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PART IV Cosmeceutical Myths

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The Stratum Corneum: A Functional Barrier for Cosmeceuticals

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SUMMARY AND KEY FEATURES

- The stratum corneum (SC) is the outermost layer of the epidermis. Interfacing with the outside world, it is responsible for protecting and maintaining an internal environment fit for life and responding to the insults and challenges of the external environment.
- The SC acts as the skin's barrier through several interrelated barrier functions: the permeability barrier, mechanical barrier, antimicrobial barrier, antioxidant barrier, and photoprotective barrier. These barrier functions are dynamic and integrated together to maintain a homeostasis for proper barrier structure, function, and renewal.
- The SC is responsible for regulating water and maintaining an environment for proper cellular function. Disease state or environmental influence can alter the composition or development of the SC, resulting in a weaker barrier, lower hydration, and dry, dehydrated skin.
- Due to its direct link with the visual appearance and mechanical properties of skin, the barrier is a relevant target for cosmeceuticals that impart hydration, barrier repair desquamation, and antioxidant protection. The barrier can also be an obstacle for cosmeceuticals and treatments intended to penetrate deeper into the epidermis.

See Videos 1.1 and 1.2.

INTRODUCTION

The science of cosmeceuticals is expanding to consider the stratum corneum (SC) as not just a barrier for actives that act deeper within the skin, but also a target for cosmeceutical activity. The dynamic and adaptive nature of the SC provides an integrated network of functions that are implicated in overall skin health and appearance. This perspective offers a new opportunity to consider the role of cosmeceuticals in supporting the skin's natural protective functions and complementing both aesthetic and medical treatments and procedures.

FUNCTIONS OF THE EPIDERMAL SKIN BARRIER

Homeostasis and Protection Centralized in the Stratum Corneum

As the outermost structure of the epidermis, the SC is the body's interface with the outside world. It is responsible for maintaining an internal environment fit for life while protecting and responding to the insults and challenges of the external environment. This requires the proper functioning of several integrated protective functions and a barrier homeostasis

TABLE 1.1 The Barrier Functions of the Stratum Corneum and the Various Mechanisms Implicated in Maintaining Barrier Homeostasis

Barrier Functions of the Stratum Corneum	Mechanisms for Barrier Homeostasis
Permeability barrier	Keratinocyte differentiation and corneocyte maturation
Mechanical barrier	Desquamation
Antimicrobial barrier	Lipid synthesis
Antioxidant barrier	pH and calcium gradients
Photoprotective barrier	Environment and physiologic factors

carefully maintained by highly regulated mechanisms (Table 1.1).

Integrated and Dynamic Functions

Permeability Barrier

The most often referenced and perceived core function of the SC is to act as a barrier to the transcutaneous movement of water and other molecules. The permeability barrier function of the SC regulates the loss of water from within and the penetration of exogenous molecules including allergens, irritants, pathogens, and topically applied bioactive agents. The highly organized lamellar lipid membranes of the SC are designed to provide selective transport of water and electrolytes to maintain the proper level of hydration for tissue plasticity and enzymatic functions. Many of the other barrier functions of the SC rely on the integrity and proper functioning of the permeability barrier. A disrupted skin barrier, whether acute or chronic, permits water loss and insult from foreign materials, triggering a cascade of reactions and processes to repair the barrier and reinstate balance.

Mechanical Barrier

The composition and architecture of the SC, described in more detail shortly, is often likened to a brick wall. The corneocyte cells, acting as the "bricks," and the highly organized and cross-linked lipid "mortar" create a framework that provides both strength and resilience against mechanical shear. Additionally, this brick wall–like arrangement contributes to a necessary rigidity of the skin. Typical of the barrier, a water-dependent balance is required to maintain the appropriate degree of stiffness and plasticity.

Antimicrobial Barrier

Beyond acting as a physical barrier to permeation of pathogens, the SC has multiple mechanisms to limit microbial colonization. A healthy skin microbiome, the microflora that inhabit the skin's surface, limits the overgrowth of pathogenic microorganisms by outcompeting for nutrients and producing select antimicrobial agents. Sweat and sebum give the skin a low pH film, referred to as the acid mantel, creating an environment that favors a healthy microbiome and prevents the growth of pathogenic microbes. The lipid components of the SC have inherent antimicrobial properties, while the epidermis produces antimicrobial peptides (AMPs) to support the skin's innate immune function.

Antioxidant and Photoprotective Barriers

In direct contact with the environment, the SC is the primary barrier to atmospheric prooxidants including pollution and ultraviolet (UV) radiation. The skin has an intrinsic antioxidant defense network that includes lipophilic antioxidants (e.g., α-tocopherol), hydrophilic antioxidants (e.g., ascorbic acid and glutathione), and antioxidant enzymes (e.g., superoxide dismutase and catalase). This network is most abundant in the epidermis but is also found in the SC protecting the lipids and proteins of the skin barrier. The skin enters a state of oxidative stress when reactive oxidative species formation exceeds the antioxidant defense ability of the affected cells which results in damaged lipids, proteins, and DNA.

The SC offers further protection from UV radiation through melanin. Formed in melanocytes and transferred into skin cells in the lower layers of the epidermis, the melanin persists in the cells of the SC. These melanin particles scatter and absorb UV rays to protect the macromolecules of the skin from direct or indirect UV damage.

Structural and Functional Components of the Epidermal Barrier

The SC is a dynamic layer, continually renewing from within and shedding from the surface. The barrier functions of the SC are reliant on the proper formation, maturation, and composition of the many structural and functional components of the epidermal barrier.

Keratinocytes and Corneocytes

Epidermal cells begin as keratinocytes formed from the anchored and proliferating basal cells at the base of the living epidermis (Fig. 1.1). As basal cells divide, new keratinocyte cells push older ones up toward the surface of the skin through the spinous layer and then the granular layer. As keratinocytes move up through the epidermis, they undergo a series of well-orchestrated maturation steps called epidermal differentiation. The final step in differentiation is called keratinization and results in the corneocytes that form the SC. In this step, the living keratinocyte cells from the middle layers of the epidermis flatten and produce large amounts of keratin and keratohyalin while their nuclei and other cell organelles disintegrate.

Corneocytes, the structural bricks of the SC, continue to evolve as they move upward through the layers of the SC, becoming flatter and more resilient and giving the SC mechanical strength, stiffness, and elasticity.

Eventually, corneocytes are shed through desquamation, a controlled and orderly process in which individual or small groups of corneocytes detach from their neighboring cells. In the deeper, denser layers of the SC, corneocytes are anchored together by proteinaceous corneodesmosomes. As they reach the peripheral layers, these corneodesmosomes are degraded in an enzymatic process catalyzed by serine proteases to allow for desquamation. The presence of water is critical for SC elasticity and corneodesmosomes breakdown. In low-humidity environments or dry skin conditions, the corneocytes lack moisture and become overly rigid while the activity of the desquamatory enzymes is reduced, leading to visible, white flakes on the skin's surface. This reinforces the importance of skin hydration and the maintenance of the water content in the skin not only for skin suppleness but also for the enzymatic reactions that are relevant for proper SC function.

Intercellular Lipids

Between the corneocytes in the SC is a cement made of highly ordered intercellular lipids (Fig. 1.2). Intercellular lipid synthesis begins in the granular layer at the top of the viable epidermis. Small lamellar bodies form within the cytoplasm of the keratinocytes and are packed with multilayer stacks of SC lipid precursors. Upon reaching the SC, the lamellar bodies release their stacks of polar lipids into the extracellular space where enzymes process them into the nonpolar lipids of the SC.

The lipids of the SC are predominantly ceramides (50%), cholesterol (25%), and free fatty acids (10–20%) present in equimolar amounts. These intercellular lipids self-assemble into stacked bilayers in a lamellar organization that provides the previously described permeability barrier function of the SC. The amount and ratio

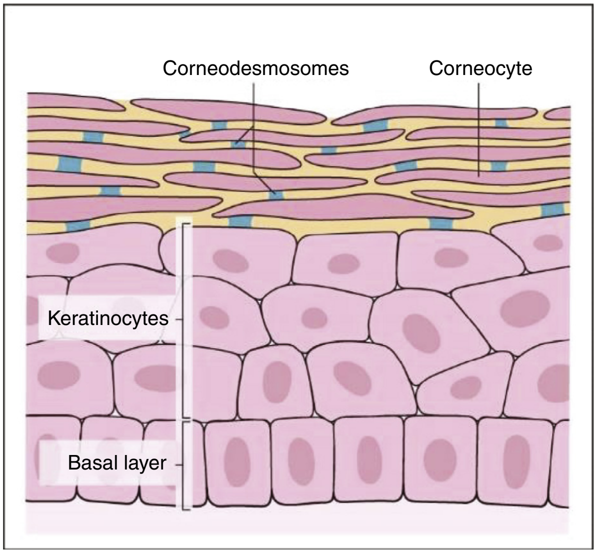

Figure 1.1 The epidermal layers of keratinocyte formation, differentiation, and cornification distinguished by cell morphology.

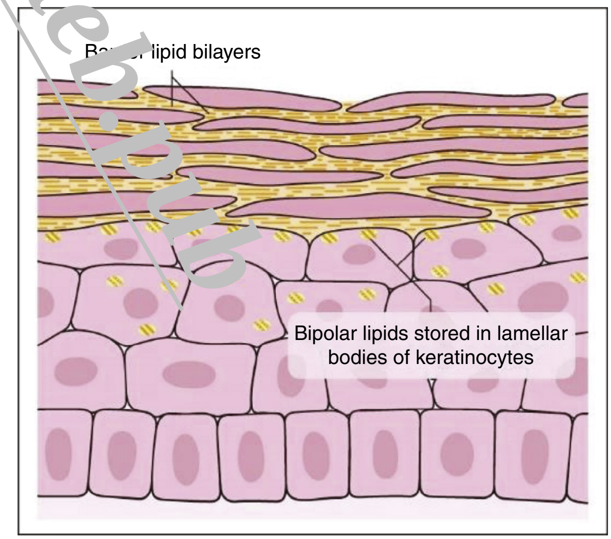

Figure 1.2 Intercellular barrier lipids, beginning as bipolar lipids within the lamellar bodies of keratinocytes, form stacked bilayers between corneocyte cells acting as a cement and barrier for the diffusion of water.

of lipids is essential for proper organization of the lipid bilayers, and any perturbation to this results in a disruption in permeability barrier function. Thus barrier lipids—particularly ceramides, which are a species of lipid characterized by a sphingoid base chain bound to a fatty acid chain—play an essential role in the water retention capacity and overall condition of the skin.

Cornified Cell Envelope

The cornified envelope (CE) is a protein-lipid composite that surrounds each corneocyte, giving a structural integrity to each cell and providing a scaffolding for the intercellular lipid bilayers. In this way the CE is critical to both the mechanical and permeability barrier functions of the SC. During the terminal differentiation process of keratinocytes, enzymes cross-link special proteins, including involucrin and loricrin, to form the insoluble, tough CE in place of the cell's plasma membrane. Covalently bound to the cross-linked proteins is a specific type of ceramide with a sphingoid base chain bound to an omega-hydroxy acid. The hydroxyl groups on these omega-hydroxyceramides form an ester linkage with the amino groups of proteins of the cornified cell envelope to form a lipophilic monolayer around the surface of each cell. The lipid envelopes serve as the scaffolding for the free lamellar lipids to assemble around.

Natural Moisturizing Factor

Bound within corneocytes by the CE are a group of humectant compounds collectively referred to as natural moisturizing factor (NMF) (Table 1.2). As humectants, which attract and hold water, NMFs are responsible for maintaining the hydration levels of the outermost layers of the SC for plasticity, enzyme-mediated desquamation, and proper barrier function. NMF is predominantly composed of amino acids and their derivatives including urocanic acid and pyrrolidone carboxylic acid (PCA). The origin of these amino acids is the proteolysis of filaggrin (filament aggregating protein) (Fig. 1.3). Filaggrin begins as profilaggrin in the keratinocytes of the granular layer. It is then processed into filaggrin in the lower SC, where it bundles keratin in the cells and helps in their differentiation to flat, compact corneocytes. Once this role is complete, filaggrin degrades into amino acids and their derivatives, forming the dominant component of NMF in the superficial layers of the SC. In addition to amino acids, glycerol, urea, and lactates are

TABLE 1.2 The Components of Natural Moisturizing Factor Responsible for Maintaining Hydration Levels in the Superficial Stratum Corneum

Components of Natural Moisturizing Factor
Free amino acids and urocanic acid
Pyrrolidone carboxylic acid
Lactate
Sugars, organic acids, peptides, and unidentified materials
Urea
Chloride
Sodium
Potassium
Ammonia, uric acid, glucosamine, and creatine
Calcium
Magnesium
Phosphate
Citrate and formate
Glycerol
Hyaluronic acid

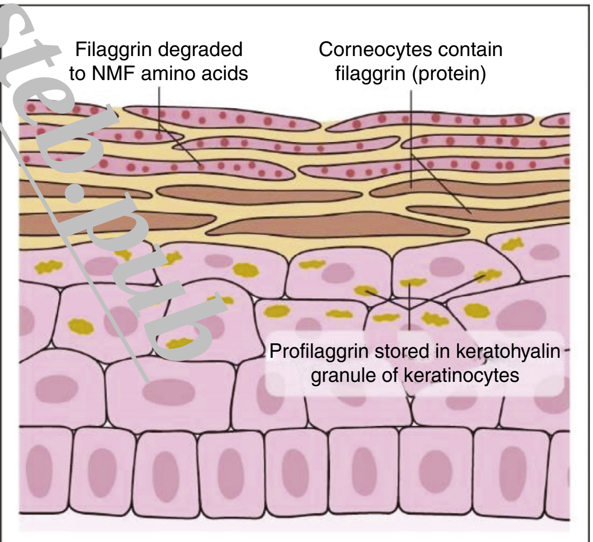

Figure 1.3 Natural moisturizing factor begins as profilaggrin in the cells of the granular layer, then evolves to filaggrin in the lower stratum corneum where it bundles corneocytes, and then finally degrades to amino acids within the terminally differentiated corneocytes. *NMF*, Natural moisturizing factor.