Skin Barrier Health: Regulation and Repair of the Stratum Corneum and the Role of Over-the-Counter Skin Care

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Abstract

The epidermis functions as a physical barrier that separates the inner body from the outside environment. The outermost layer of the epidermis, the stratum corneum, plays a key role in maintaining this barrier. There are numerous biochemical changes that take place to and in the keratinocyte as it migrates from the bottom, or startum basale, to the top layer of the epidermis in order for this barrier to function appropriately. In addition, external and internal factors, such as irritants and underlying medical diseases, can also affect the stratum corneum, both of which can potentially lead to disruption of barrier function and ultimately skin pathology. In this article, we will review keratinocyte biology as it relates to the formation and function of the stratum corneum. We will also review stratum corneum structure, physiology, and the impact of chemical agents and defective stratum corneum components that can lead to skin disease. Finally, we will briefly discuss how moisturizers repair defects in the stratum corneum and restore barrier function.

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Keratinocyte Biology and Stratum Corneum Formation

The epidermis is primarily made up of keratinocytes, in addition to melanocytes and Langerhans cells. It consists of four layers: the basal layer, spinous layer, granular layer, and cornified layer, which is also known as the stratum corneum. It takes approximately 28 days for a keratinocyte to migrate and differentiate from the basal layer and ultimately be shed from the surface stratum corneum.[1] The keratinocyte is derived from stem cells of the basal layer, the bottom-most layer of the epidermis. Keratinocytes of the basal layer are the

only viable cells of the epidermis. As these cells migrate and differentiate, they lose the ability to undergo mitosis. These specialized cells first arise from ectodermal tissues during the first few weeks of fetal life. Keratinocytes also express cytoskeletal proteins called keratins, which always form pairs with an acidic and basic subtype.[1] These proteins have structural and hygroscopic functions and also play a role in migration and cell differentiation.

As the keratinocyte migrates upwards, they differentiate into spinous layer cells, which are characterized by a more polyhedral shape and the expression of proteins called desmosomes. These proteins connect keratinocytes to each other. The formation of these desmosomal proteins is dependent on calcium dependent enzymes.[1] For these enzymes to function, the calcium gradient must increase in concentration towards the upper layers of the epidermis, facilitated by the expression of ATP-dependent calcium pumps, ATP2A2 and ATP2C1, which are mutated in Darier and Hailey-Hailey disease, respectively. As will be discussed below, this calcium gradient is crucial for differentiation of the keratinocyte as it migrates upwards.

Above the spinous layer is the granular layer, characterized by the keratohyaline granules, which consist of proteins such as profilaggrin, loricrin, involucrin, and envoplakin, that will later play a role in the formation of the cornified envelope.[1] Also unique to the granular layer are the lamellar granules, which are secretory organelles, derived from the Golgi apparatus.[1] These carry lipid products that will form the intercellular lipid content of the stratum corneum.[1,2]

The transition from the granular layer to the stratum corneum marks a point of dramatic change as keratinocyte degradation takes place leading the differentiation of these cells into corneocytes. The nucleus, organelles, and plasma membrane are lost during this phase.[1] The contents of the keratohyaline granules are released and the profilaggrin proteins are degraded into individual filaggrin monomers by a calcium-dependent enzyme.1,2 These filaggrin monomers then bind with the keratin cytoskeletal proteins, preventing further breakdown of filaggrin until the setting of corneocyte dehydration occurs where it is further degraded by capase-14 and other enzymes into amino acids and amino acid derivatives that are needed to maintain moisturization.[2,3] Of note, urocanic acid, a breakdown product of filaggrin, also plays a crucial role as protection against UV radiation.3 Filaggrin, with the other keratohyaline granule proteins, are then assembled into the cornified envelope by enzymes called transglutaminases, which are calcium-dependent and serve to give physical structure to the corneocyte.[1] During this phase, the lamellar granules are also extruded into the intercellular space and the lipid contents then form the stacked lipid bilayers, which permeate the space between corneocytes.

Stratum Corneum Structure

The overall structure of the stratum corneum in the basic sense can be modeled as a brick-mortar configuration.[1,2] The “bricks” are the interconnected corneocytes, which form

the physical structure and scaffold while the “mortar” consists of natural moisturizing factors and the intercellular stacked lipid bilayers. While the model is helpful in illustrating the components of this skin layer, the stratum corneum is more than just an inert brick wall. The interplay between these structural components combined with the ability to respond to physiologic stresses is what allows the stratum corneum to function as both a physical and moisture barrier.

The stratum corneum consists of non-viable, anucleate keratinocytes known as corneocytes.[1] These cells are flat and hexagonal in structure and are stacked in layers. Within the cells are keratins which function to bind water while on the surface are filaggrin proteins.[1,2] In place of a typical plasma membrane is the cornified envelope, which consists of crosslinked proteins derived from the keratohyalin granule.[1] The corneocytes are connected to each other physically through the desmosomes, also termed corneodesmosomes in this layer, providing structural integrity to the stratum corneum.[1,2]

Enveloping these corneocytes is a mortar-like milieu consisting of two main components, natural moisturizing factors and lipids. The natural moisturizing factor consists of a combination of amino acids, amino acid derivatives, lactic acids, urea, and salts produced from the breakdown of filaggrin.[1,4] The two most prominent amino acid derivative components are pyrrolidone carboxylic acid and urocanic acid, the latter being also involved in UV protection.[4] The main function of the natural moisturizing factor is to attract and bind water to maintain moisturization of the stratum corneum.[1,4]

The intercellular lipids are comprised of breakdown products from corneocyte cell membranes as well as the lamellar granules, which are released from the degradation of granular layer keratinocytes.[1,2] This occurs during the transition phase as the keratinocyte migrates and undergoes differentiation from the granular layer to the stratum corneum. These lipids are composed of free cholesterol, free fatty acids, and sphingolipids. Of the sphingolipids, ceramide is unique as it is composed of both a hydrophobic and hydrophilic component, which gives rise to the stacked bilayer structure of the lipids and also binds water through the hydrophilic component. The hydrophobic property of this lipid layer bestows water impermeability to the stratum corneum preventing the loss of moisture to the environment.

Moisture Homeostasis

The stratum corneum can respond in multiple ways in order to maintain moisture homeostasis. Moisture is crucial as water molecules are responsible for maintaining plasticity and texture to the skin.[2] The two main methods are the maintenance of natural moisturizing factors and desquamation.

As discussed previously, free amino acids and amino acid derivatives such as pyrrolidone carboxylic acid and urocanic acid, are derived from the breakdown of filaggrin proteins on

the exterior surface of the corneocyte.[1,4] It is the corneocyte water content that governs the rate of filaggrin break down into free amino acids.[2] The water content typically makes up 30% of the corneocyte. In dehydrating conditions such as windy or dry weather, this percentage decreases, which then activates proteolytic enzymes, such as capase-14, that degrade filaggrin.[1-3] This increases the amount of natural moisturizing factors in order to restore water content and osmotic pressure.[2]Once water molecules are absorbed into the stratum corneum, they must be incorporated into the actually corneocytes. This is thought to be facilitated through specialized channel proteins called aquaporins.[5] In the epidermis, in particular, aquaporin type 3 is expressed, which facilitates movement of both water and glycerol molecules.[3]

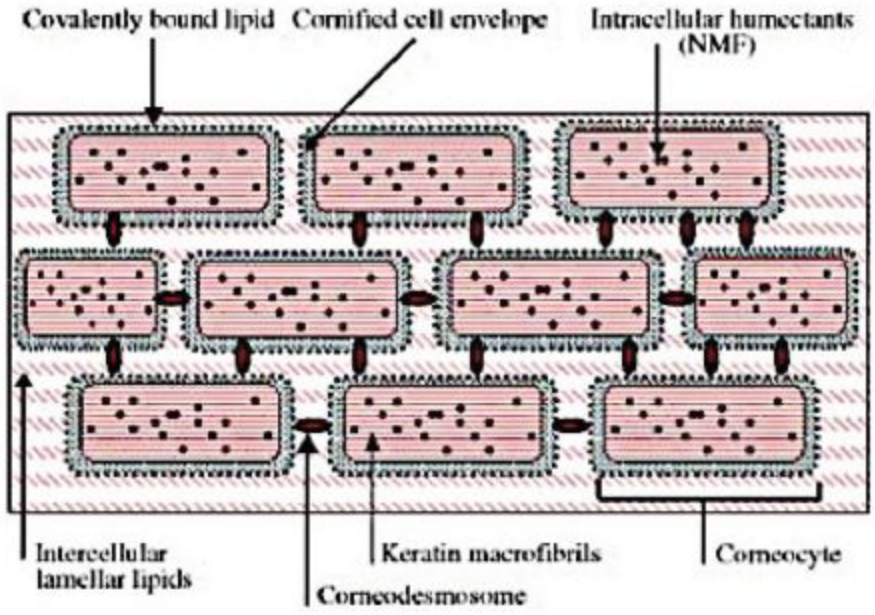
Moisture is also critical in control the rate of corneocyte shedding or desquamation.[2]Desquamation occurs as proteolytic enzymes break down the desmosomes connecting the corneocytes, which allows them to be sloughed off from the surface of the stratum corneum. This breakdown only occurs in the presence of adequate water and moisture. In dry conditions and decreased water content, desmosomes remain intact causing a build-up of corneocytes. This leads to an increase in the thickness of the stratum corneum in an attempt to bolster the physical barrier and prevent loss of moisture to the environment. Clinically, this is appreciated as thickened and scaly skin.

Exogenous and Endogenous Factors Contributing to Barrier Disruption

As discussed previously, numerous mechanisms are in place in order maintain moisture homeostasis in the stratum corneum. Both exogenous and endogenous factors can disrupt this balance leading to a dysfunctional barrier. The loss of water from the epidermis is termed transepidermal water loss (TEWL).[1,2] To limit TEWL, the hydrophobic, intercellular lipids prevent a majority of water movement between the internal body and external environment and the natural moisturizing factors with aquaporin channels keeps the corneocyte water content in balance and minimizes water lost to the environment as evaporation. However, irritants can disrupt the barrier by denaturing key proteins, removing natural moisturizing factors, and removing lipids.[2]By definition, an irritant is an agent that can cause cell damage through prolonged contact or high concentrations.

Before discussing pathology secondary to chemicals or disease states, it should be noted that genetic variation between racial groups can lead to structural and functional differences in the stratum corneum, which can be significant phenotypically and clinically. Studies have shown that African American skin has lower levels of TEWL and increased physical resistance to barrier disruption compared to Caucasian and East Asian skin.[7] Based

FIGURE 1. "Brick-and-mortar" model of the stratum corneum. Reprinted from Harding CR. *Dermatologic Therapy*, 2004.



on experimental data, it is thought that higher levels of corneocyte maturation in terms of cornified envelope formation and reduced rates of desquamation may contribute to this.[8] While these may bestow a stronger barrier, clinically these patients have been noted to be more prone to developing scaly, ashy-appearing skin. On the other end of the spectrum, East Asian skin had higher levels of TEWL and reduced physical resistance to barrier disruption compared to the other two groups. East Asian skin tended to have lower rates of corneocyte maturation but higher ceramide levels. While smoother in texture, this ethnic skin type may be more prone to eczematous skin disorders such as atopic dermatitis and contact dermatitis.[7]

Many substances we come into contact with everyday and normally consider benign can become irritants in certain conditions. Water, interestingly, while needed for moisturization, through prolonged skin contact, can be a mild irritant.[2] Overexposure to water can remove moisturization factors and lipids from the stratum corneum leading to overall dehydration and increased TEWL. Soaps and cleansers are normally beneficial surfactant agents, removing dirt, bacteria, and desquamated cells from the surface. However, prolonged exposure can denature proteins and cause loss of moisturizing factors and lipids.[2,6] Soaps tend to be basic and thus overexposure can alter pH levels can cause stratum corneum proteins and enzymes, which require an acidic environment, to denature.[4, 6] The surfactant property of soaps, while useful in maintaining hygiene, will also remove lipids from the stratum corneum with overexposure, affecting the permeability barrier.[2,4,6] Heated water can

allow deeper penetration of soaps into the stratum corneum, which can exacerbate these losses. This ultimately leads to loss of moisture and increased TEWL.

In addition to water loss, irritants can also promote pathology through other mechanisms. By altering the water and chemistry of the skin surface, irritants can also alter the bacterial flora of the skin, which can promote growth of pathologic organisms.[2,9] It has been shown that organisms associated with skin pathology, such as Staphyloccocus, Candida, and Propionbacterium, have been associated with higher rates of growth in alkaline pH and can displace the normal microbiota of the skin.[9]Disruption of the barrier can also allow environmental allergens access into the skin, which can trigger inflammation and dermatitis.[2,9]

Age has also been found to significantly impact the skin's ability to function as a barrier. With the passage of time and exposure to ultraviolet radiation from the sun, skin ages and undergoes structural and functional changes, which can often lead to a dysfunctional stratum corneum. When compared to skin from a younger age group, aged skin differs in numerous biologic parameters including decreased intercellular lipid content, natural moisturizing factors, and desmosomal proteins.[10] The deficiency in intercellular lipid content was found to be due to disruptions in the calcium gradient, alterations in enzyme activity, and increased skin pH in aged skin. The secretion of lamellar granules into the intercellular space requires the calcium gradient so there is a decrease in the volume of intercellular stacked lipid bilayers with the loss of the gradient. Key enzymes involved in the production of intercellular lipids, such as sphingomyelinase, are diminished in aged skin, while catabolic enzymes, such as ceramidases that break down vital lipids, are upregulated, compounding the lipid deficiency.[10,11] The elevated pH in aged skin, due to diminished activity of acid transporters, also down-regulates the activity of specific enzymes in lipid metabolism, such as β-glucocerebrosidase. Aside from effects on lipids, the elevated pH up-regulates the activity of serine proteases, causing increased breakdown of desmosomal proteins and, ultimately, stratum corneum fragility. In addition to diminished lipids, natural moisturizing factor levels are decreased in aged skin, which appears to be due to decreased profilaggrin production. The underlying cause of these changes may be in part due to increased cellular dysfunction and apoptosis from telomere shortening that comes from chronic aging. UV radiation-induced damage to DNA and oxidation of biochemically important enzymes may also play a role.

Aside from exogenous sources of barrier distruption, many skin diseases can lead to endogenous dysregulation of keratinocyte maturation and, in turn, barrier disruption. Many of the previously mentioned structural and enzymatic components of the stratum corneum can be defective secondary to deleterious mutations leading to disease states. By understanding the function of these proteins, one can make sense of why certain skin

diseases present with specific symptoms. The condition that illustrates this concept is atopic dermatitis, which is thought to be associated with ineffective filaggrin expression.[12] Many possible mechanisms have been suggested regarding impaired filaggrin function, including genetic variation in proteins and down regulation due to inflammatory cytokines. Studies have shown that Th2-class cytokines, which tend to be increased in patients with atopic disease, downregulate the

expression of filaggrin.[8] As a result of this deficiency in filaggrin, there is a subsequent reduced level of natural moisturizing factors in the stratum corneum leading to increased TEWL.[6,12] The itchy, scaly plaques that develop compel the patient to scratch and injure the skin causing further damage to the stratum corneum. These injuries also predispose patients to superinfection with Staphylococcus aureus, which can lead to impetiginzation and further inflammation. Defective filaggrin may also increase the baseline risk of developing Staphyloccocal infections as filaggrin-mediated expression of spingomyelinase is needed to protect keratinocytes against the bacterially produced alpha-toxin. All of these derangements are magnified in scope in a related condition, ichthyosis vulgaris, which results from a mutation in the FLG gene leading to complete loss of function in filaggrin.[1] Without filaggrin, the cornified envelope cannot be formed and there is a decrease in natural moisturizing factors. Clinically, patients develop dry, scaly plaques and have a propensity for developing eczematous dermatitis. Other enzymes involved in forming the cornified envelope can also be mutated. Lamellar ichthyosis results from a mutation in transglutaminase, the enzyme needed for crosslinking keratohyaline granule proteins to form the cornified envelope.[1] Patients present with dry, thick, platelike scales and at birth, the infant may be covered in a collodion membrane as a result of defective cornification.

In addition to filaggrin, other key genes encoding proteins and enzymes of the stratum corneum can also become mutated. As discussed previously, the calcium gradient increases in concentration towards the upper layers of the epidermis and this is critical in formation of desmosomes and cornified envelopes. Mutations in the calcium-ATPase pumps can disrupt this calcium gradient and lead to skin disease. The two classic examples include Hailey-Hailey disease and Darier disease, which are a result of mutations in the ATP2C1 and ATP2A2 proteins respectively.[1] Dyskeratosis and acantholysis can be appreciated histologically as without the desmosomes to provide intercellular connections, the keratinocytes become discohesive and the epidermis becomes fragile. Keratin proteins can also be mutated, and as these play a crucial role as cytoskeletal proteins, defects can lead to cell fragility and present with blistering clinically.[1] The classic example is epidermolysis bullosa simplex, which is due to mutations in keratin type 5 and 14. Mutations in other keratin proteins can also lead to blistering disorders such as palmoplantar

epidermolytic hyperkeratosis of Vörner, a mutation in keratin [9], which is expressed only in the palms and soles. As such, the blistering process only occurs on the hands the feet.

Components of the intercellular lipids can also become dysfunctional as a result of mutations. In X-linked ichthyosis, a mutation in steroid sulfatase results in an inability form lamellar granules needed to form the stacked lipid bilayers in the intercellular space.[1] Patients present with collidion membranes at birth, tightly adherent, scaly plaques, cryptorchidism, and corneal opacities. In congenital ichthyosiform erythroderma, lipoxygenase proteins ALOXE3 and ALOX12B are mutated, affecting free fatty acid metabolism.[1] This affects the intercellular lipid bilayers and water permeability. Patients present with fine scale and collodion membranes in infancy (See Table 1).

TABLE 1.

Acquired and Inherited Diseases Associated With Defects in Stratum Corneum Proteins	
Acquired Diseases	**Cause**
Irritant contact dermatitis	Denatured proteins and loss of intercellular lipids from
Aging	Loss of intercellular lipids, desmosomes, and natural n telomere shortening and chronic actinic damage
Inherited Diseases	**Mutation**
Atopic dermatitis	FLG, diminished function in filaggrin
Ichthyosis vulgaris	FLG, loss of function in filaggrin
Lamellar ichthyosis	Transglutaminase-1, defective cornification
X-linked ichthyosis	Steroid sulfatase, defective lamellar granules
Congenital ichthyosiform erythroderma	ALOXE3/ALOX12B, defective fatty acid metabolism
Ichthyosis with confetti	Keratin 10, cytoskeletal instability
Darier disease	ATP2A2, loss of calcium gradient
Hailey-Hailey Disease	ATP2C1, Loss of Calcium Gradient
Epidermolysis bullosa simplex	Keratin 5/14, cytoskeletal instability, basal layer
Epidermolytic hyperkeratosis	Keratin 1/10, cytoskeletal instability, spinous layer
Ichthyosis bullosa of Siemens	Keratin 2, cytoskeletal instability, granular layer
Palmoplantar epidermolytic hypkeratosis of Vörner	Keratin 9, cytoskeletal instability in acral surfaces

Moisturizers, Basic Concepts

As opposed to irritants, moisturizers function to enhance the barrier and moisturization properties of the stratum corneum. We will only introduce the basic concepts here as a more detailed discussion will be the focus of the next article. Moisturizers are chemicals that increase the water content of the stratum corneum.[2] There are three classes of chemical ingredients that can serve as moisturizers: occlusives, humectants, and emollients.[2,13] Often these chemicals are either the same as or similar to natural components in the stratum corneum.

Occlusive agents serve to reduce TEWL by forming a hydrophobic barrier film over the skin surface and prevent evaporation of water from the stratum corneum. Examples include petrolatum, lanolin, oils, and beeswax. Humectant agents attract water and moisture. When present on the skin, water from the dermis is absorbed into the epidermis. Minimal water is absorbed from the environment.[2] This serves to increase the cornecyte water content and promote adequate desquamation of the surface cornecytes through water-sensitive desmosome degradation. Examples include free amino acids, lactic acids, alpha hydroxyacids, urea, propylene glycol, and glycerine. Many of these agents are the same molecules that form the natural moisturizing factors. The third class, emollients, are chemicals that improve the “feel” of the skin by filling the spaces in between corneocytes and also provide what has been termed “skin slip” or lubricity, imparting a sense of softness and plasticity.[13] These can also have occlusive or humectant properties as well and tend to be composed of long chain fatty acids or fatty alcohols.[13,14]

Moisturizers also contain other ingredients in addition to the three main classes. “Barrier-repairing” agents, which are lipids that are similar to those found in the intercellular stacked lipid bilayers.[2] These products include various combinations of ceramide, free fatty acids, and cholesterol and serve to restore the permeability function of the barrier. The water content of a moisturizer will vary depending on the formulation and vehicle. Lotions contain up to 65-85% water and while this can serve as a temporary hydrating agent, the main purpose of the high water content is to solubilize and disperse the chemical ingredients as well as promote evaporation of the moisturizer away from the skin surface. Creams have a lower water content compared to lotions and ointments have minimal to no water content.

SUMMARY

Keratinocytes undergo numerous changes as they migrate from the basal layer to the stratum corneum, where they are ultimately desquamated. This process requires the keratin cytoskeletal proteins and a calcium gradient in order to form the desmosomal connections, cornified envelopes, filaggrin, and lipids needed to form the stratum corneum. At the end of differentiation, the stratum corneum is formed with keratinocytes forming a physical scaffold

and the natural moisturizing factors and stacked lipid bilayers forming the intercellular mortar. This unique structure imparts both a physical and permeability barrier against the external environment and water loss. In order to maintain moisture homeostasis, the stratum corneum can produce more natural moisturization factor and reduce the rate of desquamation. Irritant chemicals can remove moisture, moisturizing factors, and lipids leading to dermatitis and skin disease. Internally, defects in stratum corneum proteins and lipids can also produce a faulty barrier leading to skin pathology. To help repair these defects and restore water content, moisturizers can be used to both prevent water loss to the environment and absorb water from the dermis by utilizing ingredients that mimic natural stratum corneum components.

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DISCLOSURES

Dr. Lee has no conflict of interest to declare. Dr. Friedman indicates he has served as a Consultant for Aveeno, Exeltis, Glossier, and Galderma.

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