4

Properties of Human Integument

With the properties of non-human integumentary goals in mind, we must understand what we start from and what we must change. As such, now follows a brief overview of the relevant properties of human skin. This will allow us to identify what properties we need to retain or refit in order ensure that the patient won't suffer a loss in quality of life, as well as which properties must be significantly altered to produce a satisfactory result.

4.1 - Skin morphology and stem cell development

Skin in mammals consists of layers of cells (epidermis, dermis, and hypodermis) and follicles embedded within those layers. We discuss details of follicle morphology after our more general discussion of skin.

4.1.1 - Human skin consists of an epidermal, dermal, and hypodermal layer

Skin consists of several layers, from outer to inner: the **epidermis**, **dermis**, and **hypodermis** (subcutaneous layer). The outermost layer, the epidermis, protects us from the environment. Just underneath is a thin basement layer of fibers, separating it from the dermis. The middle dermis layer is the thickest layer, comprised of a thinner **papillary dermis** layer atop the thicker **reticular dermis**: the outer papillary dermis contains more blood vessels, and the inner reticular dermis contains the bases of hair follicles and sweat glands. The innermost hypodermis layer is composed of **adipose** fat tissue, and contains blood vessels.

The epidermis is an epithelium of **stratified squamous** (layered, flat) cells, and is primarily composed of two cell types: **keratinocytes** and **dendritic cells**. Keratinocytes create daughter cells in the epidermis's basal layer through cell division; the epidermis's basal layer contains basal cells that adhere to form a superficial squamous cell layer (Kolarsick et al., 2011). This squamous cell layer, while only known to have a thickness of approximately 5-10 cells (Yousef et al., 2022), is diverse in size and components. Dendritic cells (cells with branchlike appendages) make up the majority of the other cells in the epidermis, and consist of a few specific types. **Melanocytes** produce a pigment known as melanin, essential for protecting the skin from UV radiation (Yousef et al., 2022). This pigment is delivered to keratinocytes through the melanocytes' dendrites, or branches. **Langerhans cells** are critical in the primary immune response in regards to antigen presentation. They hold

Birbeck granules, which can provide an immune response via MHC 1 and MHC 2 molecules, indicating an ability for binding potential with all nucleated cells and antigen-presenting cells, respectively (Yousef et al., 2022). Both melanocytes and Langerhans cells are dendritic (Hashemi et al., 2012). **Merkel cells**, found more sparsely than the others here, are known to be mechanoreceptors for light touch, with presence in fingertips, palms, and soles.

The dermis is the layer below the epidermis, containing the nutritional and structural support of the integumentary system (Grymowicz et al., 2020). There is a strong, elastic, amorphous, gel-like extracellular matrix throughout the dermis, and this matrix is composed of **collagens**, **elastin**, and **fibronectin** (Kular et al., 2014). Collagen itself contributes most of the fibrous mass of the matrix, but the structure is largely determined by fibronectin, an adhering protein (Kular et al., 2014). The matrix is also able to be remodelled over time as required using a variety of enzymes that include matrix metalloproteinases, lysyl oxidase, lysyl oxidase-like proteins, and Wnt1-inducible signalling proteins (WISPs), among others (Cabral-Pacheco et al., 2020; Yuan et al., 2023).

The dermis is also home to the group of **stromal cells**, which can differentiate into connective tissue. Stromal cells are particularly responsible for releasing growth factors – stromal cells at the top of the dermis stimulate the base layer of the epidermis to continue generating more cells (Quan C et al., 2015). With the support of the structure and connective tissues, this allows the nutritional portion, which includes nerves, lymphatic vessels, blood, sweat glands, and hair roots, to remain embedded and firm within the dermis. Proper blood flow and lymphatic vessels provide resources through immune response to antigens, providing homeostasis and vasculature for basic body regulations, such as temperature control, immune response, and hormonal control (Grymowicz et al., 2020). Vasculature offers essential nutrients and elements to the skin to maintain tissue stability and provide the appropriate nutrients to maintain nerve function.

The subcutaneous layer, commonly recognized as the hypodermis layer, is composed of **adipocytes**, or fat cells. Adipocytes act as protection for internal structures and as a reserve energy source. The adipocytes are organized into lobules, or blob-like folds, which are filled in between by connective tissue called **septa**. Septa is composed of collagen and blood vessels, and it holds the fat tissue in place and the skin on the body. The adipose cells themselves come in different types, denoted by color: **white**, **brown**, **beige**, **and pink**. A majority of the adipose tissue found in the human body is white adipose, which stores energy in one large lipid droplet that takes up most of the volume of the cell. Brown adipose cells store it in many smaller lipid droplets throughout the cell instead, and are more commonly found on hibernating animals, but some brown adipose tissue is found on humans around the neck region. Beige and pink are even less common in humans; beige cells store energy in less, medium-sized lipid droplets, and pink cells secrete milk. Adipose cells participate in the endocrine system by secreting leptin, adiponectin, and resistin, which impact a wide variety of organs (such as the heart, liver, brain, skeleton, and more) and cellular functions throughout the body, including tumorigenesis (Richard, et al., 2000).

4.1.2 - Human epidermis is further subdivided into many defined layers

The outer epidermis is also divided into a number of defined layers; from inner to outer: **stratum basale or germinatum** (the basal or germinal layer), **stratum spinosum** (spinous), **stratum granulosum** (granular), **stratum lucidum**, and **stratum corneum** (Yousef et al., 2022). At the basal layer is a layer of stem cells, and at the very outside of the skin are dead, desquamating (shedding) cells. The cells throughout the layers of the epidermis are mainly **keratinocytes**, which contain keratins that give the skin structure. The **basal layer** contains melanocytes, which are responsible for pigmentation, and the **spinous layer** contains langerhans cells, which help the immune system to fight infections.

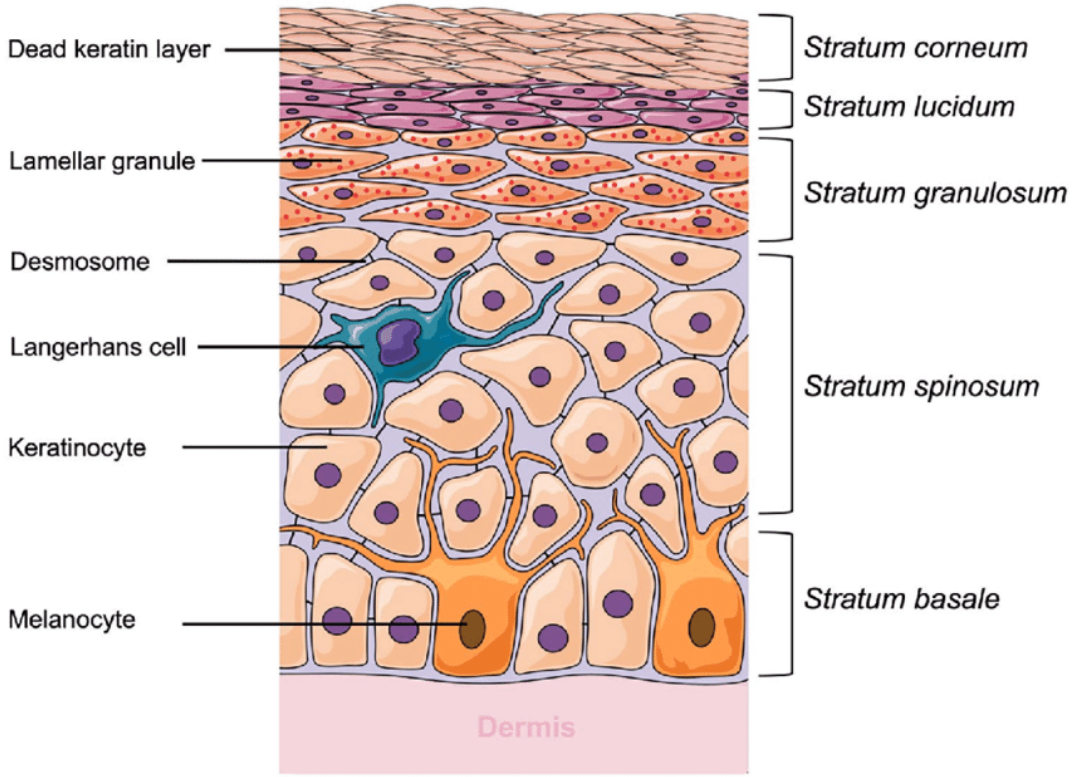

Figure 4.1: Enhancement strategies for transdermal drug delivery systems: current trends and applications — Scientific Figure on ResearchGate by Ramadon et al., 2021. Available from: https://www.researchgate.net/figure/Schematic-representation-of-epidermis-layer-of-human-skin_fig3_348644834 [accessed 3 Sep, 2023] Licensed under Creative Commons Attribution 4.0 International.

4.1.3 - Epidermis is continuously regenerated from a germinal layer of stem cells

The **skin cycle** is the process that the skin undergoes to refresh itself with new cells. This is accomplished by multiple unique pools of **stem cells** in the skin (Díaz-García et al., 2021). The basal or germinal layer of the epidermis, which is made of epidermal stem cells, is responsible for generating new cells for the epidermis. As new **daughter cells** divide off the

stem cell layer, they travel outwards to the outermost layer of the skin, undergoing terminal differentiation and keratinization.

There is also a pool of stem cells located in the basement membrane between the epidermis and dermis, and this pool contains cells that drive the renewal of **sebaceous glands** (Geueke & Niemann, 2021). Similarly, **melanocyte stem cells** are also located in the basement membrane, where they differentiate and subsequently provide melanin to other cells in the skin (Osawa, 2009).

The dermis also contains a vast reservoir of skin stem cells throughout (Brown and Krishnamurthy, 2022). These dermal stem cells are **mesenchymal**; **mesenchymal stem cells (MSCs)** originate from the bone marrow, and are **multipotent**, meaning that they can become any number of specific cells. In the skin, that often includes cells such as keratinocytes or fibroblasts.

4.1.4 - Skin colouration is regulated by the function of melanocytes

The epidermis contains **melanocytes** at its base layer, where skin cells are generated and pushed outwards. Here, melanocytes will deliver **melanin**, the pigment family responsible for skin pigmentation, to around 36 keratinocytes throughout the epidermis; melanin is transported through the branches of the melanocyte, although the exact mechanism of this transfer is not well-understood (Seiberg 2001, Benito-Martínez et al., 2021). Melanin is itself synthesized in **melanosomes** (a melanocyte organelle) in a process termed **melanogenesis**.

Melanogenesis is ultimately regulated by two inputs: (1) the pituitary gland in the brain (Slominski et al., 2004), and (2) environmental factors that directly affect the skin. In the first regulatory method, the pituitary gland releases a peptide hormone called **melanocyte stimulating hormone (MSH)**, which signals melanocytes to produce melanin (Brown & Doe, 1978). In the second regulatory method, ultraviolet (UV) light stimulates melanin production as a means to protect the skin against the sun, a process known as tanning (Benito-Martínez et al., 2021).

In both cases, two types of melanin may be produced: **eumelanin**, which is black to brown, and **pheomelanin**, which is reddish brown to yellow.

Skin colour/tone varies from light to dark around the world, with darker skin tones found in peoples who have historically lived near the equator, and lighter skin tones in peoples nearer the poles. These are evolutionary traits encouraged by **ultraviolet radiation** and **vitamin D production**, respectively (Jablonski, 2004). Human ancestors near the equator are thought to have received much more sunlight, evolving to have more melanin as a measure of protection against UV radiation. They were able to develop darker skin because there was no shortage of sunlight to stimulate vitamin D production. Human ancestors closer to the poles receive less sun, and therefore needed to maximize their vitamin D production by maximizing how much ultraviolet light penetrates their skin with a lighter tone. Protection from UV radiation was less important in these lower-sunlight areas.

4.1.5 - Skin on hand palms and feet soles, eyelids, etc., do not contain hair follicles

Different locations on the body have different properties of skin, such as **thickness**; skin is thickest on the palms of the hands and soles of the feet, and thinner around the rest of the body. Thinner skin is found at the underarms, and some of the thinnest skin is found at the eyelids (Poonawalla et al., 2008). **Follicle density** also varies across the body: the scalp has the highest follicle density, followed by the rest of the body, and lastly by places such as the palms, soles, and eyelids (with exception of eyelashes), which do not contain hair follicles at all. *Chapter 1, Section 3* of this book, *'Different species have unique hair strand morphology, density, and distribution',* discusses hair follicle density in greater detail, with comparative values between humans and other species.

4.1.6 - Sweat glands are vital for human thermoregulation

To provide proper balance in thermoregulation in humans, **sweat glands** are included in the integumentary system to aid in cooling the body (Baker 2019). A sweat gland is shaped like a convoluted tube that is bunched or coiled up in the dermis and extends to the surface of the skin. There are three primary sweat glands in humans: the **eccrine**, **apocrine**, and **apoeccrine** sweat glands (Baker 2019, Kolarsick et al., 2011).

Eccrine sweat glands are the most abundant sweat glands in the human body, with the majority of eccrine sweat glands in the **palms** and **soles**. Eccrine sweat consists of mostly sodium chloride and water. The number of eccrine glands on the body is generally constant throughout life, so their density decreases as an individual grows due to the expansion of the skin.

Apocrine sweat glands are located throughout the **armpits**, **chest**, **and head**, and grow along with terminalizing hair follicles once puberty begins (Baker 2019). These sweat glands are larger than eccrine glands, and open into the hair follicle duct rather than the skin. Apocrine glands are recognized as the **body odor** sweat glands, as they secrete ammonia, protein, and sugars (Baker 2019, Kolarsick et al., 2011).

Apoeccrine sweat glands are a more newly-recognized classification of sweat glands, and they describe glands that exhibit **characteristics of both eccrine and apocrine glands**. Their size lies in between the size of the previous two gland types. They secrete directly to the surface of the skin, but are also associated with puberty and grow in the armpits and around the anus. A single apoeccrine gland generally produces more sweat than glands of the other two types (Wilke et al., 2007).

4.1.7 - Skin contains immune system-specific cells

One more important aspect of the skin is the immune system functions that it performs. Besides providing a physical barrier between the organs and the outside world, the dermis contains a number of cells vital to the function of the immune system. Innate and resident immune cells are present in both the epidermis and dermis.

In the epidermis, there are **Langerhans cells**, **Dendritic Epidermal T-Cells (DETCs)**, and a population of **T-cells** (Heath and Carbone, 2013). (For clarity, melanocytes in the epidermis, despite their dendritic shape, are *not* DETCs). Even keratinocytes themselves have an important role in innate immunity, helping detect signs of infection and alerting the immune system accordingly (Heath and Carbone, 2013).

In the dermis, there are resident **dendritic cells** (a specific cell type in the classical immune system sense — not to be confused with DETCs or melanocytes), various **T-cells**, and **NK and other innate lymphoid cells** (Heath and Carbone, 2013). There are also **mast cells** (Kritas et al, 2013) and **macrophages** (Sim et al., 2022).

When an immune response is mounted, more cells are recruited from the bloodstream and surrounding tissues. Similar to other immune response contexts throughout the body, **neutrophils** are among the first cells recruited from the bloodstream upon wounding or infection to the target site (Brazil et al., 2019). Additional, **non-resident T-cells** and **monocytes** can also be recruited upon chemokine and cytokine activation (Heath and Carbone, 2013).

4.2 - Hair follicle morphology

Hair follicles are among the smallest and most highly mitotic organs of the body, constituting complex structures with many cell types derived from both ectoderm and mesoderm in early development — ectoderm and mesoderm are layers in early development that go on to form skin or muscle and bone, respectively (Millar, 2005). Follicles vary greatly in function and characteristics between species, as well as within the body of individual species, and so it is important to review this structure in some detail before progressing to more recent research.

4.2.1 - A single hair follicle consists of a dermal hair papilla, isthmus, and infundibulum

4.2.1.1 - Vertical regions within a follicle

Follicles consist of 3 major levels, from the base out: the inferior segment/hair bulb, isthmus, and infundibulum (Figure 4.2) (Brown and Krishnamurthy, 2023).

The **inferior segment** starts at the very base of the follicle with the dermal papilla (DP) (sometimes called the dermal hair papilla), which contains stem cells in its base that drive hair growth. It also includes the matrix above the stem cells, surrounding the hair bulb, and it is only present during the hair growth phase. The DP is composed of specialized mesenchymal stem cells which engage in complex cross-talk with hair germ (HG) epithelial cells (Nilforoushzadeh et al., 2019). Surrounding the DP are many progenitor cells that constitute the matrix, which gives rise to both the hair shaft itself and the layers surrounding it ascending to the surface. There is also a pool of melanocyte progenitor stem cells (MelSCs) that cyclically grow and regress in parallel to the hair follicle cycle, providing new melanocytes to facilitate hair pigmentation (Nishimura, 2011).

Above the DP/inferior segment is the **isthmus**. It is marked by the insertion point for the arrector pili muscle, a muscle that facilitates piloerection (also covered this section), and ends at the sebaceous duct. This point is referred to as the bulge region, and it also functions as a reservoir of morphologically undifferentiated epidermal stem cells often referred to as hair follicle stem cells (hfSCs) (Ohyama 2007). These serve a role in hair follicle renewal and engage in complex interplay with the DP cells.

The structure is completed by the **infundibulum**, the final and most superficial segment through which the hair shaft emerges to the surface. Its lowermost bound is at the duct connecting to an associated sebaceous gland. It also shows keratinization. These three major levels complete the entire pilosebaceous unit that produces a single hair.

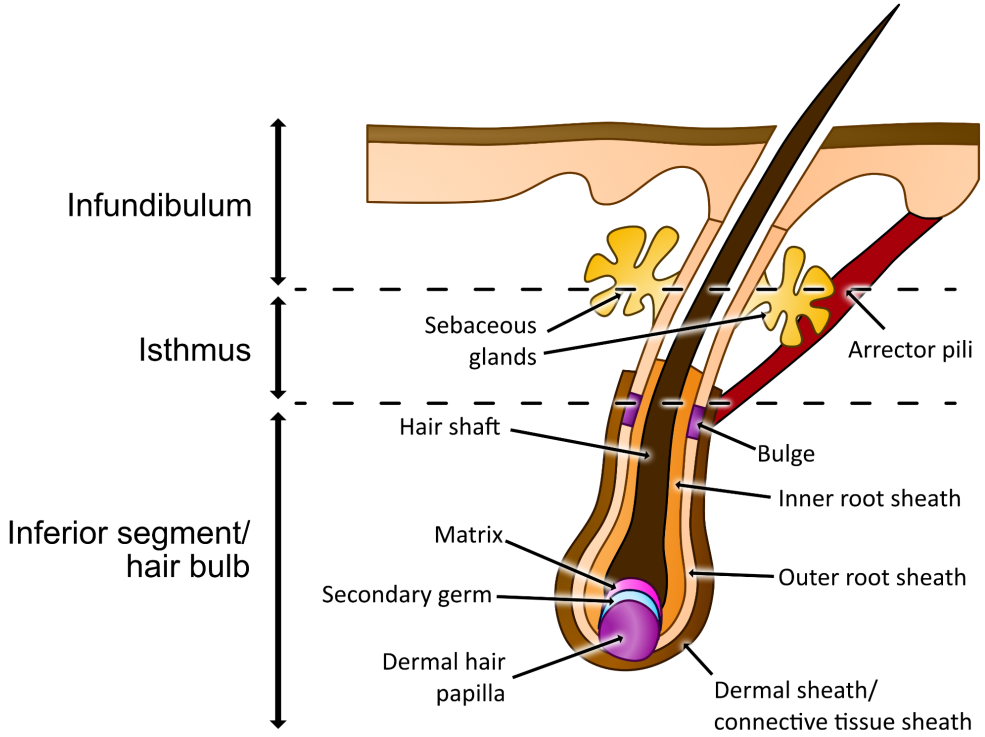

Figure 4.2: Vertical regions of a follicle. By Zennith, 2024.

4.2.1.2 - Connections to other systems

Blood supply to follicles includes many fine *capillaries* and *vascular plexuses* (complex interconnected networks of blood vessels). The dermal hair papilla is directly supplied by a capillary loop from the bottom of the hair bulb. Additionally, capillary beds wrap around the outside of the hair bulb and the sebaceous glands (Gray's Anatomy 42nd ed p 157). These capillary beds are supplied by a complex network of oxygenated blood vessels that get progressively thinner and more extensive as they get closer to the skin's surface. In **figure 4.3**, we show the follicle's blood vessels arising directly from the deep subdermal plexus, but in reality, there would be more subdivisions of blood vessels criss-crossing the picture.

Additionally, a network of lymphatic vessels, connecting between nearby follicles, drains from a region focused on the follicular bulge and isthmus. Interestingly, these lymphatic vessels experience increased activity during follicle growth (Daniel Peña-Jimenez et al., 2019). Finally, the movement of hair follicles is sensed by afferent nerve fibers that reach around the hair bulb in a structure called the **Root Hair Plexus**.

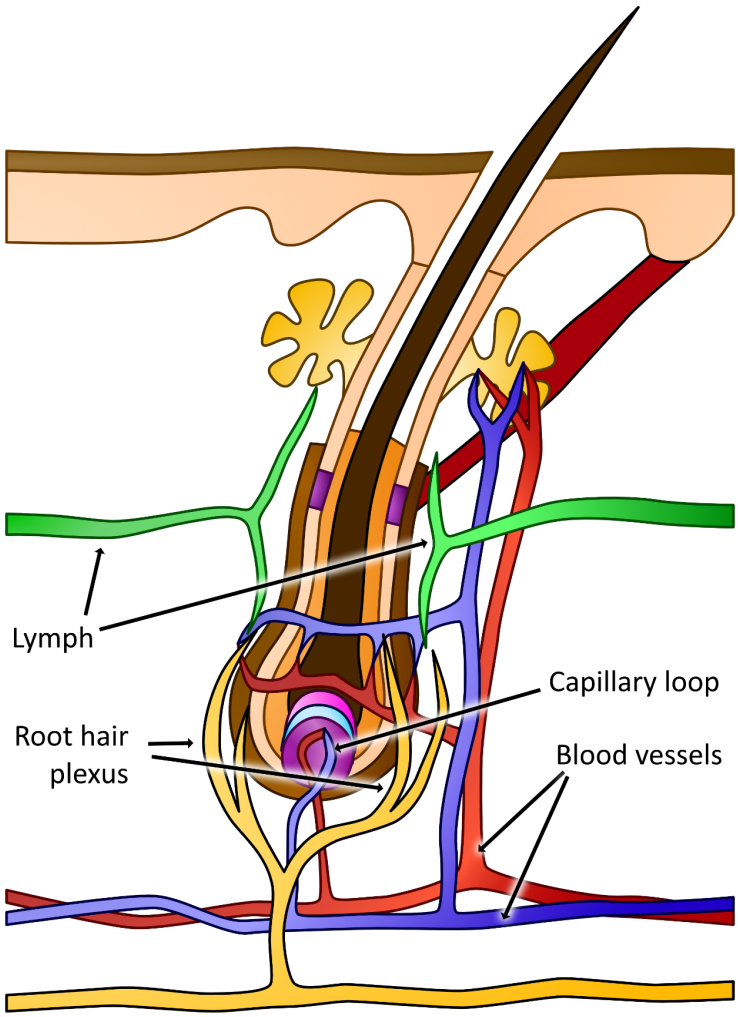

Figure 4.3: Innervation, blood supply, and lymphatic drainage of a hair follicle. ***Yellow tendrils:*** *Follicles are innervated by afferent sensory fibers that wrap around the bottom of the hair bulb.* ***Blue and red tendrils:*** *Blood supply includes a capillary loop within the dermal hair papilla, as well as capillary beds that wrap around the hair bulb as well as sebaceous glands.* ***Green tendrils:*** *Finally, lymphatic drainage extends to each hair follicle. Notably, lymphatic ducts become more active during active follicle growth* (Daniel Peña-Jimenez et al. 2019)*. By Zennith, 2024.*

4.2.2 - Humans have 3 types of hair: lanugo, terminal, and vellus

In humans, there are 3 types of hair: vellus, terminal, and lanugo (Martel et al., 2022). **Vellus hair** is the very short and fine white hair found across most of the body, measuring less than 2 mm, and does not meaningfully contribute to the macroscopic hair phenotype. Conversely, **terminal hair** is the thick, longer, pigmented hair found in specific body areas which vary by length and texture. It develops from vellus hair in a complex transition process initiated by the hormones of puberty for most body areas. The third type is **lanugo hair**, a typically unpigmented downy form ubiquitous across the fetal body, but absent in adults, usually being shed before birth. Terminal hair is the type that is commonly referred to simply as hair or fur.

4.2.3 - Terminal hair has different properties depending on body location

Terminal hair in humans can be further divided into subtypes with unique properties based on body location. Human hair on the scalp is composed of approximately 90,000 to 140,000 terminal hairs, with significantly higher numbers in intermediate and vellus hairs (Shwartz et al., 2020, Zhao et al., 2008). Here, terminal hairs emerge in clustered follicular units of multiple hair follicles averaging 3.6 hairs per unit by one estimate or 2-4 terminal hairs and 1-2 vellus hairs in another (Yazdabadi et al., 2008; Headington, 1984). These clustered follicular units may aid in the increase of total hair density on the scalp compared to body hair. Additionally, scalp hair has a very long anagen (growth) phase, lasting 2-6 years, which accounts for its ability to grow much longer than occurs in other body areas (Martel et al., 2022). This is compared to a length of several months for eyebrow hairs, for example, and thus these hairs never grow beyond a shorter length before being shed (telogen/catagen phase). Otherwise, body hair typically occurs in single hair follicles instead, and varies in density across body sites at much lower rates. While the scalp has been estimated to have about 315 hairs per cm^2 (based on 39.6 hairs per circular 4 mm biopsy in Sinclair et al., 2005), which is comparable to estimates of total follicles of all types on the forehead (292 follicles per cm^2), this is an order of magnitude higher than other body sites that vary from 14 to 32 follicles per cm^2, the latter also including vellus hairs (Otberg et al., 2004).

It is important to note that several sites, such as the palms, soles, but also various other regions, contain no hair follicles at all. The exact body sites on which this occurs can be variable, although volar skin (palms and soles) are always hairless in the standard case. As such, we cannot assume that hair is already present for us to turn into fur, and some regions may require transplantation or neogenesis to cover with hair in the first place, regardless of the method that we choose to increase the hair density.

Hair texture also varies depending on the type of hair and location around the body. Particularly, the direction that hair lays and the curl of the hair are different around the body. Humans, unlike most mammals, have variable hair curl between individuals varying from perfectly straight to tight ringlets of curly hair. Curl is another important aspect of texture for some potential species, such as sheep, but we have found that a majority of the most commonly identified fursona species have straight fur; the most popular typically-furred fursona species are wolves, foxes, dogs, big cats, and cats (International Anthropomorphic Research Project, 2020).

Table 4.1 Overview of human hair facts	
Scalp hair count	90,000 to 140,000 terminal hairs (Zhao et al., 2008)
Average # of hairs per follicular unit	3.6 (Yazdabadi et al., 2008) 2 to 4 terminal and 1 to 2 vellus (Headington, 1984)
Scalp anagen growth phase	2-6 years (Martel et al., 2022)
Scalp hair density	315 hairs per cm^2 (Sinclair et al., 2005)

4.2.4 - Hair pigmentation

The concentration of eumelanin and pheomelanin in hair strands determines the main perceived hair colour

Melanocyte stem cells, or McSCs, are often amelanotic, meaning they do not yet generate pigment. These stem cells are found in each follicular unit and are responsible for generating melanocytes for the pigmentation of hair (Slominski et al., 2005). They adhere to hair follicle stem cells around and just below the hair bulb. The hair bulb, which surrounds the dermal papilla at the base of the follicle, also holds growth factors that are vital for melanogenesis. This stem cell system is responsible for pigmenting the hair with melanin.

The hair is only pigmented during the anagen phase of the hair cycle. During telogen and catagen phases, melanocytes are inactive (Slominski et al., 2005). This is one difference between hair and skin melanation: skin melanin is produced continuously, but melanin in hair is produced cyclically, along with the rhythm of the hair cycle.

Much like with skin, there are two primary forms of melanin: eumelanin, which is black to brown, and pheomelanin, which is reddish in hair. Eumelanin can make hair black or brown, depending on its abundance, or blonde when it is scarce. Hair strands that contain mostly pheomelanin, and are scarce in eumelanin form the characteristic naturally red hair.

The concentration of melanins is modulated by the density of melanocytes in hair strands

Hair colour is determined by a combination of melanocyte density and melanin content per melanocyte, with both decreasing in later life during hair greying (Frudakis, 2008). More melanocytes can produce more melanin, and so a hair strand that is dense in melanocytes will have more melanin and more pigmentation in it. During each hair cycle, melanocytes are seeded and replaced from the melanocyte stem cells (McSCs), and after a number of these cycles, the amount of melanocytes produced begins to decrease — and therefore the concentration of melanin decreases, since the remaining melanocytes are unable to correct for the loss. As the individual ages and completes more hair cycles, the reduced number of melanocytes and therefore melanin causes the hair to be less pigmented, which causes hair graying. Grey hairs occur when there is little melanin produced, and white hairs occur when no melanin is present at all.

The perceived hair color is a function of pigment concentration and hair geometry

Although the overall melanin concentration dictates how dark or light a strand's core is, hairs in general have another interesting property: a rougher hair surface leads to a pale appearance of the hair, due to more diffuse reflection (Marschner et al., 2003). This is a common effect in unmaintained hair, which dulls over time due to damage to the surface layer of the strand. Other geometric effects, such as strand width or the medullary index, can have a similar impact on the final coloration, although these effects are more subtle than the melanin concentration overall (Yan et al., 2015). Still, for a full reconstruction of a hair's coloration, all of these factors must be taken into account. A full model describing the interactions with light is presented in chapter **1**, "Visual reflectance model of fur strands".

4.2.5 - Piloerection is controlled by small muscles in each follicular unit

Piloerection is the process where one's hairs stand on end, usually due to cold, fear, or a shock, with the skin tensing up into goosebumps. This is an involuntary reaction to a stimulus, governed by the sympathetic nervous system (McPhetres & Zickfeld, 2022). The arrector pili muscle lies along the side of the hair follicle unit, connecting the bulge region to the upper skin farther away from the follicle. When this muscle contracts, the hair stands upright and the skin bumps up. Interestingly, this mechanism is strongly evolutionarily conserved among furred mammals.

Most notably, this occurs in response to the cold. Mammals experience this because when upright, their fur can hold in more heat. Piloerection may be important to consider when discussing thermoregulation; humans are not currently adapted to regulating their temperature with a layer of fur over their skin, and the process of piloerection impacts that thermoregulation.

4.2.6 - Sebaceous glands produce skin oils and are associated with the hair follicle tract

Sebaceous glands lie along hair follicles and connect into them via a duct at the isthmus (uppermost section). The sebaceous glands secrete an oil called sebum into the hair follicle through that duct; many units can surround one duct (Gray's Anatomy 42nd ed p 154), almost like a raspberry in form. They are most dense on the face and scalp, and do not occur on the palms and soles, though they are present on other hairless skin, such as the inner lining of the eyelids as Meibomian glands (Gray's Anatomy 42nd ed p 154). Sebum is important for the skin and hair because it acts as a lubricant, prevents rapid dehydration during sweating, and helps deflect rain when cold.

In furred mammals, sebaceous glands are widely conserved, including their close structural association with hair follicles (Raghav et al., 2022). The size, density, and distribution of these glands is somewhat heterogeneous across species, and this may reflect evolutionary adaptations related to the amount of sebum required. Humans have an unusually high density of comparatively large sebaceous glands that are rarely seen in other mammals, although an exception to this exists in lemurs, which possess near-human amounts (Montagna, 1974). This may imply that furring a human without modifying sebaceous gland density is possible while still remaining hygienic, and a study of lemur grooming behaviours would be illuminating to further understand how this is possible.

4.2.7 - The Hair Cycle

The hair cycle is an intrinsic circular behaviour of hair follicles where hairs spend most of their time in a growth stage, followed by periods of recession and shedding. In fact, the length of hairs is itself controlled largely by the length of time that a follicle spends in uninterrupted growth before being shed. It is therefore essential to understand and have some control over the cycling of follicles in order to ensure correct hair length.

Functionally, the hair cycle comprises several stages which are summarized here and expanded upon in molecular detail in subsequent chapters. The stages are, briefly:

1. **Anagen phase**, where the hair shaft actively grows;
2. **Catagen phase**, where growth ceases and the follicle shrinks;
3. **Telogen phase**, where the follicle rests;
4. **Exogen phase**, where the old hair shaft detaches and is shed;
5. **T/A transition**, where the follicle regenerates and returns to active growth.

Anagen phase

During anagen phase, the hair follicle possesses its well-recognized characteristic morphology, with a well-defined large bulb at the end in which the dermal papilla sits, surrounded by matrix cells that connect it to the upper portions. The dermal papilla, matrix, isthmus, and infundibulum all comprise a continuous structure during this phase. Active growth occurs, at least for scalp hair in humans, at a generally accepted rate of approximately 1 cm per month (Xiang et al., 2017).

In human scalp hair, the anagen phase normally represents approximately 90% of a hair's overall growth cycle (Burg et al., 2017). This proportion declines with age, and proportions of around 50% are seen in patients experiencing scalp hair loss (Burg et al., 2017).

The anagen phase, as a proportion of overall hair cycle, varies by the region of the body in humans. The cheeks and underarms have anagen phase proportions of about 60%, and the lower leg has an anagen phase proportion of about 40% of the overall hair growth cycle (Bouabbache et al., 2019).

Catagen phase

Growth of the hair shaft ceases upon the beginning of the catagen phase, where the follicle detaches from its blood supply in the lower dermis and many of the matrix cells undergo apoptosis — programmed cell death. The follicle shrinks and the dermal papilla enters a quiescent state of rest.

In humans, the catagen phase normally represents approximately 1% of a hair's overall growth cycle (Burg et al., 2017).

Telogen phase

Telogen phase marks the 'end' of one round of the hair cycle, where the follicle rests in a quiescent state of non-growth. The hair shaft does not necessarily detach at this time, but it is more weakly held in place and can be detached more easily. In humans, the telogen phase normally represents approximately 9% of a hair's overall growth cycle (Burg et al., 2017).

Exogen phase and the T/A transition

This phase is simply the point of detachment when the old hair shaft falls out of the skin, leaving only the miniaturized hair follicle behind. It marks the beginning of a telogen/anagen (T/A) transition phase when the hair follicle prepares for re-entry into active growth. The T/A transition is controlled by changes to the dominant signalling pathways directed by the dermal papilla, and these will be discussed in much more granular detail in later chapters (Daszczuk et al., 2020).

4.2.8 - Dermal and epidermal stem cell pools for hair growth

The two major pools of stem cells existing in the hair follicle are specialized mesenchymal stem cells in the DP (DPCs) and epidermal hair follicle stem cells (hfSCs) in the bulge region. The location of these stem cells varies throughout the hair cycle: the DP is part of the base of the follicle during anagen phase, partially detaches during catagen, reattaches during telogen, and finally reincorporates itself into the bulb during the telogen/anagen transition before the cycle repeats. Conversely, hfSCs in the bulge during anagen and catagen subsequently sink into the bulb during telogen, followed by re-ascent at the telogen/anagen transition (Daszczuk et al., 2020).

Interplay between these two pools of DPCs and hfSCs drives the hair cycle via oscillating gene networks, especially those involved in Wnt and BMP signalling (Daszczuk et al., 2020). DPCs themselves can be thought of as ‘directing’ hair follicle growth behaviour, and in mice, they are necessary and sufficient to induce hair follicle formation when transplanted alone. However, the same approach of using expanded DPCs grown *in vitro* has been largely unsuccessful in humans, despite many clinical attempts (Aoi et al., 2012). In humans, they are likely to be necessary, but not sufficient, although this could be because DPCs that are cultured outside of the body for more than a short period tend to lose their stem cell characteristics; we will discuss this in greater detail in subsequent sections.

The hair strand itself is derived from the highly mitotic epidermal cells above the DP, referred to as the hair bulb matrix, whereas the DPCs themselves act only as directors of growth. The matrix is composed of a combination of responsive hair germ cells from directly above the DP and hfSCs from the bulge region (Daszczuk et al., 2020). Together, they form a group of transit-amplifying (TA) cells that differentiate into the various layers of hair strand.

4.3 - Human keratins and their physical properties

Abstract

Keratins are long proteins that give fur, feathers, and scales their structural properties. Humans produce many types of keratin, each expressed in different tissues. Between species, keratins differ in genetic sequence. Even so, they may have similar functional properties as those innately produced in humans, potentially allowing us to reuse human keratins to faithfully reconstruct non-human types of integument. This approach would avoid issues with immune rejection, the limited size of gene vectors, and potential cross-reactive behavior of foreign keratins inserted in human cells. To assess whether human keratins are suitable, we need to review their structural properties in detail, which this section will cover.

Introduction

Keratins have an essential role in the formation of integument in both humans as well as the non-human species we discuss in this review. Keratins are intermediate-filament-forming proteins, responsible for structural integrity of skin, hair, feathers, and scales. They act in a similar way to rubber: they form crosslinks with each other to form polymer networks that create a flexible, pliant, and tough mass that is used to strengthen many tissues. In fact, the majority of hair by mass is composed of keratin proteins, making it a highly relevant protein group to examine.

Although often associated with the integument, some types of keratins are responsible for structural integrity in other areas of the body; though that discussion is out of scope for this review. Here, we will review the properties of human keratins, their subtypes and localization, and possible relevance for transformations.

4.3.1 - Human keratins are subdivided based on acidity (Type I and Type II) and cysteine content (hard vs. soft)

Although all keratins share a polymer-like structure, there are many different types of keratin. To date, 54 human keratin genes have been classified (Jacob et al., 2018). Each keratin has unique properties, and often has a unique localization in the body. For example, some keratin types only occur in hair, while others are predominantly found in fingernails (Moll et al., 2008). The properties of individual keratin polymers dictate the structural properties of the polymer mesh. As such, it is important to review the classifications of keratins to understand these molecular properties.

Keratins can be subdivided in multiple ways. One way is based on acidity: Type I keratins are acidic, and Type II keratins are of neutral pH and relatively somewhat larger than Type I keratins (Jacob et al., 2018). Some Type I keratins have an associated Type II keratin with which they structurally pair to form heteropolymeric strands (Sun et al. 1983).

Another way to classify keratins is through their difference in material toughness (Coulombe and Omary 2002). Some keratins produce soft materials like skin, others produce hard ones like fingernails. This classification groups the keratins with respect to their functional properties, which in our case will help us to compare and match human keratins with those occurring in non-human integument. In principle, if all properties match, two types of keratins are functionally equivalent, and if we are lucky, we can faithfully reconstruct the properties of non-human integument without introducing new keratin genes.

4.3.2 - Type I and Type II keratins interact in a pairwise manner to form heteropolymeric strands

Keratins by themselves do not have a high physical strength. It is the bundling of the keratins that produces high-strength fibers. The first level of bundling is in the formation of heteropolymeric dimers, which consist of one Type I keratin and one Type II keratin (Kim and Coulombe, 2007).

Table 4.2: List of keratins and their types							
Name	**Type**	**Location**	**Cysteines**	**Name**	**Type**	**Location**	**Cysteines**
K1	Type 2	Epithelial	3	K25	Type 1	Hair Follicle Root Sheath	10
K2	Type 2	Epithelial	5	K26	Type 1	Hair Follicle Root Sheath	13
K3	Type 2	Epithelial	3	K27	Type 1	Hair Follicle Root Sheath	11
K4	Type 2	Epithelial	7	K28	Type 1	Hair Follicle Root Sheath	11
K5	Type 2	Epithelial	4	K71	Type 2	Hair Follicle Root Sheath	9
K6a	Type 2	Epithelial	5	K72	Type 2	Hair Follicle Root Sheath	11
K6b	Type 2	Epithelial	5	K73	Type 2	Hair Follicle Root Sheath	10
K6c	Type 2	Epithelial	5	K74	Type 2	Hair Follicle Root Sheath	7
K7	Type 2	Epithelial	1	K75	Type 2	Hair Follicle Root Sheath	5
K8	Type 2	Epithelial	0				
K9	Type 1	Epithelial	4	K31	Type 1	Hair	25
K10	Type 1	Epithelial	9	K32	Type 1	Hair	26
K12	Type 1	Epithelial	2	K33a	Type 1	Hair	22
K13	Type 1	Epithelial	6	K33b	Type 1	Hair	20
K14	Type 1	Epithelial	6	K34	Type 1	Hair	25
K15	Type 1	Epithelial	4	K35	Type 1	Hair	23
K16	Type 1	Epithelial	6	K36	Type 1	Hair	20
K17	Type 1	Epithelial	5	K37	Type 1	Hair	24
K18	Type 1	Epithelial	0	K38	Type 1	Hair	28
K19	Type 1	Epithelial	0	K39	Type 1	Hair	27
K20	Type 1	Epithelial	1	K40	Type 1	Hair	34
K23*	Type 1	Epithelial	3	K81	Type 2	Hair	34
K24*	Type 1	Epithelial	9	K82	Type 2	Hair	24
K76	Type 2	Epithelial	10	K83	Type 2	Hair	31
K77	Type 2	Epithelial	5	K84	Type 2	Hair	20
K78*	Type 2	Epithelial	14	K85	Type 2	Hair	27
K79*	Type 2	Epithelial	5	K86	Type 2	Hair	29
K80*	Type 2	Epithelial	9				
K76	Type 2	Epithelial	10				
K77	Type 2	Epithelial	5				
K78*	Type 2	Epithelial	14				
K79*	Type 2	Epithelial	5				
K80*	Type 2	Epithelial	9				

Source: Moll et al., 2008

Within human hair, keratin is subsequently bundled together in protofilaments, which bundle into macrofibrils, which together constitute a cortical cell (Thibaut et al., 2007; Harland & McKinnon, 2018).

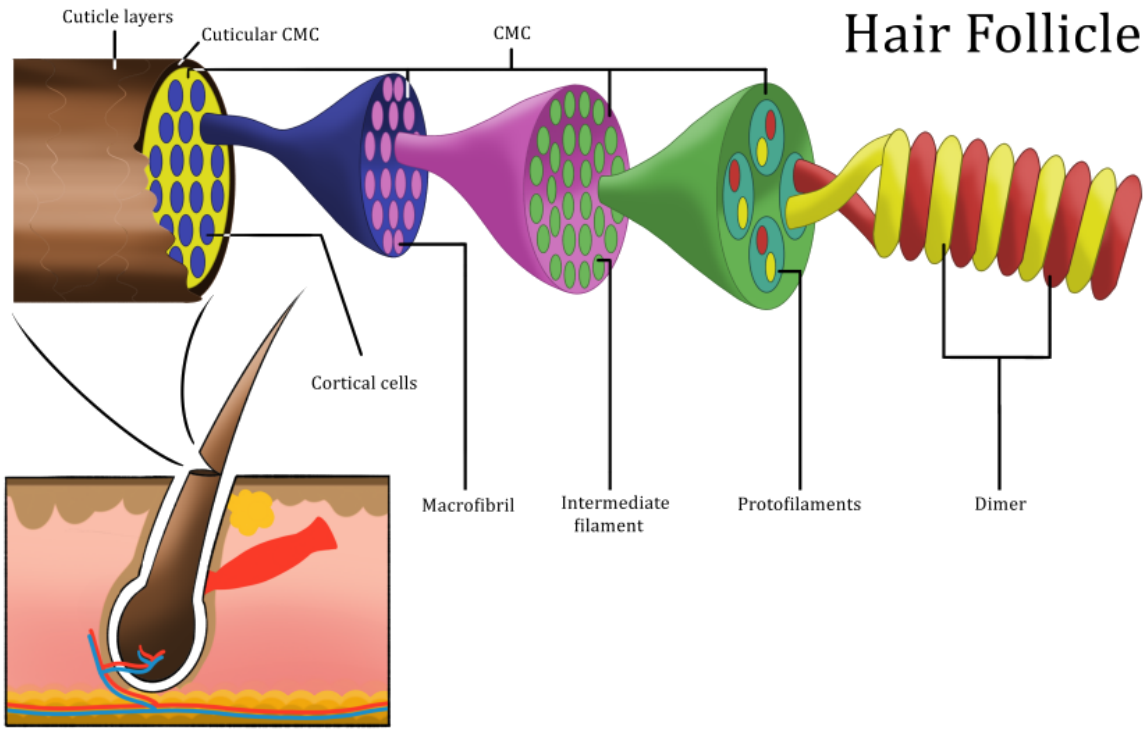

Figure 4.4: Keratins inside of a hair, by Fenris.

In other tissues, such as in skin, keratin protofilaments appear to take on a more networked structure, increasing the elasticity and anisotropic strength of skin in coordination with collagen (Madison, 2003; Kim et al., 2021). This may include complex organizations of many different types of keratins expressed together, yielding complex network arrangements (Coulombe and Omary 2002). Immunofluorescence microscopy imaging shows that within skin tissue, keratins organize in different apical-basal layers depending on their type (Müller et al., 2006). For example, human keratin 14 and 16 both organize close to the basal membrane within epithelial tissue, while human keratin 17 can arrange both near the basal membrane and near the exterior, though usually not between these layers (Donetti et al., 2020). Human keratin 10 organizes throughout the epithelium, though not near the basal membrane (Donetti et al., 2020). Each of the keratins has a pairwise bond with a keratin of the opposite type. This complex spatial organization hints that each layer within the epithelium has unique material characteristics that should be taken into account when altering the structure of skin.

The molecular details of the network structure of these skin keratins remain unclear, and require additional investigation.

4.3.3 - The number of covalent intermolecular crosslinks (disulphide bridges) between keratin fibres are proportionally related to hardness of keratinous material

It is a well-known fact that polymer materials, such as rubber or plastics, gain their strength through crosslinking. This is true for keratins too; the number of crosslinks determines the hardness of the keratinous material. Even so, the Young's modulus and bending modulus of different keratinous materials do not correlate directly to the estimated sulphur content (Guidotti et al., 2017). A likely explanation for this discrepancy is that only a fraction of the cysteines within keratin may be crosslinked, that these crosslinks may occur intramolecularly or intermolecularly, and that the overall material may be further strengthened by the presence of additional polymer materials.

There exist various rheological measurements of keratins (Ma et al., 1999; Ma et al., 2001; Yamada et al., 2003; Sivaramakrishnan et al., 2008; Guidotti et al., 2017; Esparza et al., 2018; Elbalasy et al., 2022), but a comprehensive rheological model remains undefined due to the inherent complexity of keratinous materials. Future research should investigate how the composition of keratinous materials influences its material properties in detail, such that new materials, such as scales, can be engineered from human keratins.

4.3.4 - Non-covalent crosslinks also contribute to hardness and are mediated by Keratin Associated Proteins (KAPs)

In addition to alpha-keratins, humans express *Keratin Associated Proteins* that, like alpha-keratins, form disulphide bridge cross-links between each other (Harland & McKinnon, 2018; Fraser & Parry, 2018). In addition, they also form non-covalent crosslinks that contribute to the overall strength and flexibility of the material. Keratin Associated Proteins are much smaller in molecular size, and appear to form small interconnecting elements between keratin filaments. Due to their apparent structural similarity (though not sequence similarity) with keratin associated beta-proteins (KABPs) in reptiles and avians (Alibardi, 2016), we theorize that these proteins fulfill similar roles. As such, we propose that KAPs should be investigated as a potential substitute for the reptile- and avian-specific keratin-associated proteins.

4.3.5 - Keratin gene expression patterns are tissue- and context-specific

The structure of keratin proteins determines its polymer composition, which in turn determines its material properties, which in turn determines its function. Each of the alpha-keratins encoded in the human genome have unique properties and functions, which becomes apparent in their use in different tissues. Hair, for example, consists mostly of flexible keratins, whereas nails contain harder keratins. In skin tissue, keratins provide stability, but don't inhibit flexibility. Mucous tissue, such as the tissue within the oral cavity or intestines, expresses a different set of keratins than those in skin.

Because of this, mutations in a specific keratin gene only affects the part of the body that it is expressed in. This gives us a good way to determine the function and location of keratins.

The disease models also highlight the importance of maintaining the integrity of keratins for any treatment we propose, since mutations in skin-relevant keratins could lead to uncontrollable structural defects such as ichthyosis (Gutiérrez-Cerrajero et al., 2023). Instead, altering the expression patterns and modulating the polymer gel structure of keratins is possible without altering the protein sequence of the keratins themselves, and is predicted to give us full flexibility over the material properties.

4.4 - Structural properties of nails

Fingernails form a particularly interesting feature of the human body. Although we will leave the formation or engineering of claws, horns, and other such peripheries for a later review, we opt to mention key properties of human nails due to their structural similarity with reptilian scales. After all, both are integumentary structures consisting of flat plates of keratinized tissue — although there are many differences, such as in the way nails grow, we can still use the genetic building blocks of nails already present in humans to help reduce the amount of additional genes needed to grow scales. In **chapter 11**, we will refer back to these building blocks to review if and how we can reconstruct the properties of scales from these human parts, without compromising the authenticity of scales.

We will first discuss the main structure of human fingernails and how keratins — important structural proteins — get deposited into the nail matrix. This will be important for understanding how to reconstruct keratin deposition in artificial scales. Then, we will discuss the structural properties of fingernails, such as their strength and hardness, as well as their chemical composition, which we will compare to reptilian scales in **chapter 3**.

4.4.1 - Specialized skin layers, the eponychium and hyponychium, collectively produce the nail plate

The human fingernail, from the outside at the top, begins with the cuticle layer. The eponychium is a strip of cells along the upper base of the nail that generates cells for the cuticle (which is sometimes also considered the eponychium). These cuticle/eponychium cells grow and are pushed outwards across the base of the nail, protecting it.

Beneath the cuticle/eponychium, a bit further back from where the nail erupts from the skin, is the nail matrix. This germinal matrix produces highly keratinized cells that are deposited and pushed out into the main body of the nail, called the nail plate. This nail matrix is visible through the nail plate as the lunula, a small, crescent shaped light-pink section near the base of the nail.

More distal to the nail matrix (closer to the fingertip) lies the nail bed, which appears a darker pink. The nail bed's attachment to the nail plate to the nail bed is strongest at its most distal extent, the onychodermal band (Gray's Anatomy 42nd ed p 156).

Finally, past the nail bed, closest to the fingertip, this gives way to the hyponychium, where the skin and the nail plate separate; this is the skin that you can reach under the front of your nails.

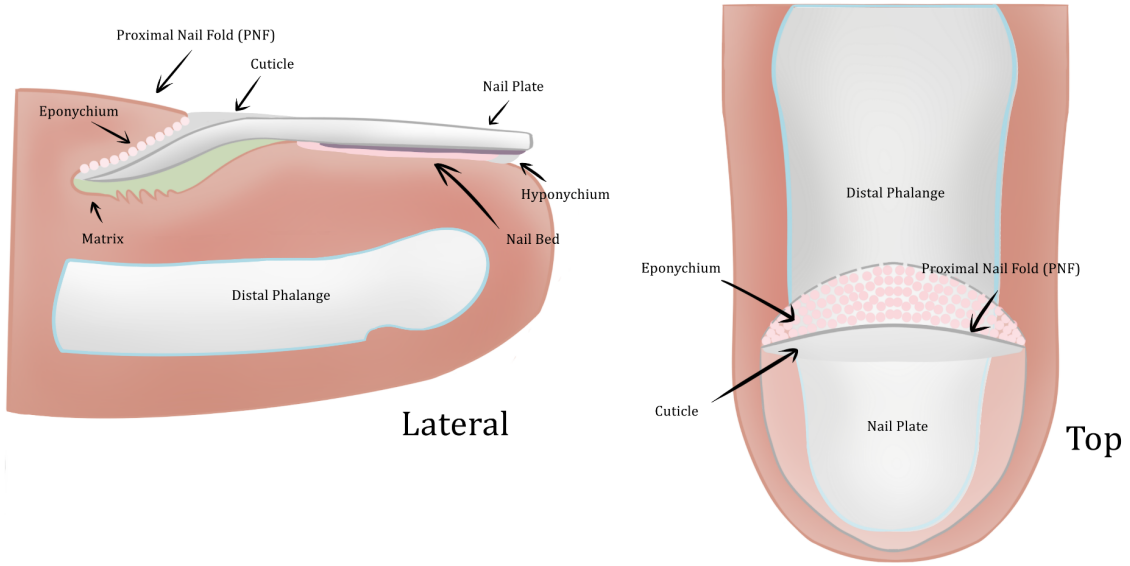

Figure 4.5: Anatomy of a human fingernail, by Fenris, 2023.

4.4.2 - The human nail plate is subdivided into layers termed the dorsal, intermediate, and ventral lamina

The nail plate's dorsal surface arises from a slightly different subpart of the germinal matrix than its ventral surface/underside. The dorsal surface of the nail plate is produced by the germinal matrix closest to the interphalangeal joint (the dorsal and intermediate matrices), while the underside of the nail plate (the side touching the nail bed) is produced by the ventral/distal nail matrix (Gray's Anatomy 42nd ed p 156).

Structurally, the plate of the nail itself can be separated into three layers (Álvarez et al., 2021). The layer exposed at the top of the nail is the dorsal layer; here, keratins are organized randomly. The intermediate layer lies in the middle, is the thickest, and has keratins aligned transversally - parallel to the cuticle and lunula. The ventral layer lies below that, along the nail bed, and is the thinnest. The cells here are the youngest and softest, and the keratins are organized randomly again (Álvarez et al., 2021).

4.4.3 - Nail growth is linear and non-cyclical

Unlike hair, which goes through stages of growth, dormancy, and shedding, fingernails grow continuously with no distinct phases. The matrix is always undergoing cell division to push more cells outwards into the nail plate, even when the nail is damaged or torn off. This is apparent with the continuous rate at which nails grow, which is a few millimeters per month (Yaemsiri et al., 2009). Fingernails grow at a faster rate than toenails (Yaemsiri et al., 2009; Gray's Anatomy 42nd ed p 157).

4.4.4 - Nails are harder than skin, but contain similar keratins

Although skin gains its strength in part through keratins just like in nails, nails are much tougher and have much different structural properties. Some of the keratins expressed in nails contain a relatively high cysteine content, which we hypothesize to lead to higher crosslinking counts. However, nails also express many types of keratins found in other regions of the body, such as normal skin, as well.

The exact chemical composition and arrangement of keratins and other molecules involved in the structure plays a big role in creating the strength of a nail, and these all form mechanisms to modulate material strength in keratinous materials. For example, **cornulin**, **filaggrin**, and **trichohyalin** are proteins that bind keratins in epithelial cells; these types of proteins, called S100 fused-type proteins, form an important modulator of keratinous tissue strength in both mammalian and non-mammalian tissue (Mlitz et al., 2014).

Table 4.3: Keratins known to be expressed in human fingernail	
Type 1:	K5, K6a, K6b, K6c, K81, K86 (Moll et al., 2008)
Type 2:	K10, K16, K17, K31, K34 (Moll et al., 2008)

This is a common sight in polymer science: many different properties, including the number of crosslinks, types of crosslinkers used, and compound ratios can drastically affect the material properties. Studying these keratins and their expression could therefore act as an interesting starting point in the quest towards developing a lizard scale-like material without requiring non-human structural proteins, as human keratins and other such biopolymers form a versatile toolbox to construct faithful scale materials.

For a comprehensive review of keratins and their organization in human integument, we refer to Moll et al., 2008.

4.5 - Skin Types

4.5.1 - Types of skin in a single human

As human skin varies in many ways around the body, such as in thickness, follicle density, or elasticity, some areas of the skin that are substantially unique are considered different types of skin. The skin on the palms of the hands and soles of the feet is particularly unique, for example, and some define skin types by volar (palm and sole skin) and non-volar or dorsal skin (Bu et al., 2022). Volar skin is thicker than the rest of the skin in the body, and this extra thickness is found specifically in the epidermis. This type of skin has a higher volume density of keratin filaments compared to skin on the arm (Swensson et al., 1996). There are no hair follicles found in volar skin, and it is more lightly pigmented as well (best seen on darker skin). Remarkably, it has also been found to have a different metabolic profile than skin found elsewhere on the body (Bu et al., 2022).

Thinner skin is found at the eyelids, armpits, and crotch area, with the eyelids being the thinnest (Poonawalla et al., 2008). Eyelid skin is particularly different because, like volar skin, it is hairless besides eyelashes, and contains specialized sebaceous glands called Meibomian glands (Gray's Anatomy 42nd ed p 154).

Lip tissue is another unique area of the body to acknowledge a significantly different. This is where the outer skin of the body transitions into the inner lining, which is different in structure and function. The body's inner lining contains mucous membranes, and the transitional lips include a specialized mucous membrane called the vermilion. The vermilion is a "hairless, highly vascularized, nonkeratinized stratified squamous epithelium" that contains no hair follicles or sebaceous glands, making it more similar to inner lining than outer skin (Piccinin & Zito, 2023). It transitions fully where the lining smooths out just inside the mouth, as the vermilion still expresses skin folds, giving way to a full mucous membrane. However, the skin outside the lips is also specialized. The philtrum is the ridged area between the nose and the lips, and it is highly elastic and full of collagen, which helps the lips stretch and function more nimbly.

4.5.2 - Skin diversity across the population

Human skin comes in many different forms. Skin can be oily, dry, or a combination of the two; this is decided by a combination of genetics and environmental factors such as diet and stress (Passeron et al., 2021). Notably, modern products can sometimes strip the oils off of skin, directly causing dry skin. Sensitive skin is also genetic, and includes sensitivity to chemicals and products, irritation from rubbing and fabrics, and even allergies.

People with different ethnic roots around the planet also have notable differences in their skin. While possible for all skin, darker skin (particularly black skin) is more susceptible to getting 'ashy' - this is when dry skin and shed skin has a dull, gray appearance (Uhoda et al., 2003). Asian and African American skin is generally more oily than other types of skin due to the presence of more sebaceous glands, as another example (Pappas et al., 2013).

However, these are also generalizations and are not necessarily true for every individual of a population. The most important takeaway of this subsection should be that subjects will have diverse skin, which deserves a thorough and inclusive approach when considering transformative effects on the skin. Diversity among researchers and technicians (especially in ethnicity) is advised, and even then, diverse skin types will need further special consideration both for the transformative techniques developed and for each individual's treatment needs.

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