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Epidermal barrier function in dry, flaky and sensitive skin: A narrative review

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Abstract

The stratum corneum (SC)—the outermost layer of the epidermis—is the principal permeability and protective barrier of the skin. Different components of the SC, including corneocytes, natural moisturizing factor, a variety of enzymes and their inhibitors, antimicrobial peptides and lipids, work interactively to maintain barrier function. The main barrier properties of the SC are the limitation of water loss and the prevention of infection and contact with potentially harmful exogenous factors. Although the SC functions consistently as a protective barrier throughout the body, variations in functions and morphology occur across body sites with age and skin type. Healthy SC function also depends on the interplay between the chemosensory barrier, the skin's microbiome and the innate immune system. Dysregulation of SC barrier function can lead to the development of skin disorders, such as dry, flaky or sensitive skin, but the complete underlying pathophysiology of these are not fully understood. This review provides insight into the current literature and emerging themes related to epidermal barrier changes that occur in the context of dry, flaky and sensitive skin. Additional studies are needed to further elucidate the underlying aetiology of dry, flaky and sensitive skin and to provide tailored treatment.

INTRODUCTION

The skin acts as a barrier by simultaneously allowing for and protecting from environmental exchange.[1] The stratum corneum (SC), the outermost epidermal layer, is the principal permeability and protective barrier.[2] SC limits water loss and prevents both infection and contact with potentially harmful exogenous factors.[1] The SC mainly consists of terminally differentiated keratinocytes called corneocytes, corneodesmosomes together with tight junction proteins, protein-degradation products, such as natural moisturizing factor (NMF), and other moisturizing molecules.[3] The corneocytes closely interact with a continuous bi-lamellar matrix of hexagonal and orthorhombically packed lipid lamellae that support the epidermal barrier and regulate water-binding homeostasis.[3] In addition, a variety of enzymes, protease inhibitors, antimicrobial peptides and antimicrobial lipids contribute to homeostasis of SC barrier function.[1] These components interact to maintain SC integrity.[2] Although SC protection functions consistently across the body, anatomical variations do occur; for example, subtle differences have been found in measurements of epidermal barrier function, SC hydration and surface pH between the arm, forearm and cheek in subjects with normal skin.[4,5] Moreover, subtle zonal differences in facial transepidermal water loss (TEWL), SC hydration and skin surface pH are reported, including differences across ethnic groups.[6] SC function also depends on the interplay between the chemosensory barrier, the epidermal microbiome and the innate immune system[1] and appears to be related to epidermal microbiome diversity.[7] Dysregulation of skin barrier function can induce an inflammatory cascade and potentially skin disorders,[1] such as dry, flaky or sensitive skin.

Dry and sensitive skin phenotypes are distinct yet common conditions partially associated with SC

dysfunction.[8,9] Although sensitive skin and dry skin are related to epidermal functions and can both occur in the same individual,[9,10] these conditions are defined and discussed separately in the literature. In this paper, the term dry skin is used to describe a spectrum from visually dry skin to rough, dry and potentially flaky skin that may also have scales or small cracks.

People with dry skin present a range of symptoms from mild scaling and acute irritation to severe fissures, pain and superinfection.[8,11] Between 26% and 60% of adults report dry skin,[8,11,12] with higher prevalence in individuals with darker skin as well as in older individuals.[11,13,14] Although dry skin can affect the entire body, it is more frequently associated with areas containing fewer sebaceous glands (e.g. the lower legs, forearms, dorsum of the hands and feet).[8] Compared with simple dehydrated skin, impaired SC function, specifically the depletion of SC lipids and protease imbalance, contributes to the underlying aetiology of dry skin.[8,15,16] Additionally, skin inflammation, which can be both a cause and a consequence of dry skin, often drives a vicious cycle of further barrier alteration[8,15,17] and can induce pruritus.[8]

Sensitive skin was defined in 2017 by expert consensus as a syndrome characterized by 'the occurrence of unpleasant sensations (stinging, burning, pain, pruritus, and tingling sensations) in response to stimuli that normally should not provoke such sensations' and that cannot be explained by lesions associated with any skin disease.[10] Approximately 50%–70% of adults report some degree of sensitive skin,[18] which can affect all body areas, particularly the face.[10] Although the underlying pathophysiology of sensitive skin has not been definitively determined, its origin appears multifactorial, with neurosensory dysfunction (possibly a subtype of small-fibre neuropathy) considered a key mechanism.[10,19]

In this review, we discuss current literature and emerging themes related to changes to the SC and the epidermal barrier that occur in the context of dry and/or sensitive skin in adults. We also consider important research gaps that, if addressed, may allow the refinement of treatment options for dry and sensitive skin.

SC lipids

The SC has a complex lipid composition of ceramides, cholesterol, fatty acids and cholesterol sulphate.[3] These components are organized as lamellar gel phases in which the lipid chains are orthorhombically or hexagonally packed together with amorphous domains, depending on body site and SC depth.[3,20] SC lipids are formed during keratinocyte differentiation followed by co-secretion of enzymes and other factors in lamellar bodies at the stratum granulosum/SC interface.[21] SC ceramides are essential for competent barrier function.[22] Most recently, >1300 unbound ceramide species and >250 covalently bound species have been described.[22] Ceramide nomenclature is described in Figure 1.

SC free fatty acids (FFAs) are primarily long-chain fatty acids with chain lengths of 22 to 26 carbon atoms; however,

chain lengths may vary.[23,24] Shorter FFA chains may enhance conformational disordering of SC FFAs and influence epidermal barrier permeability.[23] Ultimately, it is a combination of carbon chain lengths of SC ceramides and FFAs as well as the size of polar head groups together with cholesterol that determines the organization of SC lipids and thereby epidermal barrier function.[3] However, recent advancements—including more sensitive detection methods—provide a broader understanding of the role and diversity of SC lipids and their functions, particularly in relation to epidermal barrier dysfunction.[3,22,25]

SC lipid levels vary across anatomical sites and with age.[3] For example, ceramides vary by level and type in the face and are higher in the face than in the leg and hand.[26–28] Additionally, SC lipid content and organization change with increasing age[29]; one example is a reduction in ceramide EOS (Figure 1).[26] Reduced ceramide levels were also observed in the winter months.[26] Similar changes were detected in corneocyte-bound ceramides.[30]

SC lipid disorganization and altered epidermal barrier function are involved in several skin diseases and disorders, including dry skin and sensitive skin.[21,31] Common SC lipid alterations in several skin diseases include decreases in FFA chain length, ceramide composition, ceramide chain lengths and total ceramide concentration.[3,21] Although our understanding of the complexity of changes in intercellular and covalently bound SC ceramide composition is more pronounced in dermatological diseases,[21,32] changes in lipids also occur in dry skin.[3] For example, changes in epidermal barrier function and lipid organization were observed in surfactant and soap-induced dry skin.[33,34] Decreased levels and specific classes of ceramides are characteristic of dry skin.[3,35] Sensitive skin is associated with decreased SC ceramide levels in facial skin.[4,36] However, differences in the complexity of the compositions are not known in sensitive skin. Additional research, especially on the composition of intercellular and covalently bound ceramides and their molecular architecture, is needed in sensitive skin.

NMF and endogenous humectants

NMFs include a variety of compounds, in particular free amino acids, pyrrolidone carboxylic and urocanic acids, hyaluronic acid and glycerol.[2] These components support epidermal barrier homeostasis by binding and preserving water in the SC layer.[2,37,38] NMF levels correlate with corneocyte maturation and conformation[39,40] and regulate *Staphylococcus aureus* adhesion to the SC in subjects with atopic skin conditions.[41] The levels of filaggrin and corneocyte maturation are inversely related to greater quantities of NMF associated with mature corneocytes.[40] The majority of amino acid components of NMF are formed by proteolysis of filaggrin (Figure 2), a protein encoded by the profilaggrin gene, which plays an important role in corneocyte flattening and SC barrier formation.[42] Urocanic acid is formed by the deamination of histidine following filaggrin proteolysis and

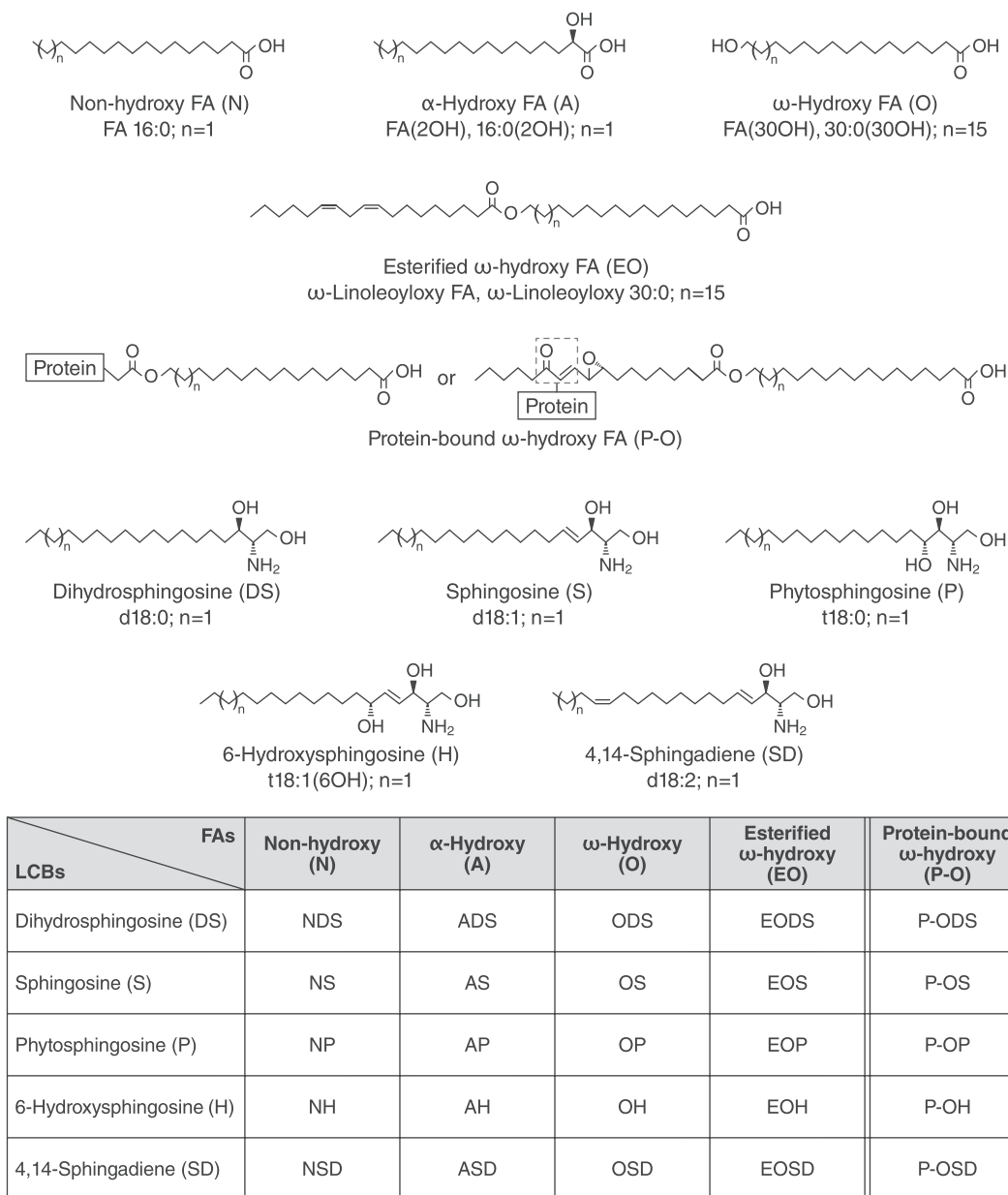|	FAs	Non-hydroxy (N)	α-Hydroxy (A)	ω-Hydroxy (O)	Esterified ω-hydroxy (EO)	Protein-bound ω-hydroxy (P-O)
LCBs						
Dihydrosphingosine (DS)		NDS	ADS	ODS	EODS	P-ODS
Sphingosine (S)		NS	AS	OS	EOS	P-OS
Phytosphingosine (P)		NP	AP	OP	EOP	P-OP
6-Hydroxysphingosine (H)		NH	AH	OH	EOH	P-OH
4,14-Sphingadiene (SD)		NSD	ASD	OSD	EOSD	P-OSD

FIGURE 1 Human ceramide nomenclature according to the structural composition of fatty acids (FAs) and long-chain bases (LCBs). Each compound name is listed below each structure, with abbreviations recommended by LIPID MAPS (https://www.lipidmaps.org) under each compound name and each number corresponding to an n value of 1 or 15. There are two proposed models for the binding of protein-bound ceramides to corneocyte envelope proteins: binding occurs via (1) the ω-hydroxyl group of the fatty acid moiety after release of the modified linoleic acid moiety[90] and (2) the enone of the modified linoleic acid moiety (dotted box).[91] The inset depicts the notation of ceramide classes, which are designated using a combination of the abbreviations for fatty acid and long-chain base types. Figure adapted with permission from Suzuki M, et al. *J Lipid Res.* 2022;63(7):100235.

2-pyrrolidone carboxylic acid is formed from glutamine and glutamic acid.[42]

Reduced levels of NMF may be related to filaggrin synthesis and/or reductions in filaggrinolysis, evidence associated with profilaggrin gene copy number variations and loss-of-function mutations and skin abnormalities.[42–44] The human profilaggrin allele contains 10, 11, or 12 profilaggrin repeats, each connected by a conserved linker sequence.[42,45] Ginger et al identified the relationship between increased profilaggrin repeats (ie, 12 vs 10 profilaggrin gene repeats) and a reduced risk of dry skin.[46] A case–control study of paediatric subjects found that those with 2 alleles containing 12 profilaggrin gene repeats had a reduced risk of developing atopic dermatitis (AD) compared with subjects with 2 alleles containing 10 profilaggrin gene repeats.[47] Loss-of-function mutations in the profilaggrin gene are recognized as the cause of ichthyosis vulgaris and increase the risk of developing AD and allergies.[42,44,48,49]

Dry skin is also associated with lower NMF levels.[50,51] Like SC lipids, NMF levels also vary seasonally, with ageing and by anatomical region (e.g. NMF levels are reduced in the cheek but elevated in the hand during winter).[52] Although
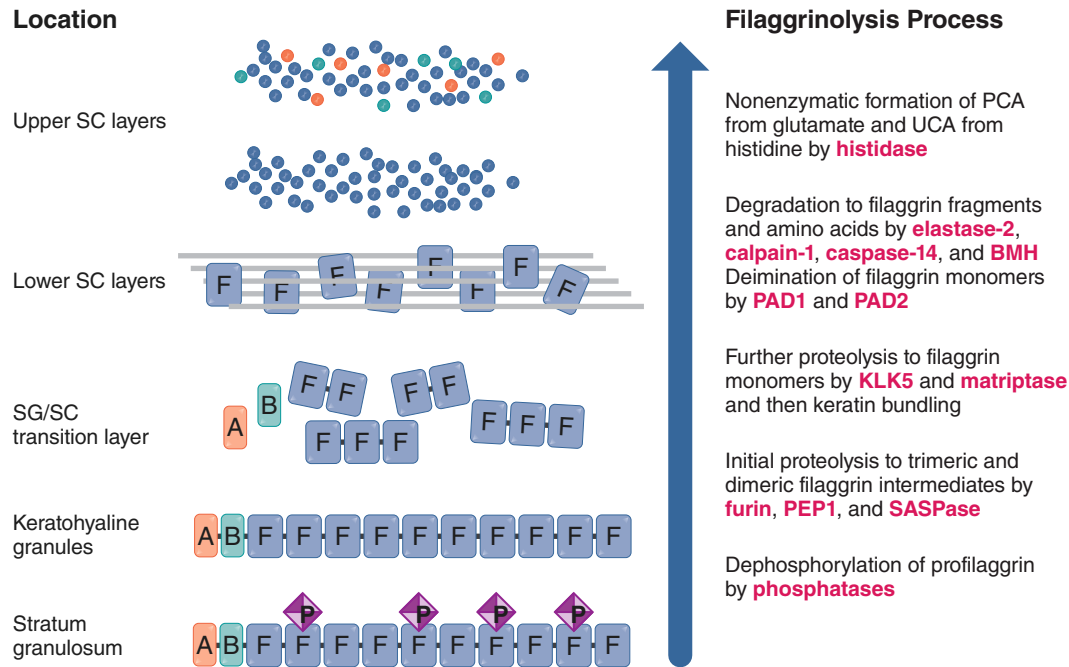
FIGURE 2 The process of filaggrinolysis during terminal differentiation leading to NMF. BMH, bleomycin hydrolase; KLK, kallikrein-related peptidase; NMF, natural moisturizing factor; PAD, peptidylarginine deiminase; PCA, 2-pyrrolidone-5-carboxylic acid; PEP, profilaggrin endopeptidase; SASPase, skin aspartic protease; SC, stratum corneum; SG, stratum granulosum; UCA, urocanic acid. Figure adapted with permission from Rawlings AV. *Br J Dermatol* 2014;171(suppl 3):19–28.
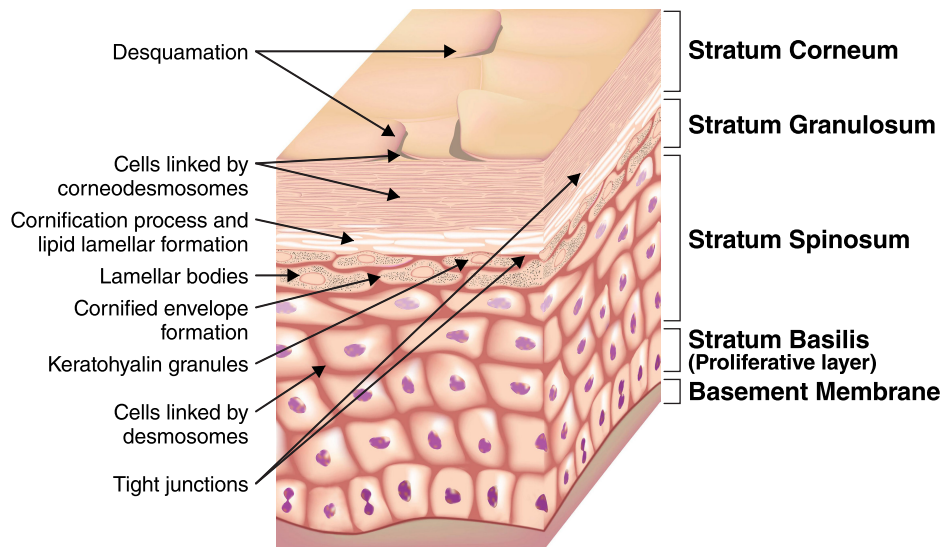

FIGURE 3 Schematic depiction of the epidermis showing corneocyte maturation and desquamation. Figure adapted with permission from Rawlings AV, et al. *J Invest Dermatol.* 1994;103(5):731–741 and Harding CR, et al. *Int J Cosmet Sci.* 2003;25(4):157–167.

evidence suggests an association between NMF levels and dry skin, little is known about NMF levels in sensitive skin. Only one study showed reduced pyrrolidone carboxylic acid levels in capsaicin-sensitive subjects vs a non-capsaicin-sensitive control group, and the control group demonstrated reduced bleomycin hydrolase activities vs the capsaicin-sensitive group; similar observations were made in dry and atopic skin conditions.[53] Thus, there is a need for additional research on filaggrin, filaggrin metabolism and NMF composition in sensitive skin.

Corneocyte maturation, Corneodesmolysis and desquamation

The integrity of the SC depends on coordinated and tightly regulated differentiation, corneocyte maturation, and coordinated corneocyte desquamation (Figure 3).[54] Corneodesmosomes are the major components responsible for the cell–cell adhesion and connectivity between corneocytes, supporting the 'brick-and-mortar' arrangement of the SC.[54–56] Non-peripheral corneodesmosomes, those found

in the central portions of corneocyte surfaces, are present in the deeper part of the SC and are degraded toward the surface of the SC as corneocytes mature; peripheral corneodesmosomes, those found on the peripheral edges of the corneocytes, ultimately are degraded during desquamation, except on the face and in plantar tissues, where they both degrade simultaneously.[55,57]

Corneodesmosome abnormalities can result in premature corneocyte shedding (hyperdesquamation), potentially leading to epidermal barrier dysfunction and inflammation.[54] Corneocyte desquamation is an essential component of SC homeostasis and is defined by continuous shedding at the surface of the skin.[54] Regulators of corneocyte desquamation include kallikrein-related peptidases (KLKs), such as KLK5, KLK7 and KLK14, and cathepsins that are controlled by a variety of protease inhibitors.[55,58] Frequently, increased protease levels are found in the skin of individuals with AD, which has been hypothesized to negatively affect barrier function.[54] SC trypsin-like enzyme levels and tryptase, plasmin and urokinase levels correlated positively with increasing TEWL.[59] Increases were also observed in eczematous skin and in particular, mass levels of plasmin and KLK11.[16,60]

Alterations in desquamation can lead to the persistence of corneodesmosomes in the outer layer of the SC, which is a clinical characteristic of hyperkeratotic and dry skin.[33,61,62] The number of corneodesmosomes and levels of desmoglein-1 and corneodesmosin (modulators of corneodesmosome adhesion) are higher in dry skin than in normal skin.[33,63] In dry skin, the SC is approximately 30% thicker than in healthy skin.[64] Levels of other enzymes involved in corneocyte maturation, such as transglutaminase, are also decreased in dry skin.[65] More recently, additional enzymes involved in the final steps of binding ceramides to the cornified envelope (Figure 4) have been shown to be reduced in dry photodamaged facial skin.[66–69]

Despite our understanding of corneocyte maturation and dry skin, less is known about corneocyte maturation and desquamation in sensitive skin. Sensitive skin is associated with an increased number of immature fragile envelopes and reduced transglutaminase activity.[53,70] KLK5, an enzyme involved in desquamation, is also decreased in subjects with sensitive skin.[71] Together, these data demonstrate a need for further research on corneocyte maturation, desquamation and the regulation of processing enzymes in sensitive skin.

Immunologic, neurosensory and skin microbiome considerations in dry skin and sensitive skin

In the past decades, the SC has been recognized as an evolving and responsive compartment (Figure 5).[65] One of the characteristics of the SC is its inherent immunologic
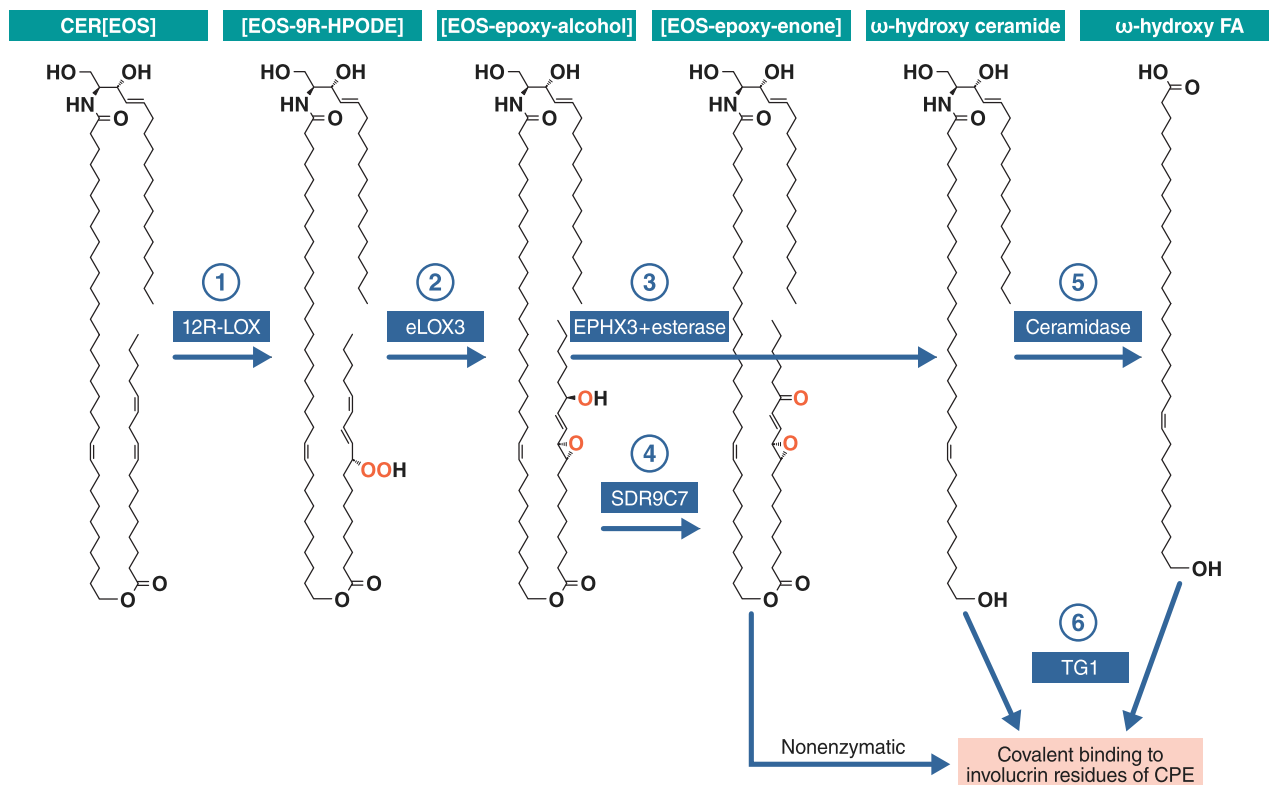

FIGURE 4 Schematic of the enzyme cascade involved in cornified envelope formation: (1) oxygenation, (2) isomerization, (3) ester cleavage, (4), dehydrogenation, (5) deamidation and (6) protein binding. 12R-LOX, 12R-lipoxygenase; CER, ceramide; CPE, corneocyte protein envelope; eLOX3, epidermal lipoxygenase-3; EPHX3, epoxide hydrolase 3; FA, fatty acid; SDR9C7, short-chain dehydrogenase/reductase family 9C member 7; TG1, transglutaminase 1. Figure adapted with permission from Rawlings AV, et al. *Int J Cosmet Sci.* 2022;44(2):166–176.
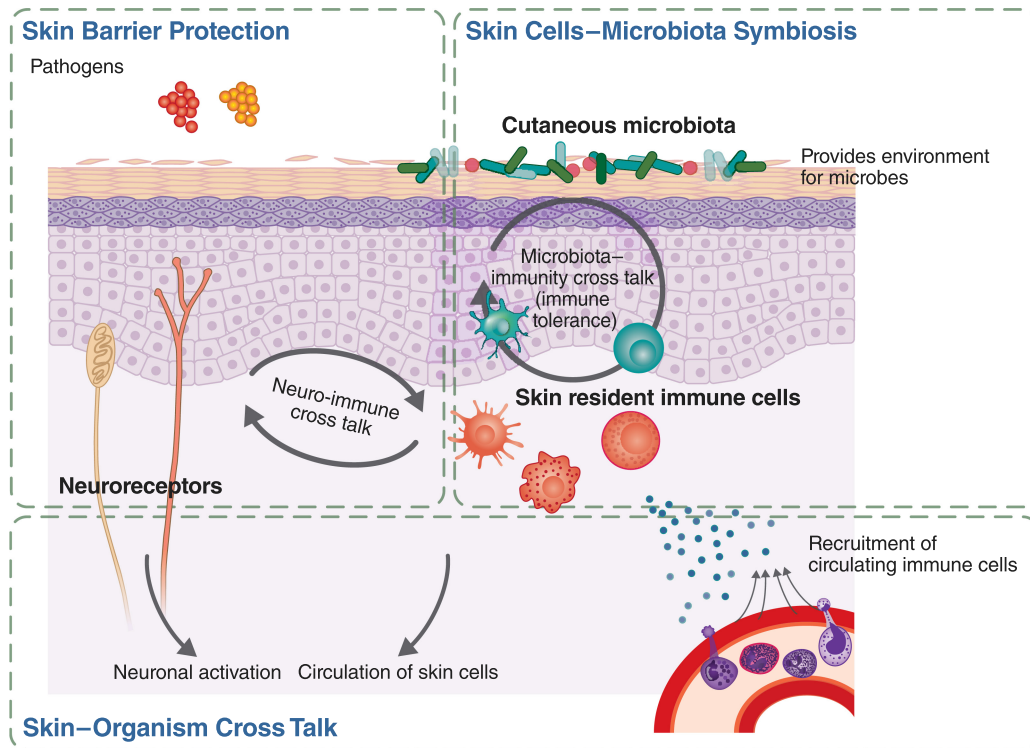
FIGURE 5 Schematic of the cross talk that occurs among innate systems of the epidermis: microbiological, immunological and sensory systems. Figure adapted with permission from Lefèvre-Utile A, et al. *Int J Mol Sci*. 2021;22(21):11676.

competence, which contributes to epidermal barrier repair and homeostasis. Resident epidermal immune cells sense and induce response signals to external pathogens, participating in a large feedback network to maintain a functional SC.[1,72] A dysfunctional epidermal barrier, as seen in adults with dry skin and sensitive skin, can facilitate the penetration of allergens, irritants and pathogens, activating the innate immune response.[1,73] Although inflammation may be promoted by epidermal barrier impairment, it is not thought to be the underlying mechanism of sensitive skin.[73] In biopsies from women with sensitive skin, no changes in the expression of inflammatory markers (eg, transient receptor potential vanilloid subtype 1 [TRPV1] and nuclear factor-κB) were detectable vs healthy skin,[73] with the exception of increased nerve growth factor[74] and prostaglandin E2[75] levels reported in sensitive skin. In an analysis of RNA transcripts from sensitive skin, a C-C motif chemokine ligand 17 as well as interferon-γ were elevated, whereas genes for the olfactory receptor were downregulated.[76] Similarly, Yang et al.[77] found an upregulation of the PI3K-Akt–mTOR signalling pathway in subjects with sensitive skin. Lower levels of adiponectin and the gene for activin A receptor type 1C were detected in subjects with sensitive skin.[78,79] These factors may contribute to altered SC differentiation and response status in sensitive skin. Additional research should explore the immune system in individuals with dry skin and sensitive skin.

The epidermis exhibits sensory functions. Epidermal nerves are modulated by environmental (e.g. exposure to irritants), physical, chemical and microbial stimuli.[1] Neuronal dysfunction is associated with sensitive skin.[53] Skin biopsies

revealed a reduced density of intraepidermal small fibre and nerve fibre reactivity to calcitonin gene-related peptides in sensitive skin.[70,73] Furthermore, a reduced chemosensory threshold was found in capsaicin-sensitive subjects.[53] Taken together, the current data support the hypothesis of sensitive skin as a small-fibre neuropathy.[19,73]

The immune and sensory properties of the epidermal barrier are also closely linked to its microbiome. The skin microbiome consists of cutaneous bacteria, fungi and viruses that participate in cross talk with the immune system and support functional epidermal homeostasis.[1] Similar to the epidermal barrier, the broad and balanced skin microbiome protects against infection and pathogenic invasion from potentially harmful microbes.[80] Several factors contribute to the stability of the skin microbiome, including endogenous factors (e.g. sebum, sweat and hormones), age and immunologic factors as well as exogenous factors (e.g. environment and lifestyle).[80] The epidermal barrier is tightly regulated by cross talk among several innate systems, including the skin's immune system and microbiome.[1] Dysfunction in any one of these systems has an influence on the others and might interfere with the integrity of epidermal function.

Although skin microbiome knowledge has advanced in recent years for skin diseases,[81] little is known of the microbiome in dry and sensitive skin conditions. However, the impact of exogenous factors on the skin microbiome is established. The skin microbiome demonstrates specific patterns in hydrated areas and regions rich in sebum.[82–84] In the facial region, a specific relationship between sebum,

hydration levels and microbiome diversity has been shown.[85–88] Furthermore, skin care has shown to be of benefit both to microbiome and epidermal barrier function in a stress model and dry and flaky skin conditions.[7,89]

CONCLUSIONS

Healthy epidermal barrier function relies on multiple interconnected processes and components of the SC, including lipids, NMF, corneocyte maturation and desquamation, enzymatic activity, the immune system, epidermal nerve fibres, antimicrobial peptides/lipids and the skin microbiome. When epidermal barrier functions are negatively influenced, dry or sensitive skin can be induced or aggravated. The full picture of the underlying pathophysiology of sensitive skin remains under research. As demonstrated through this review, more is known about dry skin and epidermal barrier alterations than sensitive skin. The most recent discovery on sensitive and dry skin were related to epidermiological findings, microbiome, skin colour and lipid metabolism. However, additional studies are needed to enhance the understanding of the mechanisms behind sensitive skin to allow individualized treatment modalities. Furthermore, the relationship between sensitive skin and stratum corneum hydration homeostasis needs more research.

CONFLICT OF INTEREST STATEMENT
Ms Lachmann is a Galderma employee. Dr Rawlings, Dr Moore and Dr Lane have nothing to disclose; Dr Fluhr discloses that he has served in the past as a consultant for Galderma.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT
Not applicable.

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