Epidermal Lipid Homeostasis

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Stratum corneum lipids, which are enriched in sphingolipids, free fatty acids, and cholesterol, are required for epidermal barrier function. When the epidermal permeability barrier is perturbed, the transepidermal water loss returns to normal by 24-48 hours in parallel with the reappearance of stratum corneum lipids, derived from secreted lamellar bodis and accelerated lipid synthesis. Recent evidence shows that topical application of individual lipids interferes with barrier recovery while complete mixtures of cholesterol, fatty acids, and ceramides facilitate recovery after barrier disruption. Metabolic imbalances and perturbed barrier function can be either the cause or the consequences of the pathobiology of scaling disease. Many skin diseases relating cornification and dryness are indeed related to abnormality of one or several combinations of lipids. Recently the cytokines which have changed during barrier recovery seem to be important in understanding of epidermal lipid homeostasis as well as barrier recovery.


Key Words: Cytokines, Epidermal barrier, Stratum corneum lipids

As a consequence of epidermal differentiation, the stratum corneum, whose primary function is to form a protective barrier and to prevent excessive loss of body fluids, is generated. Although lipids account for only 10% of total stratum corneum weight, they are crucial to the permeability barrier. What was once thought to be an inconsequential layer of loosely adherent cells in various stages of desquamation was recognized to be tough and resilient, then selectively permeable, and then recently, a heterogeneous two-compartment system was recognized, comparing the stratum corneum to a brick wall and epidermal lipid to mortar (the "bricks and mortar" hypothesis), and finally this oversimplified view is now considered inadequate for giving information about the complexity of stratum corneum cellular and intercellular compartments. However, the strategic location of lipids within the cellular interstices and their organization into membrane bilayers imparts impermeability to this tissue. The lipid enrichment of the stratum corneum interstices results from the intercellular deposition of epidermal lamellar body contents. Lamellar bodies measure 0.2 to 0.3 μm in diameter and are ovoid, secretory organelles synthesized within the spinous and granular cell layers. Lamellar body lipids appear to be compressed within the interior of the organelles as pleated sheets, and immediately after secretion these sheets begin to unfurl in the intercellular spaces. As a result of the codeposited hydrolytic enzymes, the unfurled sheets initially form more elongated sheets that transform into basic lamellar unit structure in the mid-stratum corneum. Recently, detailed information about intercellular membrane structure has resulted from the application of ruthenium tetroxide to the study of stratum corneum. This revealed finer details of the structural heterogeneity in both electron-dense and electron-lucent lamellae (Fig. 1). Lamellar body organelles are enriched in glycosphospholipids, phospholipids, cholesterol, and an array of hydrolyases. The composition of lipids changes markedly in successive epidermal layers. Stratum corneum lipids are virtually devoid of phospholipids and are selectively enriched in sphingolipids (ceramides), free sterols, and free fatty acids, with lesser quantities of nonpolar lipids.
and cholesterol sulfate. These modulations in lipid composition and architecture indicate ongoing biochemical processes, implying that stratum corneum is not inert but in fact possesses certain metabolic activities. Considering the studies on the signals initiating barrier repair, if acute disruption of the barrier was accomplished with acetone, then the animals are covered with a vapor-impermeable membrane, the increase in epidermal lipid synthesis is inhibited, the return of stratum corneum lipids is prevented, and barrier recovery does not occur. In contrast, if barrier disrupted animals are covered with vapor-permeable membrane, epidermal lipid synthesis is increased, stratum corneum lipid content returns, and barrier function recovers. These results suggest that transepidermal water loss may be an important signal initiating the repair of the barrier. However, Lee et al. have reported that, following acute barrier perturbation with acetone, the disrupted site is immersed in either an isosmolar sucrose solution or an isotonic sodium chloride solution, both of which should decrease net water transit, barrier recovery proceeds normally. Similarly, varying the osmolarity of immersion solution from hypotonic (distilled water) to hypertonic (560 mOsm/kg), which would affect the rate and direction of net water flow, also does not alter barrier repair. These observations indicate that water transit per se is unlikely to be the crucial signal that stimulates barrier recovery.

Recent studies have demonstrated that immersion in calcium and/or potassium solutions inhibit barrier recovery, suggesting that these may play an important role in signaling barrier repair (Fig. 2).

Separate requirements for cholesterol, ceramides, and fatty acids are known for barrier homeostasis. Yet, when any of these lipid species are applied either alone or as two component mixtures on a perturbed barrier, repair is impeded rather than facilitated. Instead the three key lipids must be supplied together for normal rates of barrier repair to occur. In recent studies, the normal intercellular lamellar bilayer unit structures occurred only with the application and intercellular processing of complete lipid mixture systems. Therefore selected combinations rather than individual lipids are known to be important for the barrier function. Direct approaches to determine the importance of specific lipids for barrier function include the deletion of specific lipids by application of enzyme inhibitors.
Table 1. Importance of bulk stratum corneum lipids for the epidermal barrier

1. The inverse relationship between the permeability of the stratum corneum to water and water-soluble molecules at different skin sites (e.g., abdomen versus palms and soles) and the lipid content of the first site.
2. The observation that organic solvent-induced perturbations in barrier function occur in direct proportion to the quantities of lipid removed.
3. The observation that stratum corneum lipid content is deficient or defective in pathological states that are accompanied by compromised barrier function, such as essential fatty acid deficiency.
4. Barrier function is corrected by topical application of synthetic lipids.

Hydroxymethylglutaryl-CoA (HMG-CoA) reductase or serine palmitoyl transferase inhibitors produce a delay in barrier recovery due to inhibition of epidermal cholesterol or ceramide synthesis, respectively. Elimination of specific lipids by examining essential fatty acid deficient mice (barrier abnormality is produced by feeding an essential fatty acid deficient diet of linoleic acid), suggests that depletion or substitution of selected fatty acids results in barrier dysfunction. The significance of bulk stratum corneum lipids for the epidermal barrier was summarized in Table 1.

LIPIIDS AFFECTING BARRIER FUNCTION

Sterols

Cholesterol accounts for 20–25% of total lipid weight and is one of the major constituents of stratum corneum. Evidence shows that cholesterol is crucial for epidermal barrier function and also appears to mediate stratum corneum desquamation. Most epidermal cholesterol is derived from local synthesis, even under basal conditions, and when the barrier is disturbed this synthetic process is further stimulated. Most mammalian cells including keratinocytes have a low-density lipoprotein (LDL) receptor (a cell surface receptor for plasma cholesterol transport complex), this receptor mediates the feedback control of cholesterol synthesis by regulating both HMG-CoA reductase activity as well as transcription of the gene for the LDL receptor. In epidermal cells, LDL gold labeling experiments revealed such a receptor only in basal cells. Even though the stratum basale is equipped with LDL receptors to enable the uptake of exogenous cholesterol, the basal cells actively synthesize cholesterol de novo for their own growth and requirements. Due to the paucity of plasma membrane LDL receptors in the stratum granulosum or stratum corneum, circulating levels do not affect cutaneous de novo cholesterol synthesis.

Cholesterol is synthesized in epidermal cells from acetate via the Bloch pathway, and like other lipids, is derived from the secretion of epidermal lamellar body contents into the intercellular spaces at the junction of the stratum granulosum and the stratum corneum. It is well known that the level of activity of the rate-limiting enzyme in cholesterol biosynthesis, HMG-CoA reductase, is thought to be regulated by barrier requirements. The importance of cholesterol synthesis and activity of HMG-CoA reductase for barrier function has been demonstrated in both acute and chronic models of barrier perturbation, where cholesterol synthesis increases in response to barrier disruption, and the increase in cholesterol synthesis is aborted by artificial sealing of the barrier with water vapor-impermeable membranes.

Lovastatin, an inhibitor of cholesterol synthesis, both slows barrier recovery after acetone treatment, and induces a defect in barrier function when applied to intact skin. Moreover, topically administered cholesterol, the end product of the sterol by synthetic pathway, is capable of reversing the lovastatin-induced inhibition of barrier function recovery. Thus showing that cholesterol is important for permeability barrier homeostasis.

Sterols are important precursors for vitamin D synthesis. Functionally important sterols present in the epidermis include 7-dehydrocholesterol and previtamin D3. Receptors for 1,25-dihydroxycholecalciferol of cultured human keratinocytes were demonstrated. Since 1,25-dihydroxycholecalciferol is a potent stimulator of cell differentiation, it may also participate in the modulation of differentiation of keratinocytes.

Cholesterol esters containing a high proportion of oleic acid accumulate during differentiation. These cholesterol esters are soluble at body temperature, and are not bilayer-forming lipids. Their localization within the epidermis, and especially within the stratum corneum, is uncertain, but they may be excluded from the lamellar phase domains and cornified to the
nonlamellar lacunae. Another minor cholesterol derivative important to the stratum corneum is cholesterol sulfate. This lipid is in highest concentration in the granular layer and persists in the cornified layer, and the concentration of cholesterol sulfate is lower in the outer stratum corneum than in the inner portion of this layer, and lower still in desquamated material. Cholesterol sulfate is important for the maintenance of the intercorneocyte lipid bilayers.

The decrease of cholesterol sulfate from cohesive to desquamated stratum corneum supports the hypothesis of a controlled hydrolysis of cholesterol sulfate by steroid sulfatase to destabilize the intercorneocyte lipid lamellae, leading to normal and invisible desquamation. Thus, stratum corneum levels of cholesterol sulfate mediate the stabilization–destabilization of membranes and regulate normal desquamation.

Epidermal responses to the inhibition of cholesterol biosynthesis include scaling, epidermal hyperplasia, increased transepidermal water loss and perturbations in the metabolism of other lipid classes. HMG-CoA reductase inhibitors, such as lovastatin produce a scaling disorder in experimental animals. However, the lipid content of the stratum corneum shows normal cholesterol levels with an increased content of free acids. A compensatory increase in fatty acid biosynthesis, altering the sterol and free fatty acid ratio of the stratum corneum lipids, causes membrane abnormalities, increased TEWL, and epidermal hyperplasia.

Essential Fatty Acids

The essential fatty acids (EFAs) were described when Burr and Burr found that a syndrome produced by exclusion of fat from diet could only be corrected by the administration of certain fat fractions, hence the definition of EEA is nutritional. The two families of EFAs are, the ω-6 (n-6) and ω-3 (n-3) families. Linoleic acid (C18:2n-6) and α-linoleic acid (C18:3n-3) are desaturated at ω-6 and ω-3 positions respectively. Holman et al. estimated that human daily requirement of essential fatty acids is 0.5% of the total caloric intake.

Evidence of the importance of fatty acids for barrier function is derived from the study of EFA deficiency. In EFA deficiency, the 18-carbon containing linoleic acid(18:2n-6) is replaced by its closest analogue, the 18-carbon containing oleic acid (18:1n-9). EFAs are required in the epidermis for the maintenance of normal membrane structure. Loss of epidermal barrier function is one of the first consequences of EFA deficiency. When linoleic acid is absent in the diet, lamellar granules are empty or partially filled. As a result large water soluble molecules are able to cross the stratum corneum interstices and the skin becomes scaly and more permeable to water. EFA deficiency is characterized by an increased mitotic index and scaliness of the skin indicating hyperproliferation and inflammation, as well as defective synthesis of lipid bilayer. Microscopic examination of the epidermis reveals acanthosis, hypergranulosis, and hyperkeratosis. However, topical application of linoleic acid or dietary supplements improves epidermal barrier function.

Linoleic acid is the precursor to arachidonic acid and a variety of its eicosanoid products, including prostaglandins (via cyclooxygenase pathway) and hydroxy acids (via lipoxygenase pathway). Essential fatty acids are an integral part of phospholipids in the cell membrane of the skin, liberated by phospholipase A2, and serve as precursors for the biosynthesis of prostaglandins, thromboxanes, and leukotrienes. The prostaglandins are important for the epidermal inflammation as well as the regulation of cell division. Topical application of arachidonic acid or prostaglandins on EFAD skin corrects the turnover state but not the barrier defect.

Nonessential Fatty Acids

Fatty acids prominent constituents of stratum corneus lipid both in their free and esterified forms (sterol esters, glycerides, ceramides, and phospholipids). Free fatty acids represent 10% to 25% of the lipid in stratum corneum and are composed almost entirely of saturated species ranging from 14 to 28 carbons in length, the most abundant being C16 and C18 chains. Free fatty acids and cholesterol sulfate are the only charged lipids in the stratum corneum, and may be necessary for the formation of bilayers in the absence of phospholipids. To determine whether epidermal fatty acid synthesis also is required for barrier homeostasis, 5-(tetradecyloxy)2-furancarboxylic acid (TOFA), an inhibitor of acetyl CoA carboxylase, can be applied after barrier disruption. This study reveals that TOFA inhibits epidermal fatty acid synthesis and delays barrier recovery, moreover, coadministration of
palmitate with TOFA normalizes barrier recovery, indicating that the delay is due to a deficiency in bulk fatty acids. As with the inhibition of cholesterol synthesis, the inhibition of fatty acid synthesis impairs the early phases of barrier recovery. Furthermore, fatty acid synthesis increases following both acute and chronic barrier perturbations. Therefore, these studies demonstrate that not only essential fatty acids, but bulk free fatty acids are required in epidermal barrier homeostasis.

**Sphingolipids**

One of the relatively unique characteristics of the mammalian stratum corneum lipids is the large proportion of sphingolipids. The transformation of the stratum granulosum into the stratum corneum is accompanied not only by a depletion of phospholipids, but also by an increase in total sphingolipids. Epidermal sphingolipids represent 7.3% of total lipids in the basal layers, increasing to about 15% in the stratum granulosum, 30% in the lower stratum corneum, and reaching 40% in the outer layer of stratum corneum. In contrast, the sphingolipid content of the brain and intestines, the two widely recognized repositories of these lipids, is only about 10% of total lipids. The biosynthesis of sphingolipids begins with the condensation of serine and palmitoyl-CoA to form 3-ketosphinganine, reactions catalyzed by the enzyme serine palmitoyl transferase (rate-limiting for sphingolipid synthesis).

Both glycosphingolipids and ceramides are enriched in the granular cell layer, but in stratum corneum only trace quantities of glycolipids persist and essentially all of the sphingolipid here is ceramide. Lampe et al. have demonstrated that, although there appears to be progressive enrichment of the total sphingolipid content during stratum corneum transit, perhaps due to progressive hydrolysis of other lipid fractions, this increase is largely due to ceramide, and the quantity of glucosylceramides appears to decline even further during stratum corneum transit. This progressive loss of the more polar glyceroceramides, perhaps in conjunction with hydrolysis of cholesterol sulfate may result in loss of the requisite polar moieties that are essential for bilayer maintenance, resulting in break-up of lamellar lipid into micellar droplets, and ultimately leading to desquamation. Wertz et al. and Long et al. have isolated and characterized seven forms of ceramides and glucosylceramides from pig and human epidermis. They are composed of the long-chain bases sphingosine or phytosphingosine with amide-linked nonhydroxy and α-hydroxy fatty acids. In the stratum granulosum and stratum corneum long-chain fatty acids (C22-C24) predominate in comparison to either neutral lipid or phospholipid-linked fatty acids. The ceramide structures which are specific for the epidermis, consist of a sphingosine base with an amide-linked nonhydroxy and α-hydroxy acid and as α-ester-linked nonhydroxy acids contain a high proportion of linoleic acid.

The amide-linked fatty acids contain 35 carbon atoms with two hydroxyl groups and two double bonds. The acylceramide and the structurally related acylglucosylceramide, which are carriers of linoleic acid, led to the speculation that this lipid plays specific role in barrier function.

The least polar and least abundant form of the ceramides, ceramids 1 or acylceramide, is derived from the acylglucosylceramide by removal of the sugar, and is thought to serve as a molecular rivet in stabilizing the multilamellar lipid array in the stratum corneum. The linoleate chain in the acylceramide is the only polyunsaturated chain in the stratum corneum and may provide a degree of fluidity and plasticity to these otherwise saturate membranes. Hydrogen bonding involving the hydroxyl groups of the ceramides is thought to provide a significant bilayer-stabilizing interaction. Also, the great diversity of chain length found in the ceramides must result in a great deal of chain interdigitation in the central portion of the bilayer. Ceramides 2 to 6 contain no methyl branches or cis double bonds, and the trans double bonds found in the sphingosine bases, unlike cis double bonds, do not perturb chain geometry or packing. This absence of cis double bonds and methyl branches would permit the most orderly packing of the aliphatic chains in the interior of the bilayer.

The outer surface of the cornified cell envelope is coated with a monolayer of a covalently attached α-hydroxy ceramide. The chemical reactivity of this bound lipid indicates that it is linked to the protein portion of the envelope through ester linkages, half of which involve the α-hydroxy group and half of which involve one of the sphingosine hydroxyls. The interdigitation of acyl chains between adjacent envelopes has been proposed as one factor providing cohesion between corneocytes. The importance of the ceramides can be demonstrated with the result of
the increase in the ceramide synthesis and the increase in the activity of the serine-palmitoyl transferase, in response to barrier disruption. Most importantly, inhibition of ceramide synthesis with an irreversible inhibitor of serine-palmitoyl transferase (β-chloroalanine) is associated with a delay in barrier recovery. Studies have shown that barrier disruption with acetone, tape stripping, or in essential fatty acid deficiency (EFAD), resulted in increased sphingolipid synthesis, paralleling an increase in activity of serine palmitoyl transferase (SPT) and SPT. Both of these alterations also were prevented by occlusion, providing initial direct evidence for a link between sphingolipid synthesis and barrier recovery. However, in contrast to cholesterol and fatty acid synthesis, sphingolipid synthesis showed an increase after the barrier had been recovered, suggesting that de novo synthesis may not be required for the early phase of barrier recovery. This clearly shows that sphingolipid synthesis in addition to cholesterol and fatty acids is required for the maintenance of epidermal barrier homeostasis.

Despite the evidence that each of the specific lipids is required for barrier function, topical application of these lipids individually in a perturbed barrier may actually impair rather than improve barrier function. Man et al. have tested the application of these lipids alone, then with combinations of two, and finally a complete mixture on an impaired barrier. The results show that application of single components or the incomplete mixtures of two of the key species led to a delay in barrier recovery. When a mixture of

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complete lipids in approximate proportions present in lipid extracts of stratum corneum (i.e., fatty acids, cholesterol, and ceramides) were applied following barrier disturbance the barrier function recovered normally. Since the three-lipid function that follows topical application of incomplete lipids is due to a direct toxic effect of these lipids. The abnormalities induced by the incomplete lipid mixtures were restricted to lamellar body secretory systems.

**DISEASES INVOLVING EPIDERMAL LIPIDS**

**Ichthyosiform dermatosis**

A number of disorders of the epidermis have been attributed to errors in metabolism or nutrition related to lipids. Especially, factors that affect the composition or metabolism of sterols or fatty acids are likely to have clinical sequelae. A number of genetic, pharmacologic, and acquired skin conditions are known to involve the lipid composition or metabolism of the epidermis. The majority of these seem to be manifested as scaling dermatoses (Table 2).

Cholesterol is known to play a critical role in membrane fluidity and may be involved in the regulation of normal desquamation. Winklemann et al. observed that patients treated with the hypocholesterolemic agent, triparanol, unexpectedly developed ichthyosis, first suggesting a link between pathological desquamation and aberrant sterol metabolism. A marked decrease in cholesterol content within the stratum corneum in conjunction with accumulation of the sterol precursor, desmosterol, and the reversal of the scaling abnormality by topical application of cholesterol reveals that the block in epidermal cholesterol biosynthesis is directly related to the pathogenesis of the scaling disorder.

One of the stratum corneum sterol metabolite, cholesterol sulfate, also functions as a regulator of epidermal sterologenesis. Recent interest has been directed towards the significance of cholesterol sulfate, because of the discovery that deficiency of steroid sulfatase is a cause of recessive X-linked ichthyosis (RXLI). A five-fold increase in normal cholesterol sulfate and a 50% decrease in free sterol content occurred in the RXLI patients.

Another classical disorder is Refsum's disease, a rare autosomal recessive disorder resulting from the genetic inability to degrade the phytanic acid that is derived from the phytol moiety in dietary chlorophyll. In normal individuals, phytanic acid is from the phytol moiety in dietary chlorophyll. In normal individuals, phytanic acid is first shortened by the α-oxidative removal of one carbon atom, after which oxidation can proceed. The disorder stems from inactivity of the β oxidation enzyme, leading to the accumulation of very large concentration of phytanic acid in all tissues, including the epidermis.

Multiple sulfatase deficiency is a rare autosomal recessive disorder resulting in the inability to hydrolyze any of the sulfate esters. As in RXLI, cholesterol sulfate accumulates in epidermis, and results in scaling similar to RXLI.

Congenital ichthyosiform erythroderma (CIE) has been associated with higher levels of paraffin hydrocarbons in the epidermis than in normal subjects or in patients with classical lamellar ichthyosis. There are many explanations of the source of the alkanes, but it remains to be explained why CIE patients have a very much higher content in their epidermis and whether this is related etiologically to the skin disorder. Ichthyosis and myopathy are the most consistent clinical features of neutral lipid storage disease, an autosomal recessive disorder characterized by the widespread tissue storage of triacylglycerols within nonmembrane-bound cytoplasmic droplets. Although the precise metabolic defect remains undefined, metabolic studies point to a defect in intracellular triacylglycerol lipolysis. Lipid storage is evident in basal and spinous cell keratinocytes and in other cell types in the skin. In the granular cell layer, the number of lamellar bodies is increased and their contents are distended by electron-lucent material, which may represent droplets of triacyl glycerol. These droplets coalesce and displace the lamellar bilayers after secretion into the intercellular spaces. However, the scales in neutral lipid storage disease unexpectedly showed normal amounts of triacylglycerol and free fatty acids. The nature of the lipid abnormality leading to abnormal desquamation in this disorder is still unknown.

Ichthyosis is also a striking characteristic of the autosomal recessive disorder, Sjögren-Larsson syndrome, which results from deficiency of the enzyme fatty alcohol oxidoreductase, leading to accumulation of fatty alcohols. Although the link between fatty alcohol oxidoreductase deficiency, epidermal lipid content, and the disorder has yet to be defined, the ichthyosis is at least in part due to hyperproliferation.
Several investigators have observed lipid vacuoles, unusual membrane structure, and the absence of normal lamellar bodies in Harlequin ichthyosis as an autosomal recessive disorder of unknown cause, which is characterized at birth by massive platelike scales and often early death. It appears that a defect in lamellar body formation results in the absence or paucity of intercellular membrane bilayers in the stratum corneum, with abnormal barrier function and hyperplasia. In addition, the failure of lamellar body formation would also result in the lack of delivery of hydrolytic enzyme to the interstices, contributing to abnormal desquamation.

Acne
The follicular hyperkeratinization that is an early event in acne has been explained in terms of a localized EFA deficiency in the follicular epithelium. It was proposed that the known low level of sebum linoleate in acne leads to a deficiency of linoleate in the epithelial cells resulting from the competition between sebaceous fatty acids and systemic fatty acids. The linoleate content of acylceramides from surface epidermis was found to be lower in acne patients than in matched normal subjects, and to be particularly small in comedonal acylceramides. Drug treatments for acne that lower sebum secretion rate are known to increase sebum linoleate concentration.

Psoriasis
The possibility of abnormal epidermal lipid metabolism in psoriasis has frequently been investigated. The lipooxygenase products from polyunsaturated fatty acids are greatly elevated in the involved skin in psoriasis, and are somewhat elevated in uninvolved skin relative to normal subjects. In addition, it has been suggested that sphingosine is the natural regulator of keratinocyte proliferation, and may be present in reduced concentration in hyper-proliferative disorders of the epidermis such as psoriasis.

Gaucher's disease
Gaucher's disease (GD) is an autosomal recessive disorder caused by a deficiency in beta-glucocerebrosidase(EC3.2.1.45, beta-D-glucosyl-N-acyl-sphingosine glucocerebrosidase). Since this enzyme normally catalyzes the hydrolysis of glucosylceramides to ceramides, excess glucosylceramide accumulates in the lysosomes of reticuloendothelial cells, resulting in splenic, hepatic, bone, and central nervous system involvement. Although skin involvement in GD had previously been considered uncommon and usually limited to pigmentary changes, a subgroup of type 2 Gaucher patients displaying concurrent scaling abnormalities (collodion baby) has been described recently. The lack of skin manifestations in most patients with GD may relate the residual enzyme activity, because ichthyotic skin involvement in type 2 Gaucher patients is associated with the severe form with very low residual enzyme levels in the extracellular tissues. Previous studies have demonstrated that inhibition of epidermal-glucocerebrosidase activity by topical application of bromoconuritol B epoxide, a specific and covalent inhibitor of this enzyme, induces an abnormality in permeability barrier function in association with a marked increase in epidermal glucosylceramide content and significant alterations in stratum corneum lamellar bilayer structure. The pathogenesis of skin lesions observed with glucocerebrosidase deficiency result primarily from an altered glucosylceramide and ceramide content in the extracellular domains of the stratum corneum. This shows that the conversion of glucosylceramide to ceramide is required to form the intercellular membrane structures which are necessary for normal epidermal permeability barrier function.

Atopic dermatitis
The biochemical events underlying xerotic changes in atopic dermatitis skin are unknown. Previous evidence suggests that these symptoms are mainly associated with the diminished water-permeability barrier and deficient water-holding properties of atopic skin. There is a close relationship between the mass of ceramide and the water-holding properties of the stratum corneum. In atopic dermatitis, a marked reduction in the ceramide fractions, especially ceramide 1, is shown. These suggest that an insufficiency of ceramides in the stratum corneum is an etiologic factor in atopic dry skin.

Drug-induced lipid abnormalities
Nicotinic acid triparanol, which is known to inhibit distal step of cholesterol synthesis, cause abnormal disquamation. 20,25-diazacholesterol (azaacetol) cause palmar-plantar keratoderma in man and generalized hyperkeratosis in rodents.
accompanying significant decrease in free sterol and increase in sphingolipids. 

**CYTOKINE AND EPIDERMAL BARRIER RECOVERY**

Many skin disease relating cornification, hyperkeratinization and dryness are indeed related to the abnormality of one or several combinations of lipids. However the factors governing these lipids’ synthesis are not well-known. Recent studies on the relationship between cytokines and epidermal barrier recovery showed that tumor necrosis factor (TNF)α, interleukin (IL)-1α, β, granulocyte macrophage colony stimulating factor (GM-CSF) and IL-1 receptor antagonist (RA) are increased in hairless mouse epidermis. Transforming growth factor (TGF)β, TNFα, interferon (IFN)-γ, IL-10, IL-8 and TGFα mRNA have been shown to increase in human epidermis after barrier disruption. However discrepancies in the increase of IL-1β and IFN-γ were observed in the mouse and human system. We have also confirmed the increase in IL-1α and TGF-β mRNA in hairless mouse skin. Although there are many changes in cytokines after barrier disruption, we still do not know the exact function in relation to barrier recovery. So far, TNF-α, IL-1 and Interferon α have been shown to increase fatty acid synthesis in liver. Therefore we can predict these cytokines may involve in the fatty acid synthesis in epidermis after barrier disruption. Our observation of the kinetic differences in barrier recovery by different breaking methods may be attributed to the differences in the amount of induced cytokines. Therefore the future studies on the cytokines which have changed during barrier recovery are thought to be important in understanding epidermal lipid homeostasis as well epidermal barrier recovery.

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