

The stratum corneum: the rampart of the mammalian body

Koji Nishifuji* and Ji Seon Yoont†

*Department of Veterinary Medicine, Faculty of Agriculture, Tokyo University of Agriculture and Technology, Tokyo, Japan

†Department of Dermatology, College of Medicine, Seoul National University, Seoul, South Korea

Correspondence: Koji Nishifuji, Department of Veterinary Medicine, Faculty of Agriculture, Tokyo University of Agriculture and Technology, 3-5-8 Saiwai-cho, Fuchu, Tokyo 183-8509, Japan. E-mail: kojimail@cc.tuat.ac.jp

Background – The stratum corneum (SC) is the outermost region of the epidermis and plays key roles in cutaneous barrier function in mammals. The SC is composed of ‘bricks’, represented by flattened, protein-enriched corneocytes, and ‘mortar’, represented by intercellular lipid-enriched layers. As a result of this ‘bricks and mortar’ structure, the SC can be considered as a ‘rampart’ that encloses water and solutes essential for physiological homeostasis and that protects mammals from physical, chemical and biological assaults.

Structures and functions – The corneocyte cytoskeleton contains tight bundles of keratin intermediate filaments aggregated with filaggrin monomers, which are subsequently degraded into natural moisturizing compounds by various proteases, including caspase 14. A cornified cell envelope is formed on the inner surface of the corneocyte plasma membrane by transglutaminase-catalysed cross-linking of involucrin and loricrin. Ceramides form a lipid envelope by covalently binding to the cornified cell envelope, and extracellular lamellar lipids play an important role in permeability barrier function. Corneodesmosomes are the main adhesive structures in the SC and are degraded by certain serine proteases, such as kallikreins, during desquamation.

Clinical relevance – The roles of the different SC components, including the structural proteins in corneocytes, extracellular lipids and some proteins associated with lipid metabolism, have been investigated in genetically engineered mice and in naturally occurring hereditary skin diseases, such as ichthyosis, ichthyosis syndrome and atopic dermatitis in humans, cattle and dogs.

Introduction

The skin, which covers the entire body surface in mammals, is an anatomical and physiological barrier between the environment and the organism. The stratum corneum (SC) provides a barrier function for the skin. It is the outermost region of the epidermis and is composed of ‘bricks’ (i.e. flattened, protein-enriched corneocytes) and ‘mortar’ (i.e. intercellular lipid-enriched layers).¹ As a result of this ‘bricks and mortar’ structure, the SC in the mammalian skin can be considered as a ‘rampart’, which encloses ‘citizens’ (i.e. water and solutes) essential for physiological homeostasis and protects the ‘castle’ (i.e. the host) from physical, chemical and biological ‘assaults’.

Within corneocytes are tight bundles of keratin intermediate filaments aggregated with filaggrin (FLG) monomers to provide a flattened shape and mechanical strength to the cells.^{2–5} The cornified cell envelope is formed on the inner surface of the corneocyte plasma membrane and provides structural and mechanical integrity to the cells.^{6,7} Covalent binding of the lipid envelope to the cornified cell envelope proteins provides a scaffold for extracellular lipid lamellae (ELL), which are crucial for maintaining permeability barrier function.^{8,9} Various enzymes and plasma

membrane proteins associated with the metabolism, uptake and secretion of lipids are also crucial in organizing intact ELL. Moreover, corneodesmosomes mediate cell–cell adhesion between corneocytes.^{10–12} Degradation of corneodesmosome proteins in the uppermost SC is a key step in desquamation.^{10,11}

The roles of the SC components in cutaneous barrier function have been studied in genetically engineered mice and in naturally occurring hereditary skin diseases in humans and animals. The aim of this review is to discuss recent progress in understanding the biological functions of the key SC components via the use of genetically engineered mouse models and to discuss the pathophysiology of spontaneous hereditary skin diseases related to genetic mutations or the altered expression of SC components in humans, cattle and dogs (summarized in Table 1).

Stratum corneum components crucial for barrier function

Structural proteins

Intermediate filament proteins.

Keratins (encoded by *KRT* genes) are fibrous structural proteins synthesized by epithelial cells, including keratinocytes. Keratin monomers assemble into web-like bundles to form intermediate filaments, which are cytoskeletal components that terminate at desmosomes to form a cytoplasmic network. In the mammalian epidermis, type I (acidic) keratins and type II (neutral–basic) keratins form

Accepted 22 June 2012

Sources of Funding: This study was self-funded.

Conflict of Interest: No conflicts of interest have been declared.

Table 1. Stratum corneum proteins and cutaneous abnormalities related to genetic alterations in mammals

Stratum corneum proteins			Cutaneous abnormalities in mammals		
Molecules	Genes	Functions	Mouse	Human	Other species
Intermediate filament cytoskeleton/filaggrin-related proteins					
Keratin 1	<i>KRT1</i>	Structural protein of IF	Death before weaning age in homozygous mutant mice; severe blistering; skin erosions and hyperkeratosis in heterozygous mutant mice	Epidermolytic ichthyosis	Not reported
Keratin 10	<i>KRT10</i>	Structural protein of IF	Death after birth in homozygous mutant mice; acanthosis and hyperkeratosis in heterozygous mutant mice	Epidermolytic ichthyosis	Mild recessive epidermolytic hyperkeratosis in Norfolk terrier
Keratin 2e	<i>KRT2</i>	Structural protein of IF	Scaly skin on tail, ears and feet	Superficial epidermolytic ichthyosis	Not reported
Filaggrin	<i>FLG</i>	Aggregation of IF in cornified cells	Increased desquamation; production of allergen-specific IgE by epicutaneous sensitization; contact dermatitis	Ichthyosis vulgaris; atopic dermatitis; contact dermatitis; alopecia areata	Canine atopic dermatitis?
Caspase-14	<i>CASP14</i>	Degradation of filaggrin monomers to natural moisturizing factors	Shiny and lichenified skin with increased TEWL	Not reported	Not reported
Cornified cell envelope-related proteins					
Involucrin	<i>IVL</i>	Structural protein of CCE	No histopathological changes	Not reported	Not reported
Loricrin	<i>LOR</i>	Structural protein of CCE	Increased susceptibility to mechanical stress	Loricrin keratoderma	Not reported
Transglutaminase-1	<i>TGM1</i>	Cross-linking of CCE proteins	Defective SC; early neonatal death owing to excessive water loss	Lamellar ichthyosis; congenital ichthyosiform erythroderma	Recessive lamellar ichthyosis in Jack Russell terrier
Cathepsin D	<i>CTSB</i>	Processing of transglutaminase-1 precursor protein	Reduced expression of involucrin, loricrin and filaggrin	Not reported	Not reported
Desquamation-related proteins					
Kallikrein-related peptidase 7 (KLK7)	<i>KLK7</i>	Proteolysis of corneodesmosome proteins	Not determined	Atopic dermatitis	Not reported
Lympho-epithelial Kazal-type-related inhibitor (LEKTI)	<i>SPINK5</i>	Inhibits KLKs etc.	Neonatal lethality, exfoliative erythroderma and severe dehydration with detached SC in homozygous mutant mice	Netherton syndrome	Not reported

Table 1. (Continued)

Stratum corneum proteins			Cutaneous abnormalities in mammals		
Molecules	Genes	Functions	Mouse	Human	Other species
Extracellular lipid-related proteins					
ATP-binding cassette subfamily A member 12 (ABCA12)	<i>ABCA12</i>	Lipid transporter responsible for cholesterol efflux from epidermal keratinocytes	Neonatal lethality with defective skin development in homozygous mutant mice	Harlequin ichthyosis; lamellar ichthyosis	Ichthyosis fetalis in cattle
Lipoxygenase 3	<i>ALOXE3</i>	Lipid metabolism of lamellar granule contents and/or intercellular lipid layers in the epidermis?	Not determined	Lamellar ichthyosis; congenital ichthyosiform erythroderma	Not reported
12R-Lipoxygenase	<i>ALOXE12B</i>	Releasing protein-bound ω -hydroxyceramides	Neonatal lethality with decreased protein-bound ω -hydroxyceramides and increased TEWL	Lamellar ichthyosis; congenital ichthyosiform erythroderma	Not reported
β -Glucocerebrosidase	<i>GBA</i>	Hydrolysis of glucosylceramides into free and protein-bound ceramides	Increased TEWL and incompetent ELL with decreased ceramides in Gaucher mice	Type II Gaucher disease	Not reported
Fatty acid transport protein 4 (FATP4)	<i>FATP4</i>	Uptake of exogenous fatty acids into cells	Neonatal lethality with disturbed cutaneous permeability barrier function	Ichthyosis prematurity syndrome	Not reported
Steroid sulphatase	<i>STS</i>	Degrading cholesterol sulphate to cholesterol for lipid barrier and desquamation	Cutaneous abnormalities have not been reported	Recessive X-linked ichthyosis	Not reported
Abhydrolase domain containing 5 (ABHD5)	<i>ABHD5</i>	Metabolism of triglycerides	Cutaneous abnormalities have not been reported	Chanarin–Dorfman syndrome	Not reported
Sphingosine-1-phosphate lyase (SGPL1)	<i>SGPL1</i>	Inactivation of sphingosin-1-phosphate	Cutaneous abnormalities have not been reported	Atopic dermatitis (upregulated gene transcription level)	Canine atopic dermatitis (upregulated gene transcription level)
Phospholipase domain-containing protein 1 (PNPLA1)	<i>PNPLA1</i>	Synthesis or remodelling of glycerophospholipids	Not determined	Autosomal recessive congenital ichthyosis	Autosomal recessive congenital ichthyosis in golden retriever
Cytochrome P450, family 4, subfamily F polypeptide 22 (CYP4F22)	<i>FLJ39501</i>	Role in 12R-lipoxygenase pathway?	Not determined	Lamellar ichthyosis	Not reported
Nuclear interaction partner of ALK-like domain containing 4 (NIPAL4)	<i>NIPAL4</i>	Membrane receptor for trioxilins A3 and B3?	Not determined	Lamellar ichthyosis; congenital ichthyosiform erythroderma	Not reported

Abbreviations: CCE, cornified cell envelope; ELL, extracellular lipid lamellae; IF, intermediate filament; SC, stratum corneum; TEWL, transepidermal water loss.

heterodimers via disulphide bonds. Specific keratins are found more prominently in various layers of the epidermis. For example, keratin 5 (K5) and keratin 14 (K14) form heterodimers in basal keratinocytes, whereas keratin 1 (K1) and keratin 10 (K10) form heterodimers in keratinocytes in suprabasal layers; keratin 2 (K2) is expressed in the stratum granulosum (SG).¹³

The functional importance of K1, K2 and K10 to cutaneous barrier function has been studied in mice by genetic engineering of keratin genes (*Krt*). Mice heterozygous for a mutation in the *Krt1* gene or transgenic mice expressing a truncated human *KRT1* gene exhibit suprabasilar blistering and skin erosions immediately after birth and develop marked scaling with increasing age.^{14,15} In addition, mice homozygous for a mutation in the *Krt1* gene exhibit severe blistering and widespread desquamation at birth, and die due to severe dehydration.^{14,15} Likewise, mice heterozygous for mutations in the *Krt10* gene or heterozygous transgenic mice generated by introduction of a *Krt10* mutation develop hyperkeratosis with age.^{16–18} Mice homozygous for the gene knockout or transgene exhibit very fragile skin with severe suprabasilar blistering and erosions, and die shortly after birth.^{16–18} In addition, a point mutation in the *Krt2* gene (T500P) in mice with dark skin (*Dsk2*) causes scaling on the tail, feet and ears owing to impaired intermediate filament assembly, in both homozygous and heterozygous mice, even though abnormalities in cutaneous barrier function in relation to the *Krt2* mutation have not been documented in the literature.¹⁹

These findings imply that keratins are crucial for the structural integrity of epidermal keratinocytes, and

targeted ablation of some *Krt* genes causes fragility of the epidermis and/or a scaly phenotype.

Filaggrin and related proteins.

Profilaggrin, the precursor protein of FLG, is the major constituent of keratohyalin granules in the SG.^{2,4,5} Profilaggrin (encoded by the *FLG* gene) is an insoluble, large, highly phosphorylated, histidine-rich protein, which contains tandemly arranged FLG repeats (10–12 repeats in humans) that are flanked on either side by two partial FLG repeats and N- and C-terminal domains.^{4,5} The N- and C-terminal domains in profilaggrin are thought to be important in processing of profilaggrin to FLG monomers during epidermal differentiation.^{4,20,21}

In humans, each FLG repeat consists of 324 amino acids and shows significant amino acid homology.^{22–24} Meanwhile, two types of FLG repeats are distributed randomly in the mouse profilaggrin precursor protein.^{25–27} The precursor protein itself has no keratinocyte-binding activity.⁴ During the differentiation of keratinocytes, keratohyalin granules degranulate in response to increased Ca^{2+} levels, and profilaggrin is dephosphorylated and proteolysed into FLG monomers at the border between the SG and SC.^{2–5} Filaggrin monomers specifically aggregate the keratin intermediate filament cytoskeleton into tight bundles (Figure 1a), thereby collapsing the cells into a flattened shape.^{2–5} In the upper SC, FLG monomers undergo subsequent degradation into hygroscopic peptides (e.g. pyrrolidone carboxylic acid and urocanic acid), which are natural moisturizing factors (NMFs), by a variety of proteases, including caspase 14.^{4,28,29}

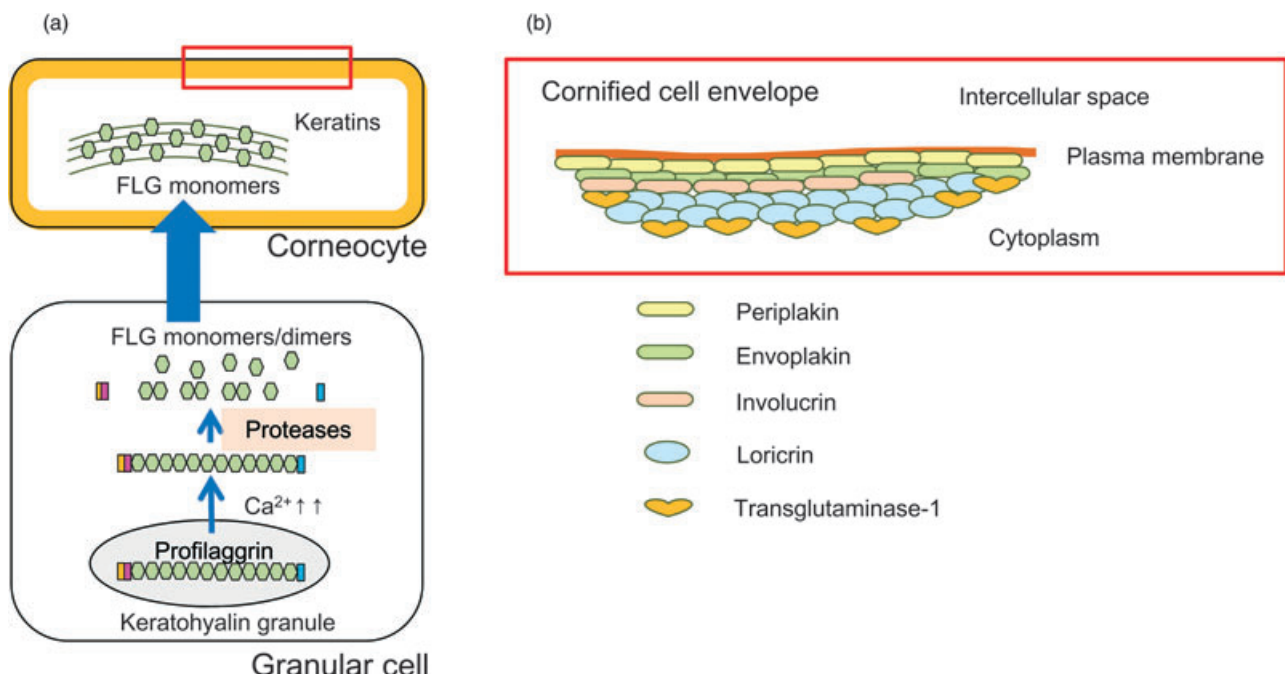


Figure 1. The key structural components of a corneocyte to form a solid 'brick'. (a) In corneocytes, filaggrin (FLG) monomers aggregate with keratin intermediate filaments and form tight bundles in the cytoplasm of corneocytes. Filaggrin monomers are the degradation product of profilaggrin, which contains tandemly arranged FLG repeats flanked on either side by two partial FLG repeats and N- and C-terminal domains. During the differentiation of keratinocytes, keratohyalin granules degranulate in response to increased Ca^{2+} levels, and profilaggrin is solubilized into FLG monomers by various proteases at the border between the stratum granulosum and the stratum corneum. (b) The cornified cell envelope located on the inner surface of the plasma membrane is formed by several proteins, including involucrin, loricrin, envoplakin and periplakin, which are cross-linked by transglutaminase-1.

The role of FLG in cutaneous barrier function has been studied by the use of two lines of mutant mice. Flaky tail mice, which have the two spontaneous genetic mutations *ft* and *ma*, have been reported to develop spontaneous atopic dermatitis (AD)-like disease.³⁰ Recently, it was found that a 1 bp deletion (5303delA) in the murine *Flg* gene is associated with the *ft* genotype in flaky tail mice.²⁷ Moreover, topical application of ovalbumin or *Der-matophagoides pteronyssinus* to *ft/ft* mice causes percutaneous allergen sensitization, with allergen-specific IgE production, increased transepidermal water loss (TEWL) and enhanced AD-like phenotypes.^{27,31} The association of the *ma* mutation with the AD-like dermatitis phenotype, however, has not yet been demonstrated. Recently generated filaggrin gene knockout mice (*Flg*^{-/-}) exhibit dry skin and increased desquamation under mechanical stress.³² Furthermore, *Flg*^{-/-} mice exhibit enhanced penetration of foreign materials into the SC, leading to hapten-induced contact hypersensitivity and allergen-specific humoral immune responses.³² In these mice, SC hydration and TEWL are normal, despite the fact that the NMF level is decreased in the SC of *Flg*^{-/-} mice.³²

Caspase 14, which belongs to a family of cysteine-dependent aspartate-directed proteases, is known to degrade profilaggrin and FLG monomers directly into NMF. Caspase-14-deficient mice show shiny and lichenified phenotypes, with decreased skin hydration and increased TEWL.^{28,29}

In summary, FLG appears to be responsible for hampering a foreign invasion (e.g. penetration of allergens) through the SC rather than performing a water-holding function. In flaky tail mice and *Flg*^{-/-} mice, data suggest that allergens passing through the SC may be captured by the dendrites of Langerhans cells that penetrate tight junctions located immediately beneath the SC, as previously demonstrated by three-dimensional visualization of mouse epidermis.³³ However, the water-holding capacity of FLG-degraded NMF products is debatable and needs to be evaluated further.

Cornified cell envelope proteins.

The cornified cell envelope is a 15-nm-thick layer of proteins (in humans) located on the inner surface of the keratinocyte plasma membrane. The cornified cell envelope is formed by the assembly of several precursor proteins, including involucrin, loricrin, envoplakin, periplakin and small proline-rich proteins (Figure 1b). Transglutaminases in the epidermis are thought to be responsible for the assembly of the precursor proteins that form the cornified cell envelope.^{7,13,34,35} Among the three subtypes of transglutaminases, transglutaminase-1 is known to be a membrane-located transglutaminase in the epidermis.^{36,37} Transglutaminase-1 is synthesized in the epidermis as an inactivated precursor protein, which is later processed by cathepsin D for activation.³⁸

Transglutaminase-1-deficient mice exhibit a defective SC that causes neonatal death owing to increased TEWL. Additionally, cathepsin D-deficient mice exhibit reduced transglutaminase-1 activity and reduced expression of the cornified cell envelope proteins.³⁸ In contrast, loricrin-deficient mice exhibit transient congenital erythroderma, with a shiny, translucent skin at birth and increased susceptibil-

ity to mechanical stress.³⁹ However, the neonatal mutant mice do not exhibit increased TEWL, and lose the skin phenotypes at 4–5 days after birth.³⁹ This phenotypic change may be associated with increased expression of other cornified cell envelope components. Targeted ablation of the murine involucrin gene alone does not cause any histopathological changes in the epidermis which shows an ultrastructurally normal cornified cell envelope.⁴⁰ However, triple knockout of involucrin, envoplakin and periplakin in mice leads to the development of phenotypes characterized by postnatal hyperkeratosis, defects in the assembled cornified cell envelope and increased susceptibility to mechanical stress.⁴¹ Conversely, hyperkeratosis is not evident in the epidermis of involucrin, envoplakin or periplakin single knockout mice.⁴¹

Thus, evidence obtained through the use of genetically engineered mice suggests that the assembly of cornified cell envelope proteins is crucial for the normal desquamation process and the structural and mechanical integrity of corneocytes in the epidermis, even though targeted ablation of single protein genes did not cause lethal or life-long cutaneous abnormalities.

Functional proteins in the stratum corneum

Desquamation-related proteins.

Corneodesmosomes are the main adhesive structure in the SC (Figure 2).^{10–12} On the cytoplasmic side of corneodesmosomes, desmosomal plaque proteins are incorporated into the cornified cell envelope and separated from tonofilaments attached to the intermediate filament cytoskeleton.^{6,42} The extracellular part of corneodesmosomes is comprised of desmosomal cadherins, such as desmoglein (Dsg)1 and desmocollin (Dsc)1, as well as corneodesmosin, a unique extracellular component of corneodesmosomes.^{11,43–46} During desquamation, the

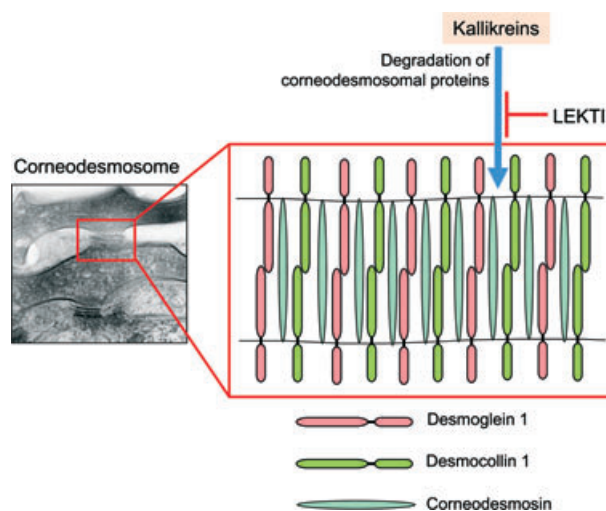


Figure 2. Corneodesmosomes mediate adhesion of corneocyte 'bricks'. The extracellular components of corneodesmosomes include two desmosomal cadherins, desmoglein 1 and desmocollin 1, as well as corneodesmosin. The extracellular components of corneocytes are degraded by kallikreins, which leads to desquamation. The enzymatic activity of kallikreins is inhibited by lymphoepithelial Kazal-type 6 serine protease inhibitor (LEKTI), which is crucial for maintaining the normal desquamation process.

extracellular components of corneodesmosomes are degraded by kallikreins (KLKs) and cathepsins.^{47–49}

The KLKs are a family of 15 trypsin- or chymotrypsin-like serine proteases (KLK1–KLK15).^{50–53} In human skin, at least eight KLKs, including KLK5 and KLK7, are expressed and secreted into the extracellular space between the SG and SC.⁵⁴ Kallikrein 5 degrades all extracellular components of corneodesmosomes, while KLK7 degrades only Dsc1 and corneodesmosin but not Dsg1.^{42,53} The enzymatic activities of KLK5 and KLK7 are known to be inhibited by lymphoepithelial Kazal-type 6 serine protease inhibitor (LEKTI), which is encoded by the *SPINK5* gene (Figure 2).^{55,56} The LEKTI is synthesized in the SG and released by lamellar granules into the extracellular space.⁵⁷

The generation of *Spink5* gene knockout mice has provided insight into the detailed biological functions of LEKTI and KLKs in the skin. *Spink5*^{−/−} newborn mice have very fragile skin, with severe erosions, and die within a few hours of birth.⁵⁸ A deficiency of LEKTI in the epidermis causes hyperactivity of KLK5 and KLK7, as well as desmosomal separation at the SG–SC interface.⁵⁸ In addition, *Spink5*^{−/−} embryo skin grafted onto nude mice exhibits parakeratotic hyperkeratosis and desmosomal cleavage resembling human Netherton syndrome.^{58,59} It is therefore suggested that regulation of the enzymatic activity of KLKs by LEKTI is crucial for maintaining the normal desquamation process and thus cutaneous barrier formation.

Extracellular lipids and related proteins.

In the upper stratum spinosum (SS) and SG, lamellar granules, which originate from a part of the Golgi apparatus, contain precursors of intercellular lipids in the SC, such as phospholipids, glucosylceramides, sphingomyelin and cholesterol.^{7,60,61} During the differentiation of keratinocytes, lamellar granules move to the apex of granular cells, fuse with the plasma membrane and secrete their contents into the extracellular space at the SG–SC border by exocytosis.³⁴ Two epidermal lipoxygenases, lipoxygenase 3 and 12R-lipoxygenase, are presumed to be associated with lipid metabolism of the lamellar granule contents and/or extracellular lipid layers in the epidermis.³⁵ Targeted ablation of the murine 12R-lipoxygenase gene results in neonatal death, with progressive dehydration, increased TEWL and decreased protein-bound ω -hydroxyceramides.^{62,63}

Secreted lipids are subsequently processed and arranged into ELL in the intercellular space of the SC (Figure 3a).⁶⁴ Some lipid classes are covalently bound to cornified cell envelope proteins, such as involucrin, envoplakin and periplakin, and form a lipid envelope that acts as a scaffold for the ELL.^{7,65} Ceramides (CERs), cholesterol and long-chain free-fatty acids are the three major lipid constituents in the SC and critical ingredients to form the 'mortar' of the epidermal 'rampart'.^{64,66}

Ceramides are a class of lipid molecules consisting of sphingoid bases that are amide linked to fatty acids. It is generally accepted that CERs are the main constituents of the SC and play important roles in maintaining permeability barrier function.^{67,68} In the suprabasal layer, CERs newly synthesized by the *de novo* pathway are immedi-

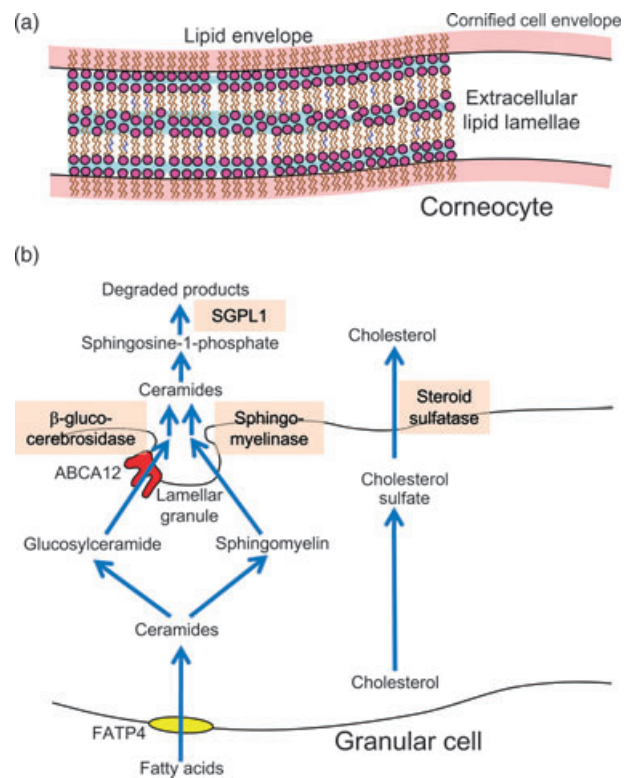


Figure 3. Lipids in the intercellular spaces are arranged into extracellular lipid lamellae and compose 'mortar' in the stratum corneum. (a) Lipids secreted into intercellular spaces during cornification are subsequently processed and arranged into extracellular lipid lamellae in the intercellular space of the stratum corneum. Some lipid classes are covalently bound to cornified cell envelope proteins and form a lipid envelope that acts as a scaffold for the extracellular lipid lamellae. (b) In granular cells, fatty acids are incorporated into the cytoplasm through fatty acid transport protein 4 (FATP4) and converted to ceramides. Ceramides are subsequently converted to glucosylceramides and sphingomyelins. The two precursor lipids are then packed into lamellar granules. The ATP-binding cassette subfamily A member 12 (ABCA12) is a membrane-transporter protein that, at least in part, plays a role in the incorporation of glucosylceramide into lamellar granules. When lamellar granules secrete their contents into the extracellular space, precursor lipids are catalysed by β -glucocerebrosidase and sphingomyelinase and are converted back to ceramides. Ceramides are degraded into sphingosine-1-phosphate and irreversibly inactivated by sphingosine-1-phosphate lyase (SGPL1). Cholesterol in the cytoplasm is catalysed into cholesterol sulphate and further converted back to cholesterol by steroid sulphatase in the extracellular space.

ately converted to glucosylceramides and sphingomyelins. The glucosylceramides and sphingomyelins are then incorporated into lamellar granules and secreted into the interface of the SG and SC, where they are converted back to CERs by β -glucocerebrosidase and amide sphingomyelinase (Figure 3b).^{69–73} Deficiency of β -glucocerebrosidase in type 2 Gaucher mice results in increased TEWL, increased glucosylceramides, decreased SC CERs and incompetent structure of ELL.^{72,74} The ATP-binding cassette subfamily A member 12 (ABCA12) is a lipid transporter that plays a role, at least in part, in the incorporation of glucosylceramides into lamellar granules (Figure 3b).⁷⁵ Mice homozygous for the *Abca12* null allele exhibit neonatal lethality, with skin fissures and severe weight loss that are probably due to increased TEWL.⁷⁶

In the epidermis of *Abca12*^{-/-} mice, there was remarkable hyperkeratosis, lipid droplets in the SG suggestive of lipid congestion in lamellar granules, and sparse SC CERs.⁷⁶

Free extractable CERs in the human SC were formerly divided into eight fractions corresponding to 10 classes.^{77,78} However, recent studies using liquid chromatography–mass spectrometry revealed that free extractable CERs in human and canine SC could be divided into 11 groups according to their sphingoid and fatty acid structures, as follows: CER[EOH] (combination of ω -hydroxy fatty acids and 6-hydroxylsphingosines), CER[EOP] (combination of ω -hydroxy fatty acids and phytosphingosines), CER[EOS] (combination of ω -hydroxy fatty acids and sphingosines), CER[AH] (combination of α -hydroxy fatty acids and 6-hydroxyl sphingosines), CER[AP] (combination of α -hydroxy fatty acids and phytosphingosines), CER[AS] (combination of α -hydroxy fatty acids and sphingosines), CER[ADS] (combination of α -hydroxy fatty acids and dihydrosphingosines), CER[NH] (combination of nonhydroxy fatty acids and 6-hydroxyl sphingosines), CER[NP] (combination of nonhydroxy fatty acids and phytosphingosines), CER[NS] (combinations of nonhydroxy fatty acids and sphingosines) and CER[NDS] (combination of nonhydroxy fatty acids and dihydrosphingosines; Figure 4).^{79,80} Among the 11 classes of human SC CERs, seven CER classes, including esterified ω -hydroxyceramides with very long carbon chains (CER[EOS], CER[EOP] and CER[EOH]), are expressed exclusively in the SC.^{79,80} It is well recognized that the esterified ω -hydroxyceramides play important roles in epidermal barrier function owing to their extremely long fatty acid chains, although their composition ratios are relatively low among all free extractable SC CERs.^{79–83} Moreover, nonesterified ω -hydroxyceramides (CER[OS], CER[OP] and CER[OH]), which are degraded products of esterified ω -hydroxyceramides, covalently bind to the cornified cell envelope and form a lipid envelope.⁸⁴ In human SC, CER[OS] and CER[OH] are two major protein-bound

CERs.⁸⁵ In contrast, CER[OS] and CER[OP] are two major protein-bound CERs in canine SC.⁸⁶ Ceramides are cleaved to generate sphingosine, which is then phosphorylated to sphingosine-1-phosphate (S1P) by sphingosine kinase. Sphingosine-1-phosphate is irreversibly inactivated by a S1P lyase (SGPL1; Figure 3b).^{87,88}

The epidermis also contains free fatty acids, as well as fatty acids bound to triglycerides, phospholipids, glycosylceramides and CERs.³⁴ Fatty acid transport protein 4 (FATP4) is known to be a lipid transporter that plays a crucial role in the uptake of fatty acids into keratinocytes (Figure 3b).⁶¹ Mice with spontaneous mutations in, or targeted disruption of, the gene encoding FATP4 exhibited disturbed epidermal barrier function and neonatal lethality.^{89,90}

Cholesterol, the third major lipid class in the SC, is synthesized in keratinocytes, and at least a part of the cholesterol is metabolized into cholesterol sulphate. During cornification, steroid sulphatase is secreted into the intercellular spaces of the SC, where it degrades cholesterol sulphate into cholesterol (Figure 3b), which is incorporated into the ELL.^{34,61}

In summary, interactions between heterogeneous lipid classes and metabolic pathways are important for providing structural and functional integrity to the ELL and their scaffold structure lipid envelopes. Genetic engineering of some protein genes associated with lipid transfer/metabolism has led to an understanding of not only the biological function of the proteins but also the importance of lipid constituents (e.g. mortal) to permeability barrier function (e.g. to curb the population drain from the castle).

Cutaneous manifestations associated with the alteration of SC components in humans and other mammalian species

Ichthyosis and ichthyosis syndrome in humans

Ichthyosis is a clinically and aetiologically heterogeneous group of hereditary cornification disorders. Ichthyosis in

Sphingoid Fatty acid	6-hydroxy sphingosine [H] 	Phytosphingosine [P] 	Sphingosine [S] 	Dihydrosphingosine [D] 
Esterified ω -hydroxy fatty acid [EO] 	CER[EOH]	CER[EOP]	CER[EOS]	CER[EODS] (Not detected in SC)
α -hydroxy fatty acid [A] 	CER[AH]	CER[AP]	CER[AS]	CER[ADS]
Nonhydroxy fatty acid [N] 	CER[NH]	CER[NP]	CER[NS]	CER[NDS]

Figure 4. Ceramide (CER) classes recognized in human and canine stratum corneum (SC). Human and canine CERs can be divided into 11 groups according to their sphingoid and fatty acid structures. Ceramide classes recognized exclusively in the SC are surrounded by a red rectangle. CER[ADS], which is recognized exclusively in the SC and hairs in humans, is surrounded by a green rectangle. CER[EODS] has not been detected in mammalian SC.

humans is classified into six major distinct clinical subtypes: harlequin ichthyosis (HI), congenital ichthyosiform erythroderma (CIE) and lamellar ichthyosis (LI), epidermolytic ichthyosis (EI; formerly called bullous congenital ichthyosiform erythroderma), recessive X-linked ichthyosis (RXLI) and ichthyosis vulgaris (IV).³⁵

Harlequin ichthyosis is the most devastating, often fatal, autosomal recessive congenital ichthyosis (ARCI) in humans. Affected newborns exhibit cracks in the skin, ectropion (turning outwards of the lower eyelids), eclabium (turning outwards of a lip) and flattened ears. Ultrastructurally, human HI is characterized by abnormal lamellar granules in the SG and the absence of the ELL in the SC. In 2005, truncation or deletion mutations in the *ABCA12* gene were first reported to underlie human HI.⁹¹ These findings indicate that defects in the key lipid transporter, *ABCA12*, in lamellar granules cause malformation of the ELL and disrupt cutaneous barrier function in human HI.

Congenital ichthyosiform erythroderma and LI in humans are other forms of ARCI that share similar clinical features, but the scales in LI patients are rougher and larger than those in CIE patients. Affected babies are born in a collodion membrane, which is a shiny extra layer of the skin. After the membrane is shed, the skin becomes erythematous, with extensive hyperkeratotic scales. The molecular pathogenesis of human CIE and LI varies among cases. Mutations in a gene encoding transglutaminase-1, a cornified cell envelope-associated protein, have been reported since the mid-1990s in humans with LI and CIE.^{92–95} Moreover, a combination of missense mutations in the *ABCA12* gene has been reported to underlie human LI.⁹⁶ Mutations in the genes encoding lipooxygenase 3 and 12R-lipoxygenase,⁹⁷ as well as nuclear interaction partner of ALK-like domain containing 4 (NIPAL4),⁹⁸ have also been reported to underlie certain cases of human CIE and LI. Furthermore, mutations in *FLJ39501*, which encodes cytochrome P450, family 4, subfamily F polypeptide 22 (CYP4F22), were identified as causative genetic defects in human LI.⁹⁹ The exact physiological roles of NIPAL4 and CYP4F22 in the SC have not been fully elucidated.

Epidermolytic ichthyosis in humans is caused by mutations in either *KRT1* or *KRT10*.^{100–102} Affected patients exhibit widespread blisters and erosions, with a histopathology of keratinocyte vacuolation in the upper epidermis from birth. The blisters subsequently cease, and generalized hyperkeratotic scales become prominent. Ultrastructurally, irregular, clumped intermediate filaments are seen in the keratinocytes in the upper SS and SG. Epidermolytic ichthyosis in humans usually exhibits an autosomal dominant inheritance.

Genetic defects in the steroid sulphatase gene^{103,104} and *KRT2*^{105,106} have been identified to underlie human RXLI and superficial EI (formerly called ichthyosis bullosa of Siemens), respectively. Also, the homozygous and compound heterozygous mutations R501X and 2282del4 in *FLG* have been identified to cause human IV.¹⁰⁷ In addition, mutation in the gene encoding FATP4 has been reported to underlie human ichthyosis prematurity syndrome.¹⁰⁸ Mutations in *SPINK5*¹⁰⁹ and *ABHD5*¹¹⁰ have been reported to underlie human Netherton syndrome and Chanarin–Dorfman syndrome, respectively. These

two diseases are classified into the disease group ‘ichthyosis syndrome’, in which cornification disorders are accompanied by internal organ failure.

Ichthyosis in other mammals

Hereditary keratinization disorders comparable to HI, LI and EI in humans have also been reported in veterinary research publications.

Ichthyosis fetalis has been reported in Chianina cattle as an autosomal recessive skin disorder. Affected calves show deep skin fissures, ectropion and eclabium reminiscent of human HI.¹¹¹ Genome-wide association studies and sequence analysis identified a homozygous missense mutation in A5804G that resulted in a H1935R substitution in the *ABCA12* gene in three affected cattle.¹¹² Comparison of the genetic evidence with the severe clinical phenotype suggests that the histidine 1935 residue in *ABCA12* has key structural or functional importance.

An autosomal recessive LI associated with a LINE-1 insertion in the transglutaminase-1 gene has been reported in the Jack Russell terrier dog.¹¹³ Very recently, a novel homozygous insertion–deletion mutation in the gene encoding phospholipase domain-containing protein 1 (PNLPA1), which is expressed in the upper epidermis and synthesises or remodels glycerophospholipids that play an important role in epidermal lipid barrier function, has been identified in 120 golden retrievers affected by a form of LI resembling human ARCI.¹¹⁴ This discovery led to the identification of novel mutations in *PNLPA1* in six human individuals affected by ARCI.¹¹⁴ Moreover, a homozygous mutation in the consensus donor splice site of intron 5 in *KRT10* has been identified in seven Norfolk terrier dogs affected by mild recessive EI.¹¹⁵

Hereditary keratinization disorders compatible with other forms of ichthyosis or ichthyosis syndrome have not been reported in the veterinary literature.

Human AD

Atopic dermatitis is a genetically associated, chronically relapsing and pruritic skin disease that is commonly recognized in humans and dogs. It is believed that multiple factors, such as immunological abnormalities, environmental factors and impaired cutaneous barrier functions, are involved in the onset and/or aggravation of AD.

In human AD, lower levels of CERs in the SC are believed to be associated with a change in the organization of ELL, acceleration of TEWL and reduced water capacitance, leading to atopic dry skin.¹¹⁶ In addition, the profiles of the SC CER classes are altered in humans with AD, and a significant negative correlation has been found between the TEWL value and the quantities of total CERs and some CER classes, such as CER[NP], CER[EOS] and CER[EOP].^{117–119} Moreover, it has been reported that the quantities of protein-bound ω -hydroxyceramides are decreased both in lesional and in clinically nonlesional skin of humans with AD.¹²⁰

Possible mechanisms that underlie decreased SC CERs have been proposed in the literature. Jensen *et al.*¹²¹ reported that the activity of epidermal acid sphingomyelinase was decreased in lesional and clinically nonlesional skin in human AD, correlating with reduced SC

CER content and disturbed barrier function. In addition, Imokawa and his group proposed that novel sphingomyelin and glucosylceramide deacylases, which hydrolyse sphingomyelin and glucosylceramide into degraded products, compete with sphingomyelinase and β -glucocerebrosidase and lead to SC CERs deficiency in human AD.^{122–124} This increased enzymatic activity is recognized specifically in AD but not in contact dermatitis. Moreover, it has been reported that the transcription level of the *SGPL1* gene encoding S1P lyase, which hydrolyses the CER degradation product S1P, is increased in human AD.¹²⁵

Human AD is known to develop frequently in patients with IV, probably owing to disrupted cutaneous barrier function. In 2006, an association of loss-of-function mutations (R501X and 2282del4) in *FLG*, which were initially identified in human IV,¹⁰⁷ in human AD and/or asthma cohorts, was first reported.¹²⁶ To date, the association of more than 40 *FLG* mutations with AD has been reported, and approximately 25–50% of AD patients possess *FLG* mutations.^{3,35} Most of the human patients with AD have heterozygous mutations in *FLG*.³

A mutation in the gene encoding KLK7 has been reported in human patients with AD.¹²⁷ In addition, increased protein expression and protease activity of KLKs in human AD have also been reported.^{128,129}

Canine AD

Decreased CER contents in the SC of dogs with AD have also been reported in the veterinary literature. Electron microscopic analysis revealed that the continuity and thickness of the ELL were significantly reduced in clinically nonlesional SC of dogs with spontaneous AD and an experimental model of canine AD sensitized with house dust mites.^{130–132} Previously, we reported that the proportion of free extractable CERs, but not that of cholesterol or free fatty acids, in the SC was negatively correlated with TEWL in dogs with AD.¹³³

Reiter *et al.*¹³⁴ reported that the proportions of free extractable CER1 (CER[EOS]) and CER9 (CER[EOP]) were lower in clinically nonlesional skin of dogs with AD than in skin from breed- and age-matched healthy dogs. We recently reported that the quantities of total free extractable CERs and their CER[EOS], CER[EOP] and CER[NP] subclasses, as well as mixtures of CER[NDS/NS] and CER[AS/NH], were significantly lower in clinically nonlesional skin of dogs with AD than in breed- and age-matched healthy dogs.⁸⁰ In that study, the greatest differences between CER content in atopic dogs and control animals were in the quantities of CER[EOP] (3.2-fold), a mixture of CER[AS/NH] (2.3-fold) and CER[EOS] (2.2-fold), whereas the differences in other CER classes were <1.6-fold.⁸⁰

Popa *et al.*¹³⁵ recently reported that the amounts of protein-bound CER[OS] and CER[OP], which are degradation products of free extractable CER[EOS] and CER[EOP], respectively, were decreased in clinically nonlesional skin of dogs with AD compared with healthy dogs. Furthermore, recent studies indicated that dogs with AD have lower amounts of S1P in the skin and plasma, and increased transcription of the *SGPL1* gene.^{88,136}

These findings indicate that free and protein-bound CERs, particularly the ω -hydroxyceramides believed to be crucial for maintaining permeability barrier function, are decreased in the SC of dogs with AD. In addition, the above findings suggest the importance of S1P lyase in the pathophysiology of canine AD.

The association of *FLG* with canine AD has also been investigated. Wood *et al.*¹³⁷ reported that a single nucleotide polymorphism within *FLG* is associated with AD in Labrador retrievers in the UK. The association of *FLG* with canine AD has not been reported in other breeds.^{137–139} Changes in the immunostaining pattern of *FLG* and its C-terminus in dogs with AD have been reported;^{140,141} however, mutations in *FLG* have not yet been identified in canine AD. Moreover, changes in KLKs have not been reported in the veterinary literature.

Other diseases in humans

Loss-of-function mutations in *FLG* may be associated with contact dermatitis^{142–144} and alopecia areata¹⁴⁵ in humans.

Gaucher disease is the most common type of lysosomal storage disease in humans and is associated with a genetic deficiency of β -glucocerebrosidase. It has been reported that a subset of infants with type II Gaucher disease exhibit congenital ichthyosis and neonatal death.¹⁴⁶

A disease entity of loricrin keratoderma, in which 1 bp insertions in *LOC* cause aberrant loricrin synthesis, has been proposed in human medicine. Histopathologically, affected patients exhibit marked hyperkeratosis and hypergranulosis. Nuclear accumulation of loricrin was confirmed by immunohistochemistry and immunoelectron microscopy.¹⁴⁷ These disease entities have not been reported in the veterinary literature.

Implications and future perspectives for biological and clinical research

Investigations using genetically engineered mouse models and spontaneous skin diseases in humans and other mammals have shed light on the biological properties of SC-related proteins and lipids, which are crucial in forming the impregnable epidermal 'rampart' to protect the mammalian 'castle'. In particular, genetic mutations in hereditary ichthyosis and ichthyosis syndrome in humans, as well as their mouse models, have provided greater understanding of the roles of targeted proteins in the maintenance of cutaneous barrier function. In contrast, there is limited evidence to explain the gene mutations in naturally occurring ichthyosis in other mammalian species. Future studies, including genome-wide analysis, will lead to the discovery of genetic mutations that underlie hereditary keratinization disorders with unknown aetiology in domestic and companion animals. This approach will accelerate the development of perinatal diagnosis and gene therapies for hereditary diseases, and prevent the breeding of animals with unaffected carriers.

Atopic dermatitis is heterogeneous owing to genetic, environmental and immunological factors. Although mutations in *FLG* are clearly associated with the pathogenesis of human AD, the mutation does not fully

describe the pathogenesis of AD, because approximately half of the humans with AD do not possess *FLG* mutations. In addition, it has not been fully elucidated whether CER deficiency is the primary factor that causes AD or whether it is secondary to AD. It has been reported that bacterial ceramidases cause reduction of SC CERs; thus, CERs are not always reduced as a result of congenital abnormalities.¹⁴⁸ Moreover, it has not been fully elucidated whether the reduction of CERs in human and canine AD accelerates the percutaneous entry of allergens through the SC (outside-to-inside barrier dysfunction), even though the reduction is associated with increased water permeability (inside-to-outside barrier dysfunction). Future studies are expected to determine whether reduction of CERs is recognized from early life and permits percutaneous allergen entry in AD. Moreover, future genome-wide analysis to identify undiscovered mutations in genes crucial for structural integrity or lipid metabolism in the SC of humans or animals with AD will be expected.

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Résumé

Contexte – Le stratum corneum (SC) est la zone la plus externe de l'épiderme et joue un rôle clé dans la fonction de barrière cutanée des mammifères. Le SC est composé de « briques » représentant des cornéocytes aplatis riches en protéines, et en « mortier », représentant les couches intercellulaires riches en lipides. Cette structure en « briques et mortier » confère au SC un rôle de « rempart » qui emprisonne l'eau et les solutés essentiels pour l'homéostasie physiologique et qui protège les mammifères des assauts physiques, chimiques et biologiques.

Structures et fonctions – Le cytosquelette des cornéocytes contient des faisceaux serrés de filaments intermédiaires de kératine regroupés avec des monomères de filaggrine qui sont dégradés par la suite en composés hydratants naturels par diverses protéases, comme la caspase 14. Une enveloppe de cellule cornée est formée par la surface interne de la membrane plasmique du cornéocyte par liaison catalytique de la transglutaminase à l'involucrine et à la loricrine. Les céramides forment une enveloppe lipidique par liaison covalente à l'enveloppe cellulaire cornifiée et la matrice extracellulaire de lipides joue un rôle important dans la fonction de perméabilité de barrière. Les cornéodesmosomes sont les structures principales d'adhésion dans le SC et sont dégradées par des protéases à sérine, telles que les kallikréines, au cours de la desquamation.

Conséquence clinique – Les rôles des différents composants du SC, comme les protéines de structure des cornéocytes, les lipides extracellulaires et des protéines associées au métabolisme lipidique, ont été étudiés chez des souris génétiquement modifiées et naturellement porteuses de dermatoses héréditaires, telles que l'ichtyose, le syndrome ichtyosiforme et la dermatite atopique chez l'homme, les bovins et les chiens.

Resumen

Introducción – El estrato corneo (SC) es la región más exterior de la epidermis y juega un papel clave en la función cutánea de barrera en mamíferos. El SC está compuesto de “ladrillos”, representados por corneocitos aplanados enriquecidos en proteínas, y el “mortero”, representado por capas intercelulares enriquecidas con lípidos. A consecuencia de esta estructura de ‘ladrillos y mortero’, el SC puede ser considerado como un “muro” que mantiene los elementos esenciales de agua y solutos para la homeostasis fisiológica y que protege a los mamíferos de ataques físicos, químicos y biológicos.

Estructuras y funciones – El citoesqueleto de corneocitos contiene ovillos apretados de filamentos intermedios de queratina agregados con monómeros de filagrina, que son posteriormente degradados a compuestos humectantes naturales tras la acción de varias proteasas, incluida caspasa 14. Una envoltura celular cornificada se forma en la superficie interior de la membrana plasmática del corneocito mediante la acción de unión de la transglutaminasa entre la involucrina y la loricrina. Las ceramidas forman una envuelta lipídica tras la unión por enlaces covalentes a la envoltura cornificada, y los lípidos lamelares extracelulares juegan un papel importante en la función de permeabilidad de la barrera. Los corneodesmosomas son las principales estructuras adhesivas en el SC y son degradados por ciertas serin-proteasas, tales como calicreínas, durante la descamación.

Importancia clínica – las funciones de los diferentes componentes del SC, incluidas las proteínas estructurales en el corneocitos, los lípidos extracelulares y algunas proteínas asociadas con el metabolismo de los lípidos, han sido investigadas en ratones genéticamente manipulados y en enfermedades hereditarias espontáneas de la piel, como ictiosis, síndrome de ictiosis y dermatitis atópica en humanos, vacuno y en perros.

Zusammenfassung

Hintergrund – Das Stratum corneum (SC) ist die äußerste Schicht der Epidermis und spielt eine Schlüsselrolle bei der Funktion der Hautbarriere der Säuger. Das SC besteht aus „Ziegeln“, die repräsentiert werden durch abgeflachte, Protein-angereicherte Korneozyten und „Mörtel“, welcher durch interzelluläre Lipid-angereicherte Schichten repräsentiert wird. Als Ergebnis dieser „Ziegel und Mörtel“ Struktur kann das SC als Schutzwall betrachtet werden, welcher Wasser und lösliche Stoffe eingrenzt, die für die physiologische Homöostase essentiell sind und der die Säuger vor physischen, chemischen und biologischen Angriffen schützt.

Strukturen und Funktionen – Das Zytoskelett der Korneozyten beinhaltet enge Bündel an intermediären Keratinfilamenten, die durch Filaggrin Monomere, die in der Folge durch verschiedene Proteasen, wie der Caspase 14, in natürliche feuchtigkeitsspendende Komponenten zersetzt werden. Eine verhornte Zellohülle wird an der inneren Oberfläche der Plasmamembran der Korneozyten ausgebildet, was durch eine kreuzweise Verknüpfung von Involucrin und Loricrin, welche wiederum durch Transglutaminasen katalysiert wird, erfolgt. Ceramide bilden durch ihre kovalente Bindung an die verhornte Zellohülle eine Fetthülle, extrazelluläre lamelläre Lipide spielen eine wichtige Rolle bei der Durchlässigkeit der Hautbarriere. Korneodesmosomen sind die bedeutendsten Bindemittel im SC und werden durch spezielle Serinproteasen, wie Kallikreine, während der Desquamation abgebaut.

Klinische Relevanz – Die Rolle der verschiedenen SC Komponenten, so wie die Strukturproteine in den Korneozyten, die extrazellulären Lipide und einige Proteine, die mit dem Fettstoffwechsel in Zusammenhang stehen, sind in genetisch manipulierten Mäusen und in natürlich vorkommenden hereditären Hauterkrankungen, wie der Ichthyose, dem Ichthyose Syndrom und der atopischen Dermatitis des Menschen, des Rindes und des Hundes untersucht worden.

要約

背景 – 角層は皮膚の最外層に存在し、哺乳動物における皮膚バリア機構の鍵となっている。角層は「レンガ」（平坦かつ蛋白質に富んだ角質細胞）および「モルタル」（細胞間脂質層）により構成されている。この「レンガ&モルタル」構造により、角層は生理的恒常性に必須となる水や溶質を取り囲むとともに、哺乳動物の生体を物理的、化学的ならびに生物学的な攻撃から守る「城壁」に例えられる。

構造と機能 – 角質細胞の細胞骨格は、フィラグリンの単量体により凝集されたケラチン中間系線維束からなる。このフィラグリンの単量体は、やがてカスパーゼ14などのプロテアーゼによって分解されて天然保湿因子となる。周辺帯は角質細胞の細胞膜を裏打ちする細胞内構造で、トランスグルタミラーゼの触媒作用により架橋されたインボルクリンとロリクリンにより構成される。セラミドは周辺帯と共有結合して角質細胞脂質外膜を形成するだけでなく、皮膚の透過性保持機構に重要となる細胞外ラメラ構造を形成する。コルネオデスモソームは角層の主な接着構造であり、この構造がカリクレインなど特定のセリンプロテアーゼによって分解されると落屑が認められる。

臨床との関連 – 角質細胞の構造蛋白質、細胞外脂質、ならびに脂質代謝に関連する蛋白質などの生物学的役割については、遺伝子改変マウスを用いた研究や、ヒト、ウシおよびイヌに自然発症する魚鱗癬・魚鱗癬症候群などの遺伝性皮膚疾患、ならびにアトピー性皮膚炎における病態を基に解析されている。

摘要

背景 - 角质层 (SC) 位于表皮最外层，在哺乳动物皮肤屏障功能中起关键作用。角质层由“砖块”和“泥浆”组成，蛋白丰富的扁平角质细胞代表“砖块”，细胞间的脂质层代表“泥浆”。拥有“砖和泥浆”结构的 SC 可被看成是围住水和溶质的“堡垒”，对生理性自体调节和避免哺乳动物受到物理，化学和生物性攻击很重要。

结构和功能 - 角质细胞骨架包含由丝聚蛋白单体紧密组成的束状角蛋白中间丝，随后通过各种蛋白酶被分解为天然的保湿成份，包括半胱天冬酶 14。通过谷氨酰胺转移酶催化内被蛋白和兜甲蛋白交联，在角质细胞质膜内表面形成角质细胞被膜。神经酰胺通过共价键结合在角质细胞被膜上形成脂质包膜，细胞外层状脂质在渗透性屏障功能中起重要作用。角化桥粒是 SC 中主要的胶接结构，在皮屑脱落时，可通过某些丝氨酸蛋白酶降解，如激肽释放酶。

临床相关性 - 研究转基因小鼠和自然发生的遗传性皮肤病，如人，牛和犬的鱼鳞癣，鱼鳞病综合征和异位性皮炎，其角质层不同成份的作用，包括角质细胞结构蛋白，细胞外脂质和角质细胞中一些与脂质代谢相关的蛋白。