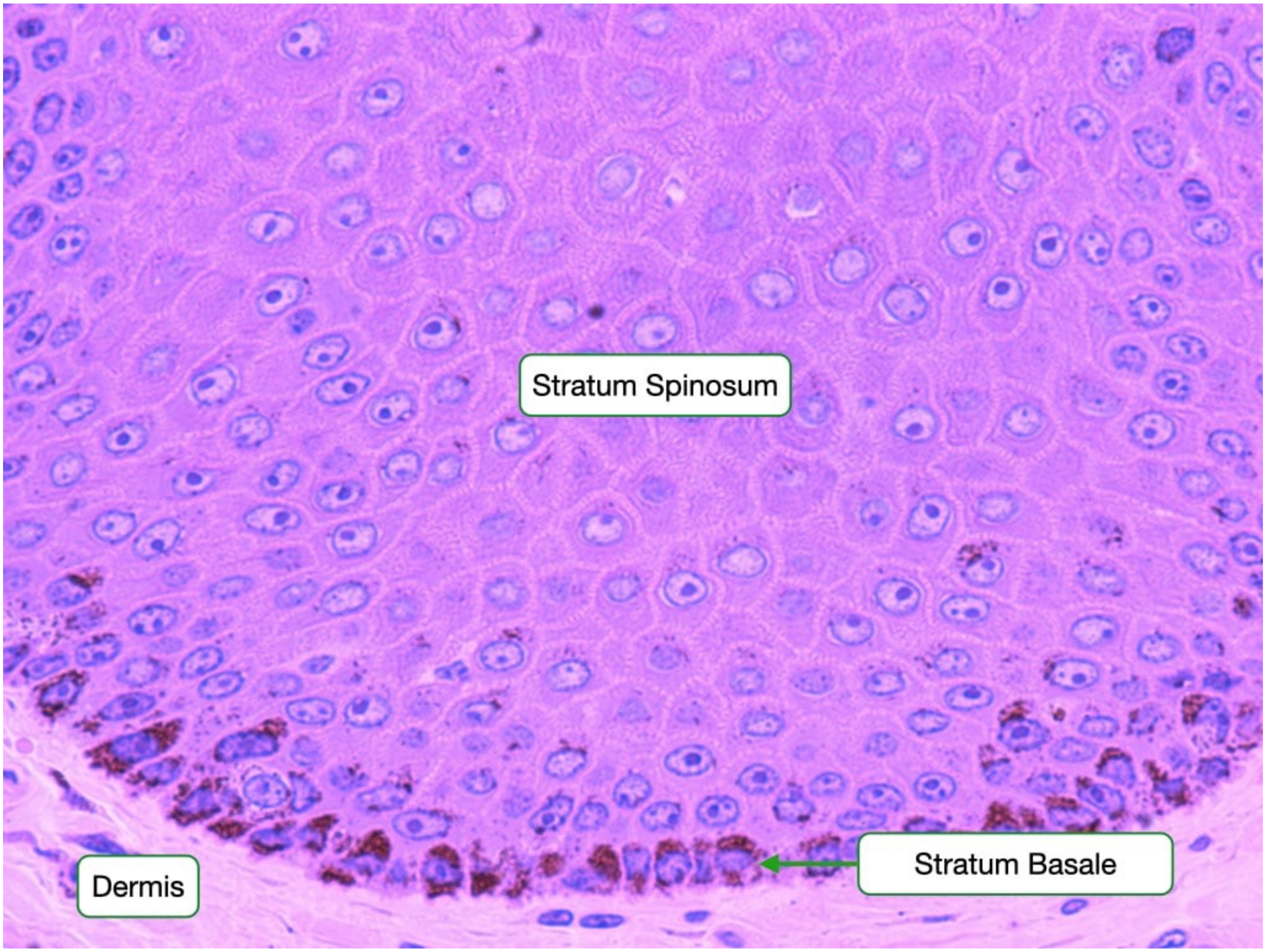
The stratum corneum is the most superficial layer of the epidermis. Here, the keratinocytes have lost their nuclei and undergone apoptosis. This layer includes the final keratin product, a combination of cytokeratin and keratohyaline, that is coated in a lipid-rich substance that helps prevent loss of water.



The epidermis comprises four histological layers: basale, spinosum, granulosum and corneum.

Stratum Basale and Spinosum

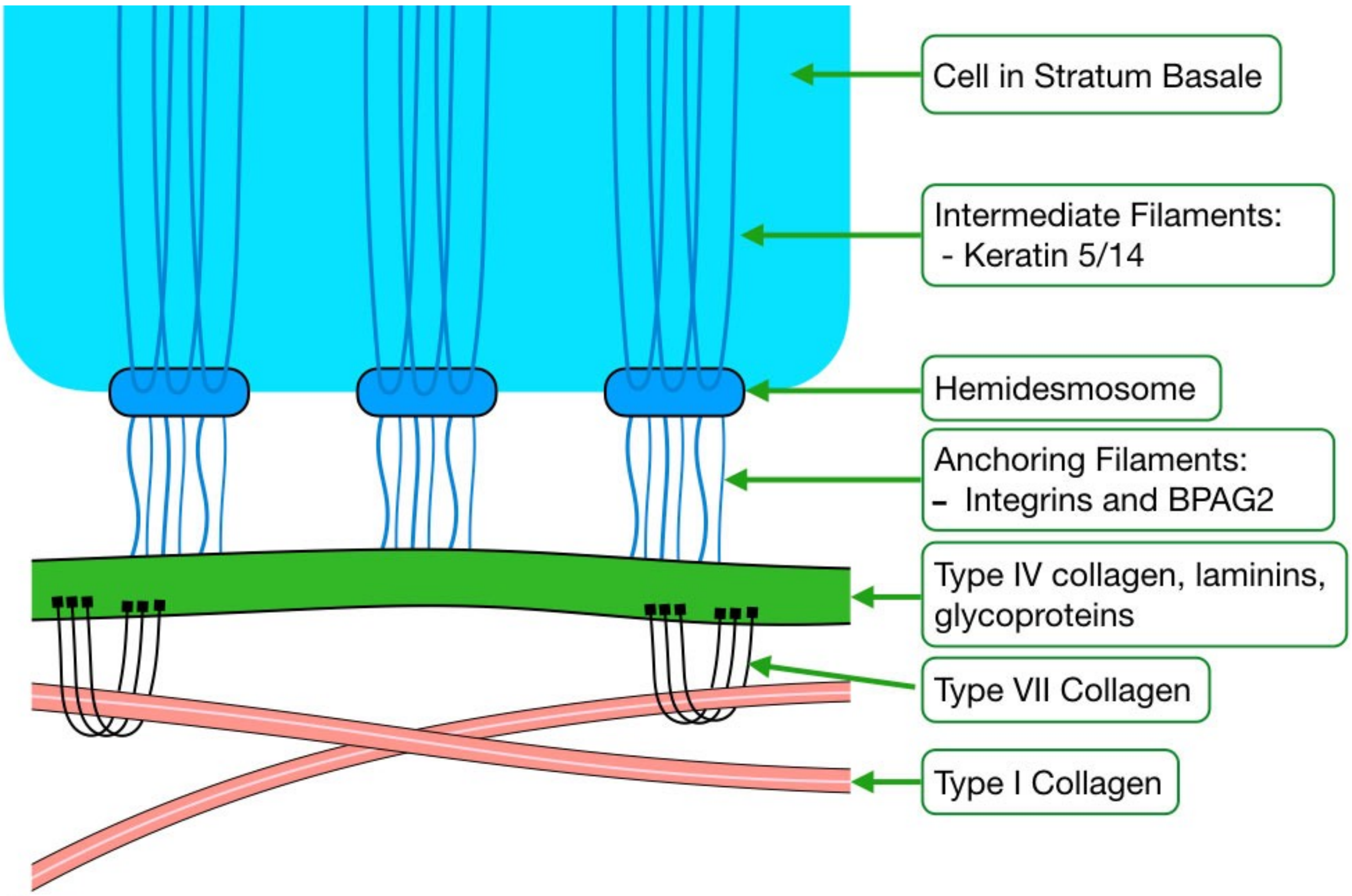
This image shows the stratum basale and stratum spinosum at higher magnification. The cells of the stratum basale are cuboidal to columnar. Note the dark staining material in some of the cells of the basale. This is melanin that gives skin its color and absorbs UV-light to protect DNA in the underlying tissue from damage. Also note the numerous, prickly connections between keratinocytes in the stratum spinosum. These are intercellular connections made by desmosomes. During the fixation process kertinocytes shrink and retract from each other, but the desmosome connections remain intact. Note the prominent nucleoli in the nucleus of the keratinocytes in the stratum spinosum.



Cells in the spinosum appear spiny due to strong desmosome attachments.

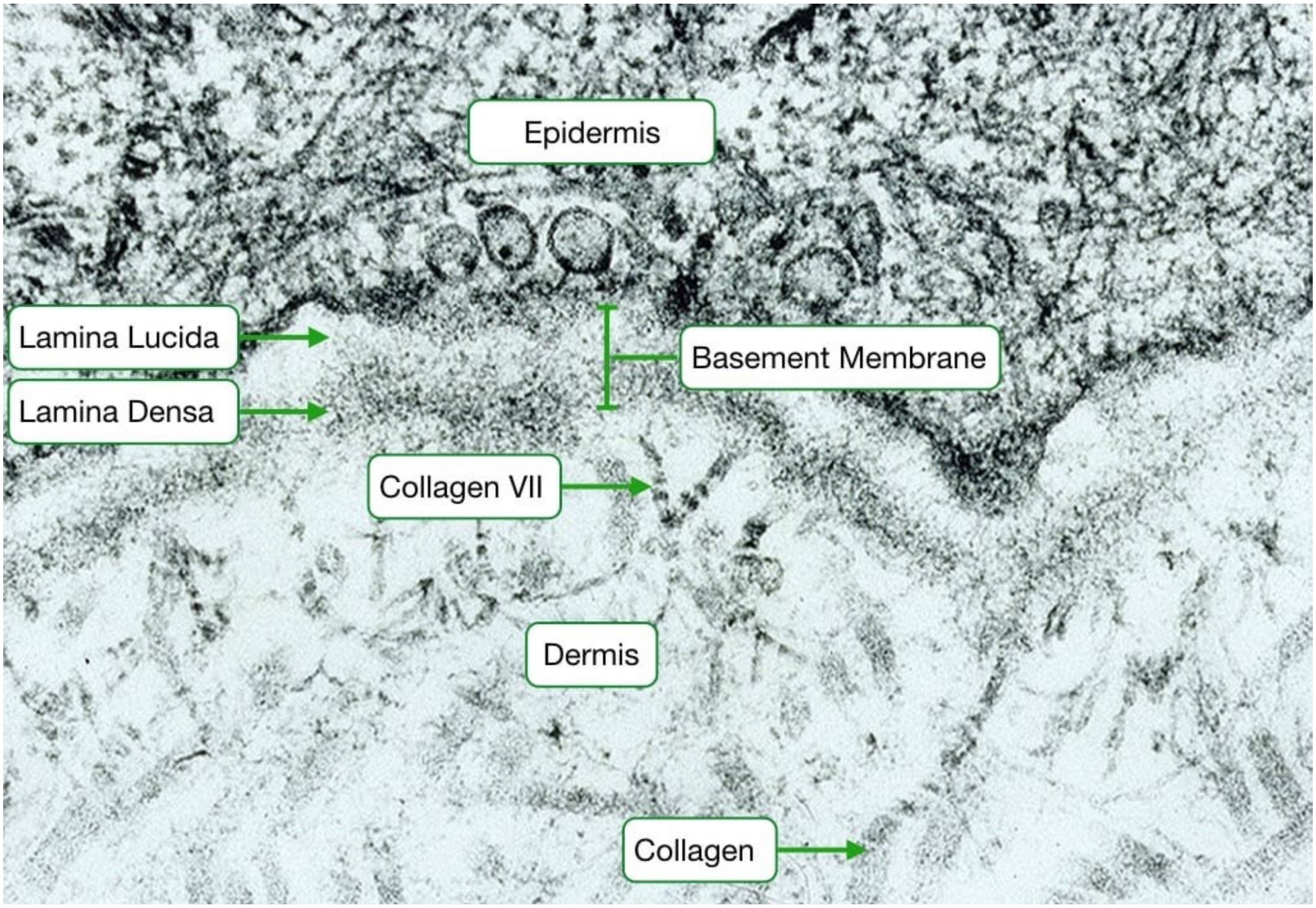
Basement Membrane

The basement membrane mediates attachment of the epidermis to the underlying dermis. Cells in the stratum basale attach to the underlying basement membrane through integrins (primarily α6β4) and a protein called bullous pemphigoid antigen 2. These adhesion proteins assemble into hemidesmosomes that are linked intracellularly to intermediate filaments composed mostly of keratin 5 and 14. The basement membrane beneath the epidermis contains type IV collagen, laminins and various proteoglycans. These proteins are linked to type I collagen in the dermis via a set of proteins that include type VII collagen. All of these proteins listed above are critical for maintaining a stable attachment of the epidermis to the dermis.



Integrins links cells to the basement membrane and type VII collagen links the basement membrane to dermis.

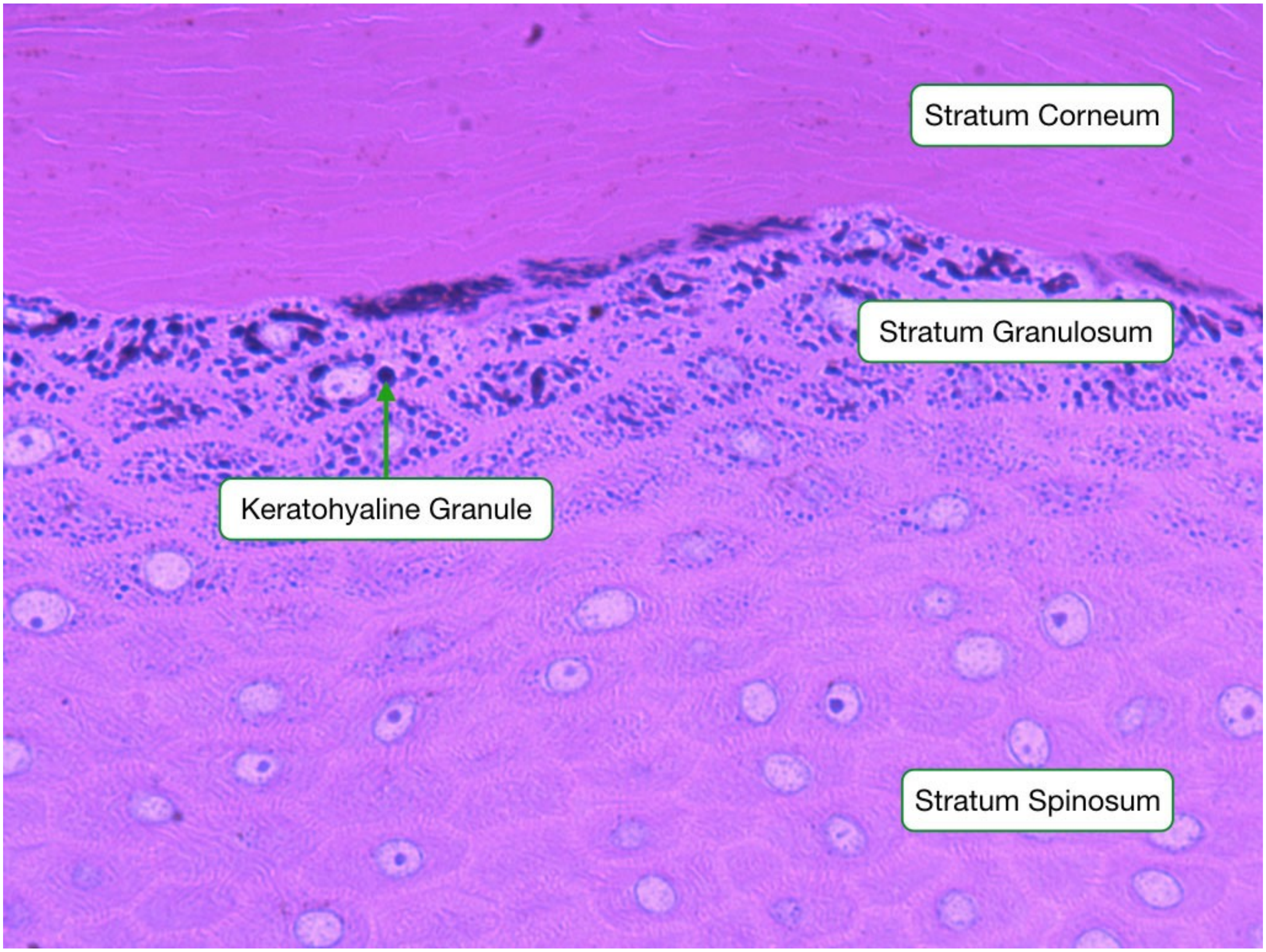
Electron micrographs reveal several of the components that attach the epidermis to dermis. The basement appears as two layers: a lighter lamina lucida and darker lamina densa. The lamina lucida contains the integrins and other adhesion molecules that reside in the cell membrane of cells in the basale. The lamina densa contains the structural components of the basement membrane such as type IV collagen, laminins and glycoproteins. Also note type VII collagen that loops from the lamina densa into the dermis where it contacts type I collagen fibrils. This interaction maintains a stable connection between the basement membrane and dermis.



Electron micrographs reveal the structures that link epidermis to dermis.

Stratum Granulosum and Corneum

The keratinocytes of the stratum granulosum become more flattened and accumulate numerous dense, dark-staining granules. These are keratohyaline granules that contain proteins which will aggregate cytokeratin to form keratin filaments in the cytoplasm. The cells in the granulosum also produce vesicles that contain lipids, including phospholipids and sphingomyelins. The cells will secrete the lipids and enzymes in the extracellular space will modify the lipids to make them more hydrophobic.



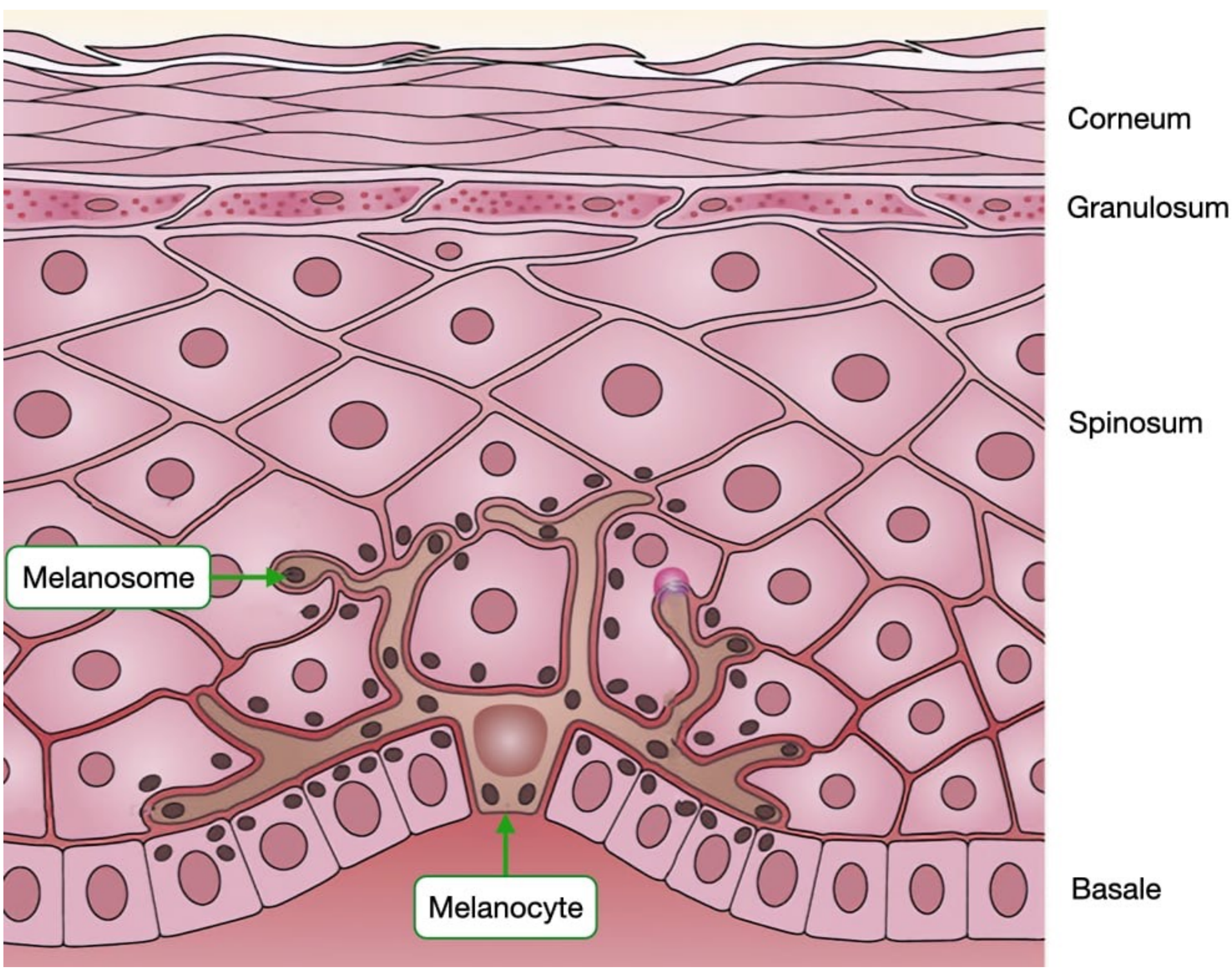
Cells in the granulosum contain large granulues and the corneum consists of layers of keratin and lipid.

The architecture of the stratum corneum is important for the prevention of desiccation and deterrence of foreign organisms and chemicals. The corneum is a composite material comprising sheets of keratin and lipid. Their arrangement in the corneum is similar to a wall of brick and mortar with the keratin forming the bricks and the lipids forming the mortar. As described above, the lipid in corneum is produced by cells in the granulosum layer. The keratin in the corneum derives from keratinocytes that have crosslinked their cytokeratin and begun the process of apoptosis to become anucleated. The thick layer of keratin and lipid creates a hydrophobic barrier to prevent loss of water and physical barrier that deters penetration by microorganisms and chemicals.

Melanocytes and Protection from UV Light

Perhaps one the most important functions of skin is to protect the DNA in the rest of the body from damage caused by ultra-violet (UV) light. UV light generates pyrimidine dimers in DNA which if not repaired, can lead to cell death or the development of tumorigenic cells. Skin reduces the amount of UV light that reaches underlying tissues in two ways. First, the thick layer of keratin and epithelia in the epidermis reduces the amount of UV light that reaches the dermis. Second, cells in the skin called melanocytes produce melanin which absorbs UV light.

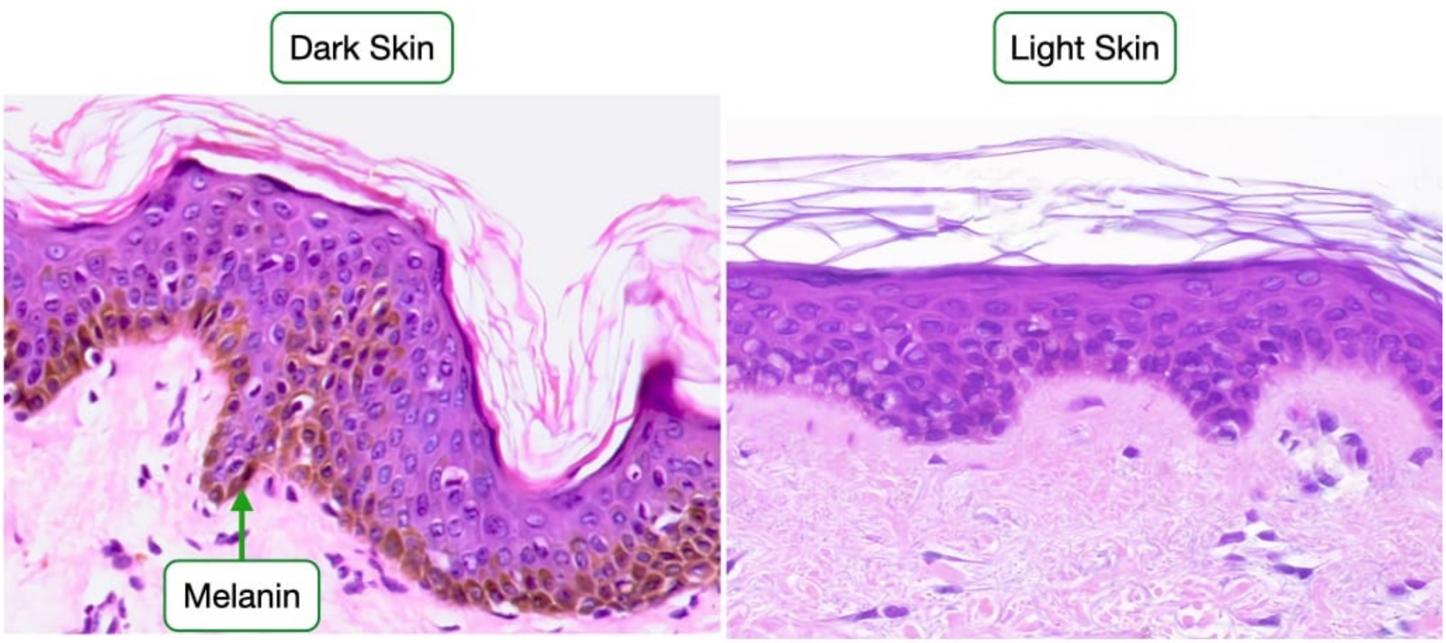
Melanocytes are found in the stratum basale and extend processes between the keratinocytes of the stratum basale and spinosum. Melanocytes synthesize melanin from tyrosine in membrane-bound organelles called melanosomes that derive from the Golgi. Motor proteins, such as kinesins and myosins, transport melanosomes to the ends of the melanocyte processes. Here, melanocytes release the entire melanosome into the extracellular space and nearby keratinocytes phagocytose the melanosomes.



Melanocytes synthesize melanin in melanosomes and release melanosomes to keratinocytes.

Because melanin absorbs light, the amount and type of melanin produced by melanocytes will alter the appearance of the skin. Melanocytes produce two types of melanin: eumelanin which appears dark brown to black and pheomelanin which appears yellow or red. Both types of melanin are produced from tyrosine and which type melanocytes produce appears to depend on the concentrations of the enzyme tyrosinase and the amino acid cysteine in melanosomes. Melanocytes also differ in the amount of melanin they produce. Some individuals have melanocytes that produce less melanin of which most is pheomelanin and consequently have lighter appearing skin. Individuals with more active melanocytes that produce more eumelanin will have darker appearing skin. Skin with more eumelanin is more efficient in absorbing UV light.

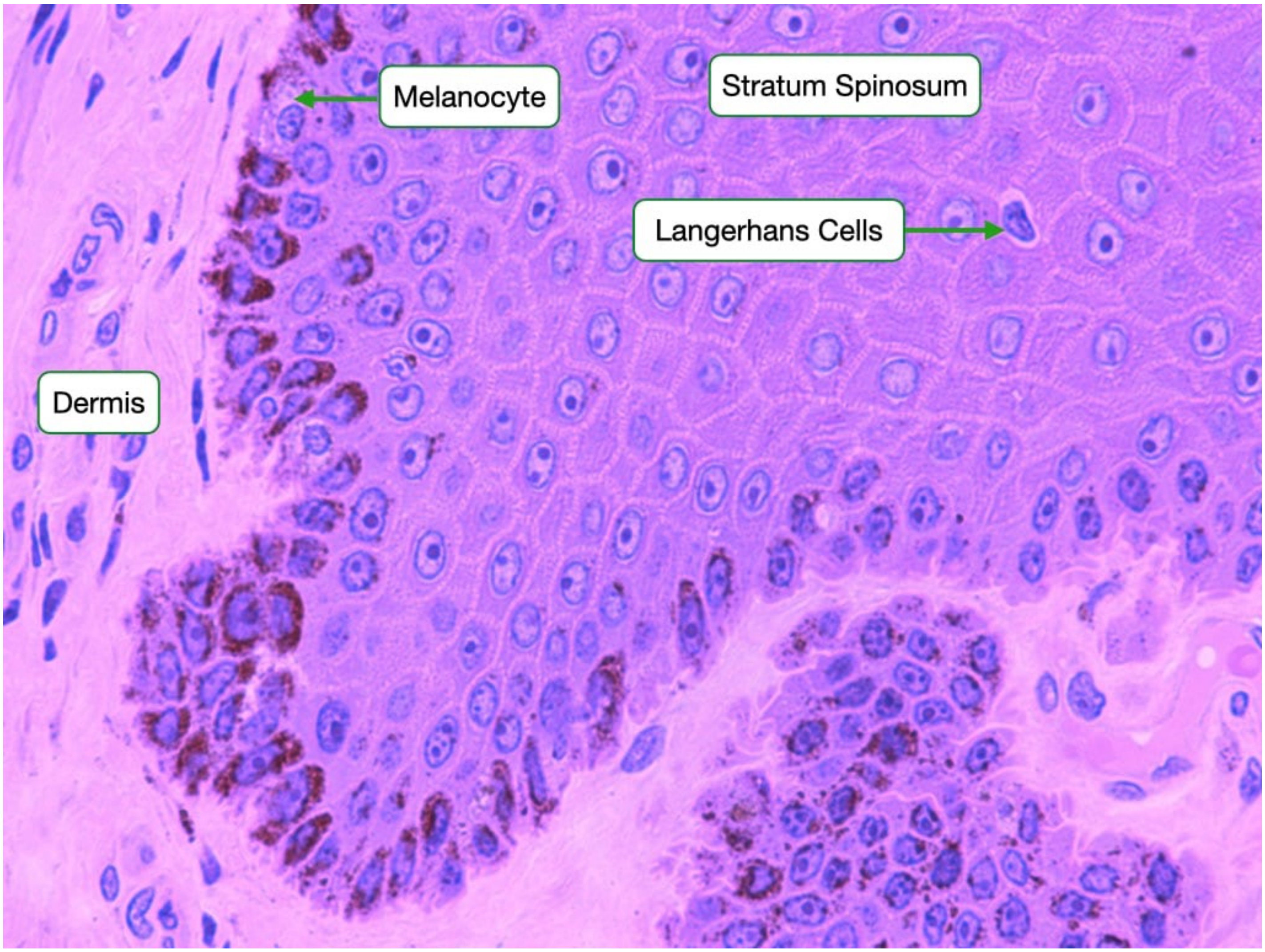
The images below show the difference histologically between dark and light skin. Dark skin contains more melanin which is the brownish material seen throughout the basal layer of the epidermis. Note also that keratinocytes which have migrated upward from the basal layer retain melanin. In contrast, light skin has little detectable melanin in H&E stained samples.



Keratinocytes in dark skin contain more melanin compared to keratinocytes in light skin.

Although melanocytes produce melanin, the cytoplasm of melanocytes is pale in comparison to the keratinocytes that surround them. Note the keratinocytes that surround the melanocyte contain dark-staining material in their cytoplasm which are the melanosomes that were produced and released by the melanocytes.

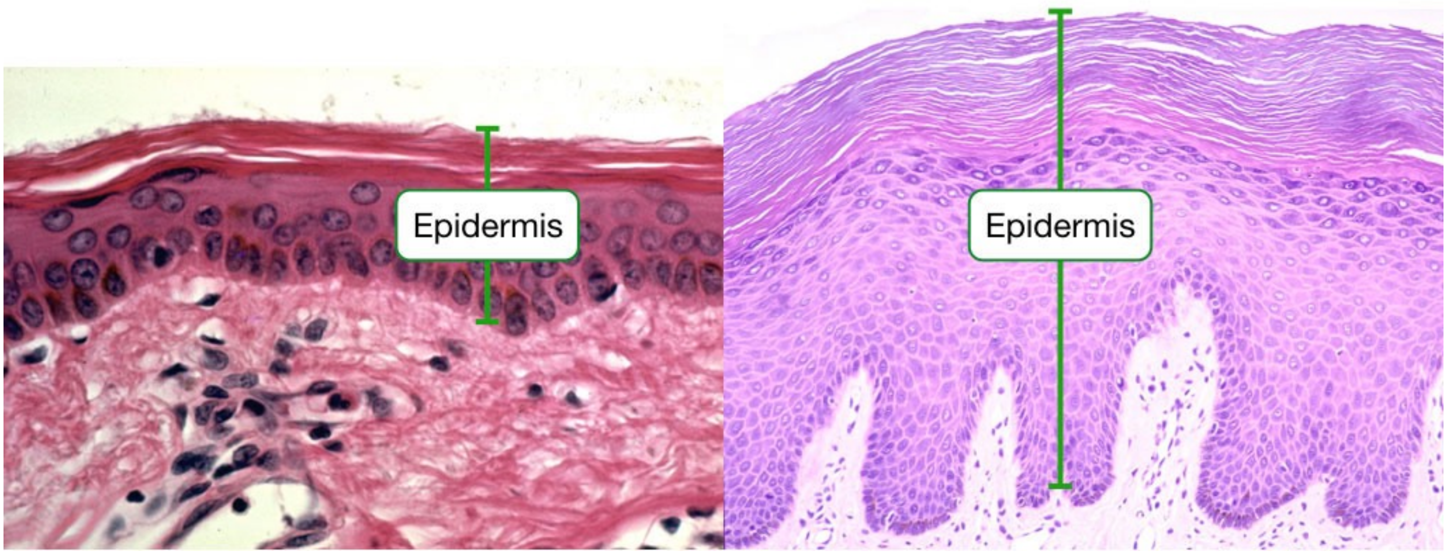
The epidermis also contains cells that have roles in generating an immune response. Langerhans cells are antigen-presenting cells in the immune system. They capture antigen and then enter lymphatic vessels to reach a local lymph node where they present antigen to T-cells.



Melanocytes produce melanin which absorbs UV-light and Langerhans cells capture antigen.

Variations in Skin Throughout the Body

As discussed below, skin varies across regions of the body based on the presence of hair and type of sweat gland. In addition, the thickness of the epidermis differs across the body surface. The epidermis is thickest in regions that receive the most mechanical stress, such as the palms and soles of the feet. A thicker epidermis contains more layers of keratinocytes and a thicker layer of keratin on its surface. In addition, rete ridges and dermal papillae will be more prominent to strengthen the attachment of epidermis to dermis. Surfaces that are less impacted by mechanical forces have a thinner epidermis and less prominent rete ridges and dermal papillae.



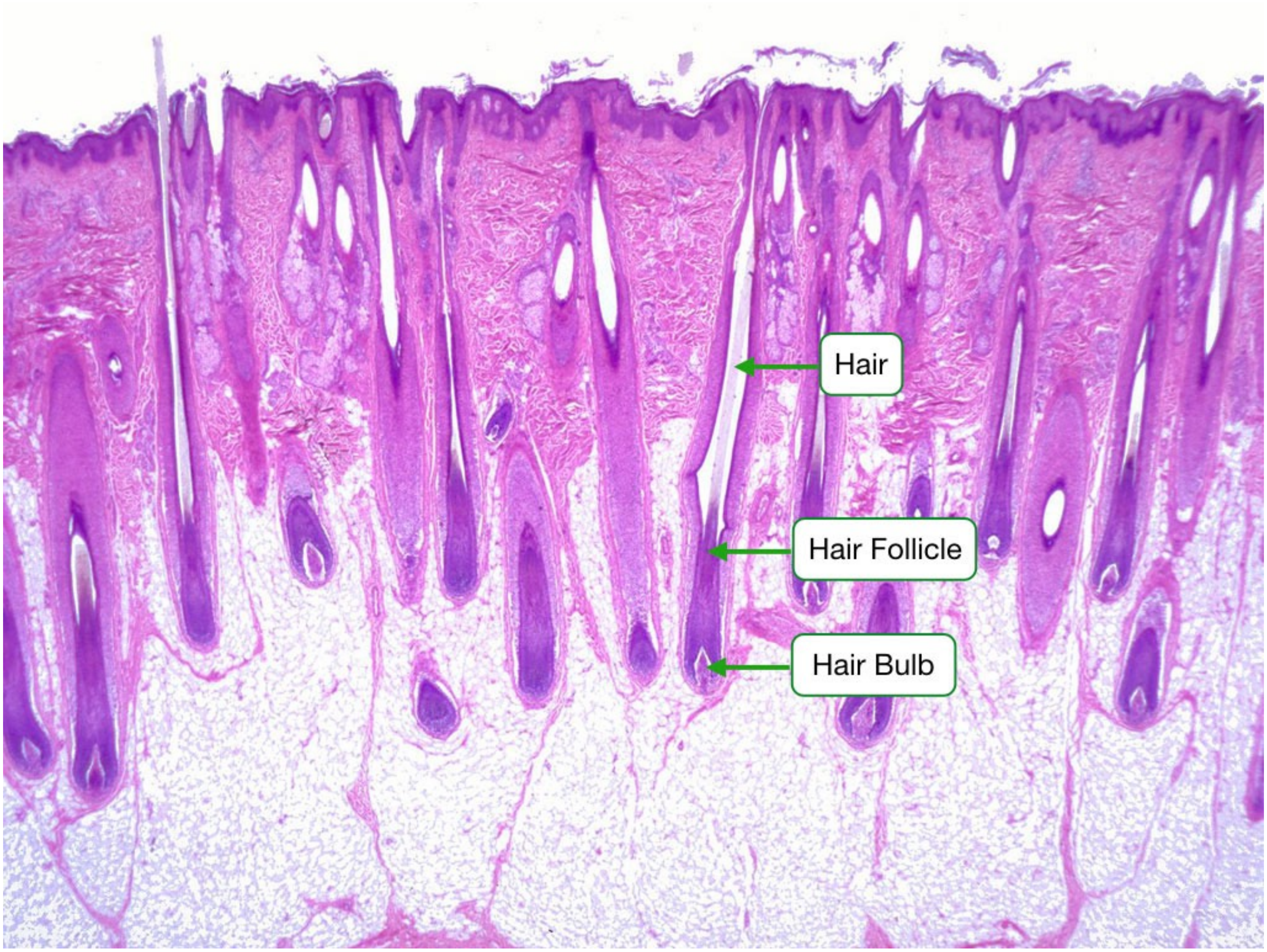
The thickness of epidermis varies across the body.

Special Structures of Skin

Skin contains a number of important functional structures that develop from down growth of the epidermis into the dermis. The epithelial cells differentiate into structures that produce hair or secrete fluids that are deposited on the surface of the skin (sweat glands).

Hair

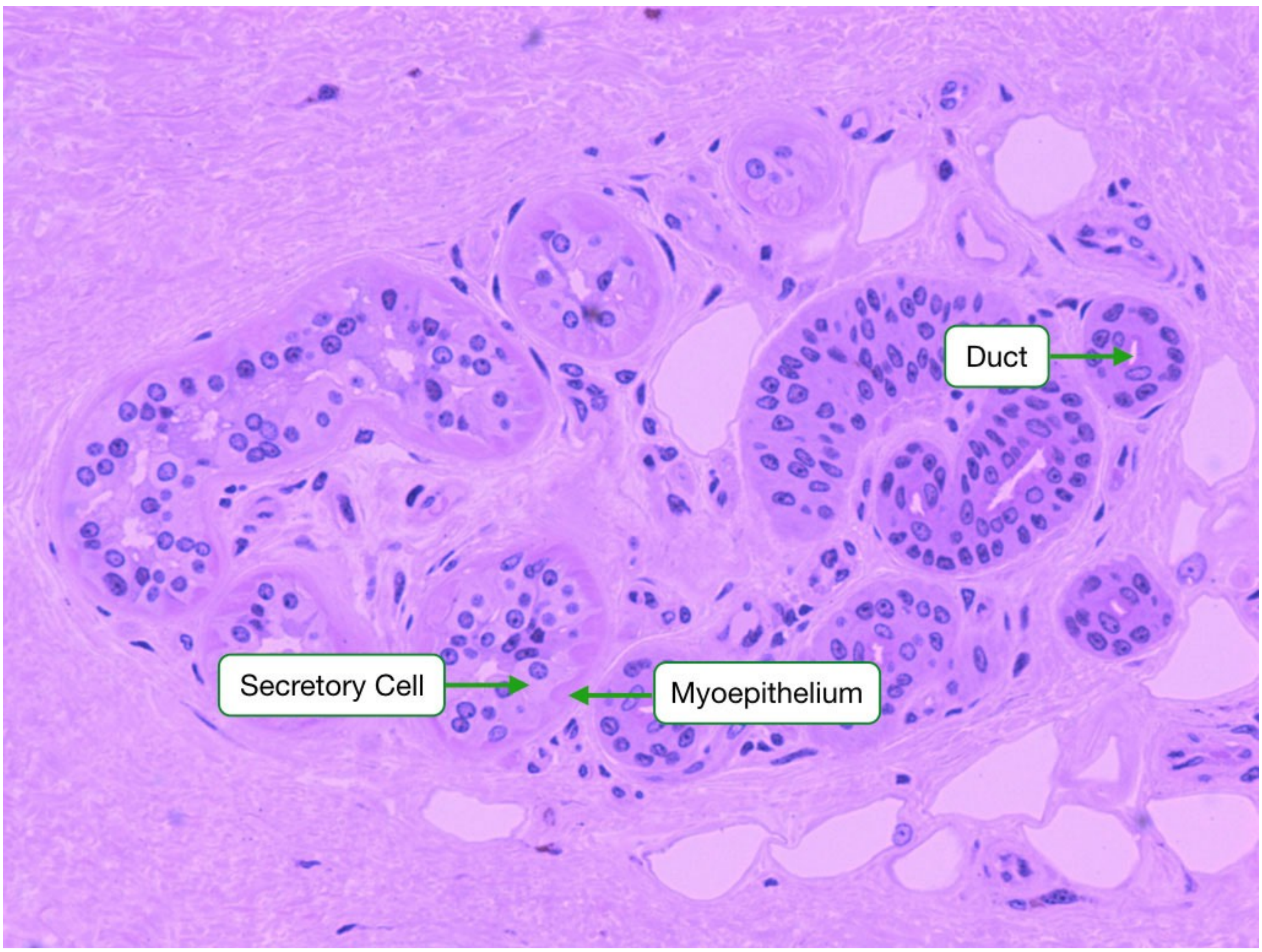
Hair is present over most of the body and plays an important role in regulating body temperature and absorbs UV light. Hair is composed of concentric layers of epithelial cells that undergo different degrees of keratinaztion. The hair follicle is where hair production and growth of occur. The hair bulb contains stems cells that will differentiate into the different layers of epithelial cells that make up hair. Although the structures of hair are derived from epithelial cells in the epidermis, cells in the dermis play a critical role in regulating the proliferation and differentiation of epithelial cells in the hair bulb. Melanocytes transfer melanosomes to cells in hair which gives hair its color.



Hair is a specialized structure formed by the epidermis.

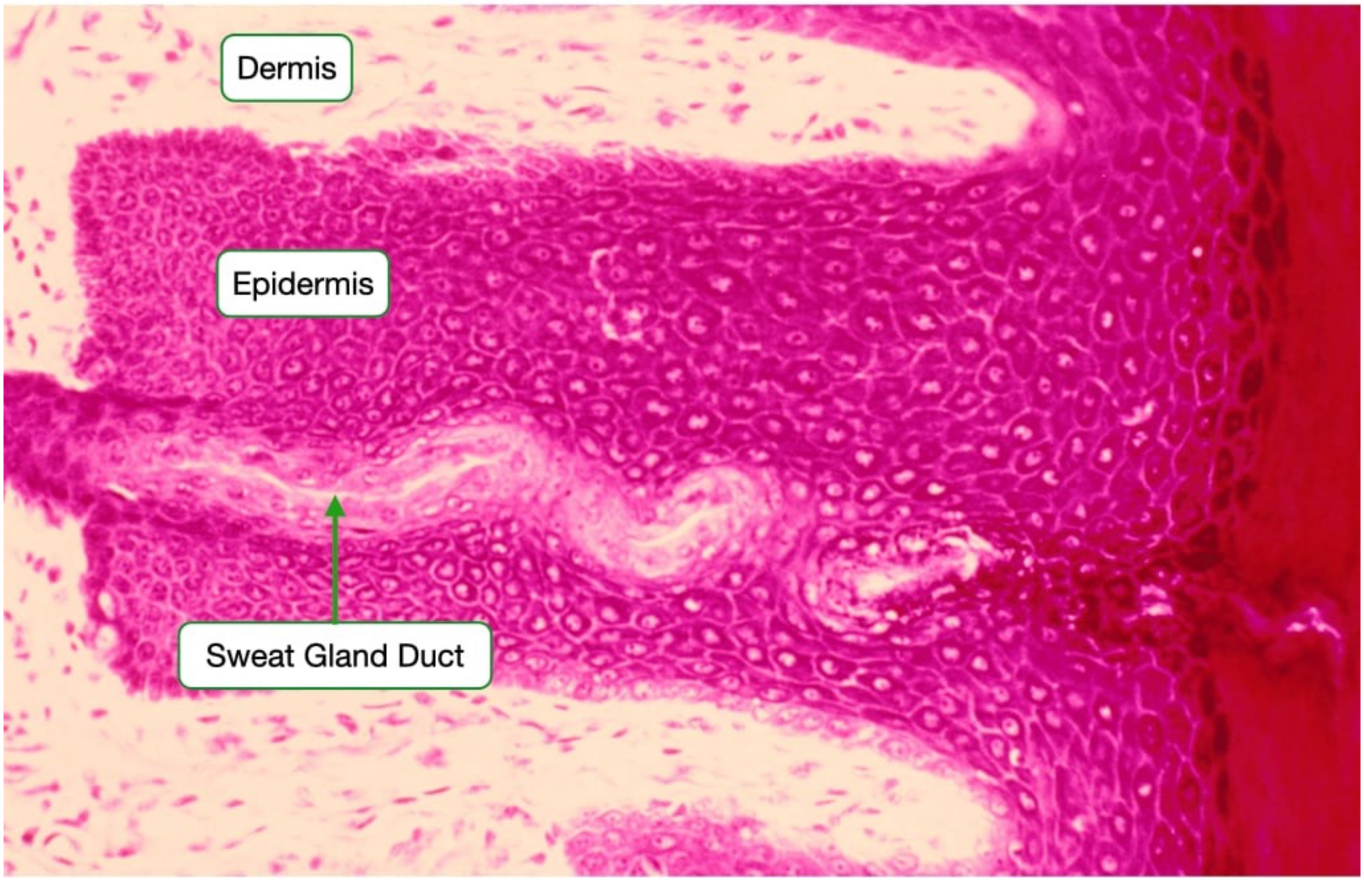
Eccrine Sweat Gland

Eccrine sweat glands occur throughout most of the skin. They arise from downgrowth of the epidermis into the dermis to form of long tubules that lead to secretory glands. The secretory portion of each gland is tightly wound and appears as a collection of cross-sectioned tubules. It consists of of secretory cells and an outer layer of myoepithelial cells that are contractile. The myoepithelial cells receive input from nerve fibers, which cause them to contract and expel sweat from the gland. The secretory cells are a mix of light and dark staining cells. The light staining cells produce a watery substance similar in composition to an ultrafiltrate of blood, whereas the dark staining cells secrete glycoprotein. The ducts stain darker and have a double layer of cuboidal cells which reabsorb sodium and chloride to generate a hypotonic fluid.



Eccrine sweat glands are coiled and release a hypotonic fluid on the surface of skin.

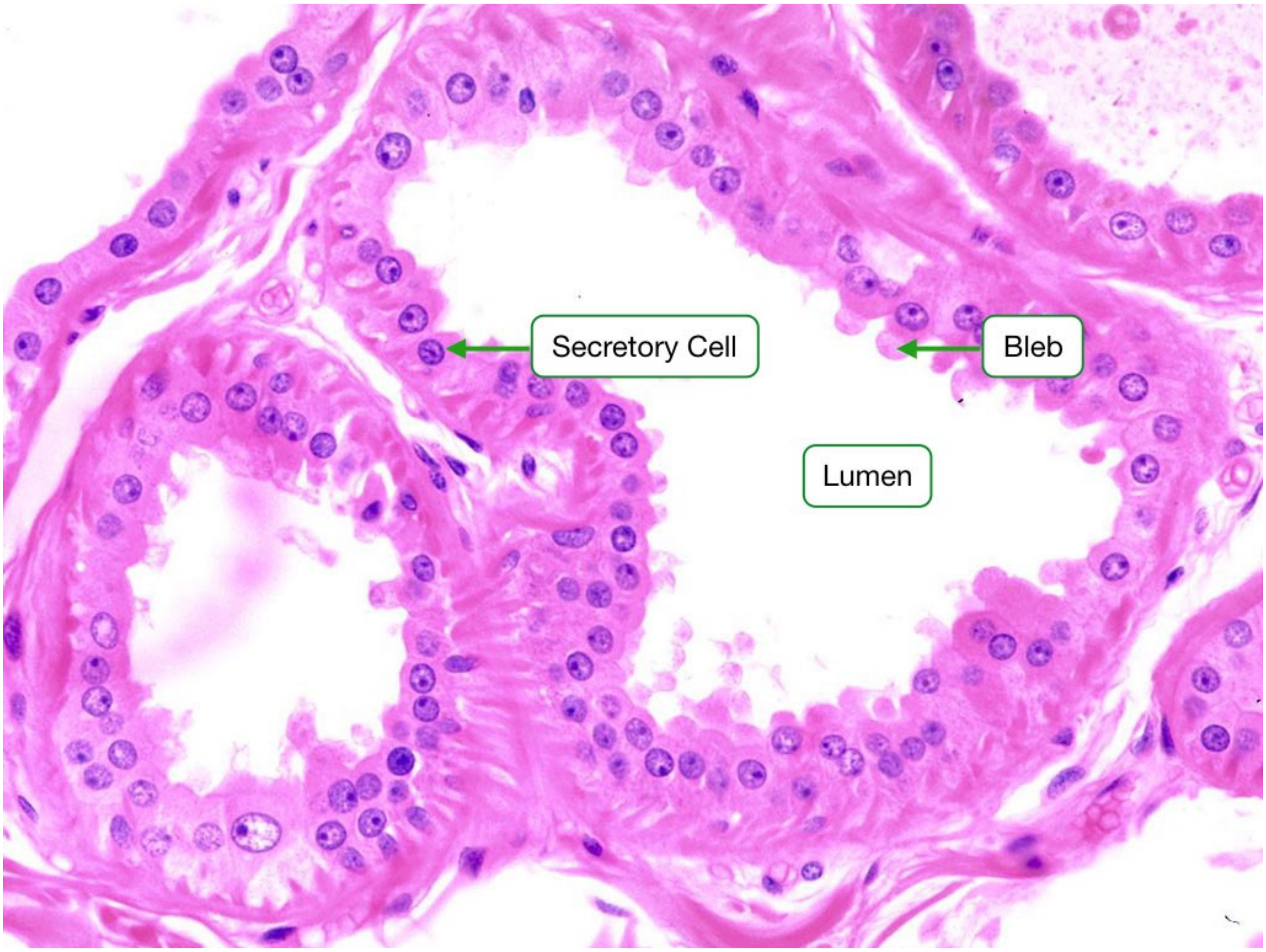
The ducts spiral to the surface of the epidermis to release hypotonic sweat. Sweat evaporates on the surface of the skin to help lower body temperature.



Ducts from eccrine sweat glands deposit hypotonic sweat on the surface of the epidermis.

Apocrine Sweat Gland

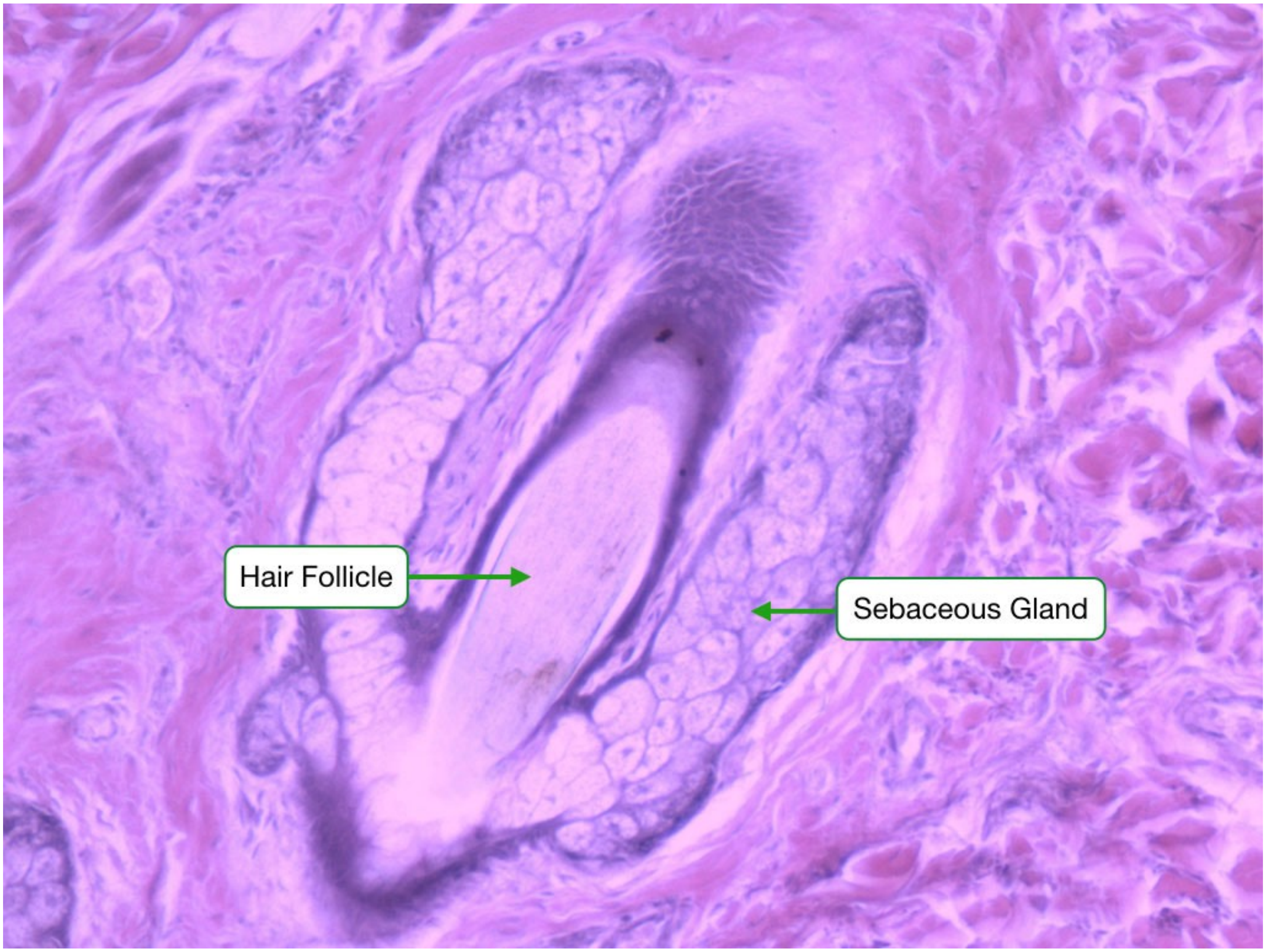
Apocrine sweat glands occur in the axilla, the areola of the nipple, the labia majora, and the circumanal region. They are much larger than eccrine glands and produce a thicker secretion, which is rich in protein, lipid, carbohydrate, ammonium and other organic compounds. The glands are characterized by a simple cuboidal epithelium and widely dilated lumen that stores the secretory product.



Apocrine sweat glands are larger than eccrine glands and localized to certain regions of the body.

Sebaceous Sweat Gland

Sebaceous glands are pear-shaped glands that secrete an oily substance called sebum, which moisturizes and waterproofs hair. They are usually attached to hair follicles near the arrector pili muscle, which causes hair to "stand up". The glands connect with the hair follicle via a short duct called the pilosebaceous canal.



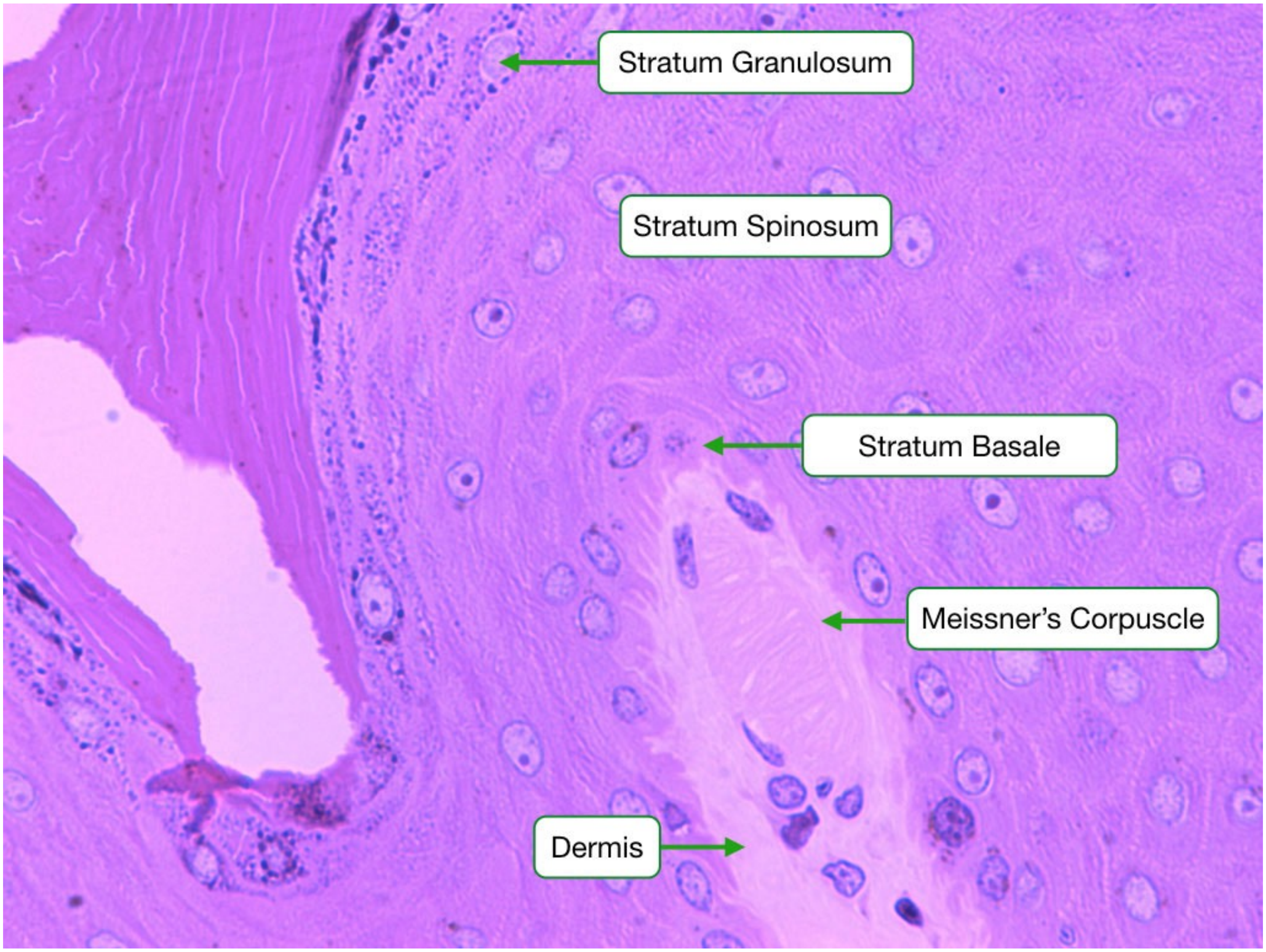
Sebaceous sweat glands produce an oily substance that protects hair.

Sensory Structures of Skin

Skin contains a several different types of sensory structures which allows it to detect a variety of mechanical forces and changes in the external environment.

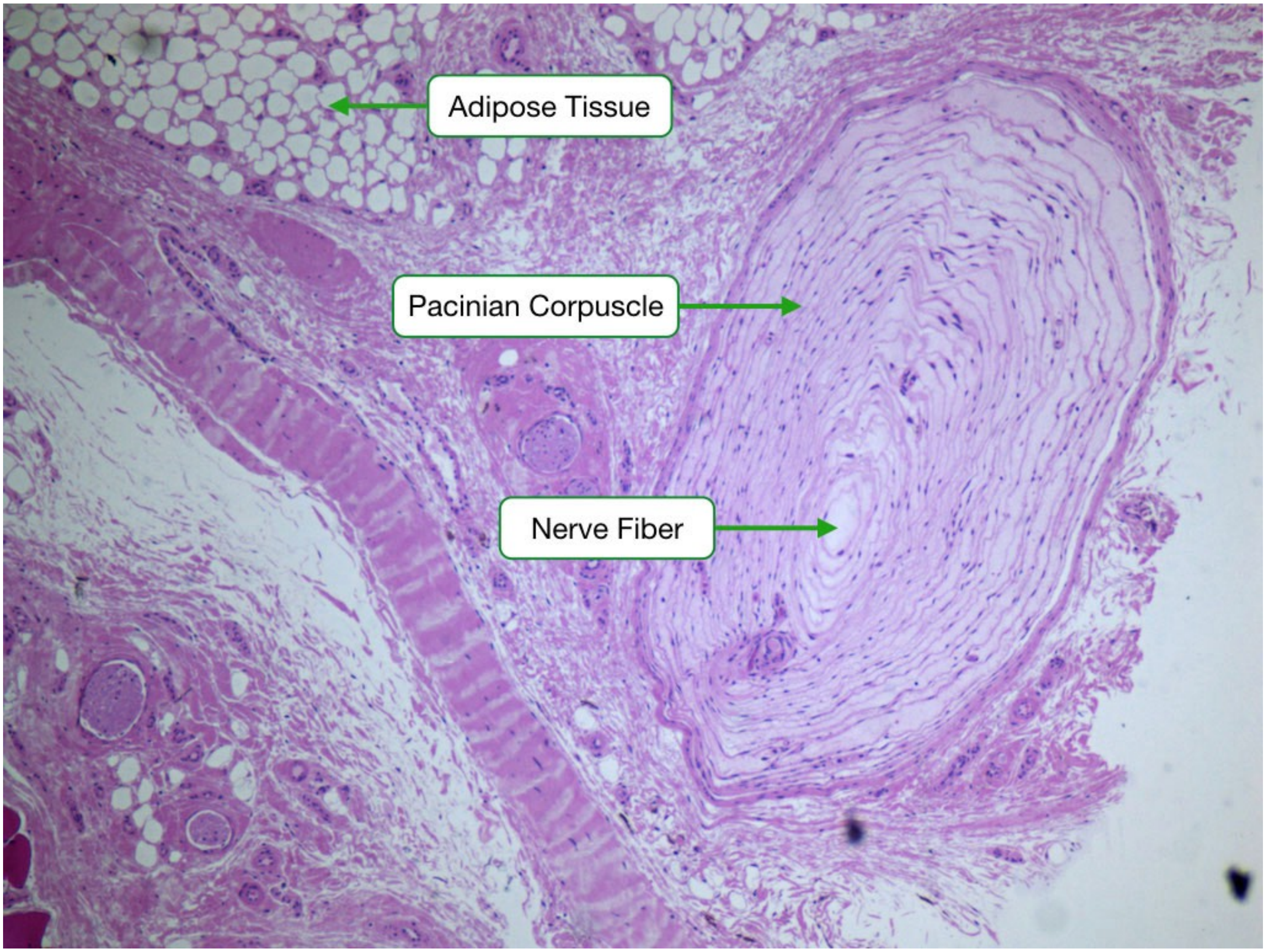
The epidermis contains two major types of sensory structure. The first is free nerve endings which are the termini of sensory neurons that extend axons from the spinal cord. Free nerve endings detect temperature, light pressure and tissue damage. The second sensory structure are Merkel cells that reside in the stratum basale. These cells respond to low-frequency vibration and very small displacements. When stimulated, Merkel cells release serotonin from intracellular granules onto adjacent nerve terminals. These afferent nerves then transmit this signal back to the spinal cord. Merkel cells have a clear cytoplasm with small granules and are difficult to distinguish from melanocytes.

Sensory structures are also found in deeper layers of skin. Meissner’s corpuscles are found in the dermis at the very tips of dermal ridges. The corpuscles detect light touch and are composed of a collagenous capsule that surrounds several support cells and sensory nerve fibers.



Meissner's corpuscles are found in dermal ridges and are sensitive to light pressure.

Pacinian corpuscles are large encapsulated nerve structures that reside in hypodermis. These corpuscles are sensitive to deep pressure and course touch. The corpuscles contain several layers of support cells, thin collagen fibers and interstitial fluid around a central nerve fiber.



Pacinian corpuscles are found in the hypodermis and are sensitive to deep pressure.