thematic review

Thematic review series: Skin Lipids

The role of epidermal lipids in cutaneous permeability barrier homeostasis

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Abstract The permeability barrier is required for terrestrial life and is localized to the stratum corneum, where extracellular lipid membranes inhibit water movement. The lipids that constitute the extracellular matrix have a unique composition and are 50% ceramides, 25% cholesterol, and 15% free fatty acids. Essential fatty acid deficiency results in abnormalities in stratum corneum structure function. The lipids are delivered to the extracellular space by the secretion of lamellar bodies, which contain phospholipids, glucosylceramides, sphingomyelin, cholesterol, and enzymes. In the extracellular space, the lamellar body lipids are metabolized by enzymes to the lipids that form the lamellar membranes. The lipids contained in the lamellar bodies are derived from both epidermal lipid synthesis and extracutaneous sources. Inhibition of cholesterol, fatty acid, ceramide, or glucosylceramide synthesis adversely affects lamellar body formation, thereby impairing barrier homeostasis. Studies have further shown that the elongation and desaturation of fatty acids is also required for barrier homeostasis. The mechanisms that mediate the uptake of extracutaneous lipids by the epidermis are unknown, but keratinocytes express LDL and scavenger receptor class B type 1, fatty acid transport proteins, and CD36. Topical application of physiologic lipids can improve permeability barrier homeostasis and has been useful in the treatment of cutaneous disorders.—Feingold, K. R. **The role of epidermal lipids in cutaneous permeability barrier homeostasis. *J. Lipid Res.* 2007.** 48: **2531–2546.**

Supplementary key words stratum corneum • lamellar body • cholesterol • fatty acids • ceramides

JLR: DR. FEINGOLD, WHAT IS THE KEY FUNCTION OF THE SKIN?

KRF: The chief function of the skin is to form a barrier between the external hostile environment and the internal milieu of the host (1). The skin must protect the host from mechanical insults, ultraviolet light, chemicals, pathogenic microorganisms, etc. Most importantly, to survive in a terrestrial environment without desiccating, the skin must provide a barrier to the loss of water and electrolytes (1). Without a permeability barrier, survival on land would be impossible. Severe burns abrogate these barrier properties and lead to an increased risk of infection and difficulties with maintaining fluid and electrolyte balance. Similarly, in premature infants, the skin is not fully developed and barrier function is impaired; therefore, they also have great difficulties in maintaining fluid and electrolyte balance (2, 3). More subtle functional abnormalities in skin barrier function occur in neonates, in the elderly, and in association with several cutaneous diseases, including psoriasis and atopic dermatitis (4–6).

JLR: WHERE IN THE SKIN ARE THESE BARRIER PROPERTIES LOCALIZED?

KRF: The permeability barrier properties are primarily localized to the outer epidermal layer, the stratum corneum (1). The stratum corneum consists of corneocytes, keratinocytes that have undergone terminal differentiation, surrounded by a neutral lipid-enriched extracellular matrix. The mechanical strength of the skin is provided by the corneocytes, which are encased by a cornified envelope consisting of extensively cross-linked proteins such as involucrin and loricrin. The hydrophobic extracellular lipid matrix provides the barrier to the movement of water and electrolytes (1).

JLR: WHAT LIPIDS ARE IN THIS EXTRACELLULAR MATRIX?

KRF: The lipids that constitute the extracellular matrix of the stratum corneum have a unique composition and

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are very different from the lipids that constitute most biological membranes. On a total lipid mass basis, human stratum corneum is 50% ceramides, 25% cholesterol, and 15% free fatty acids (7). Very little phospholipid is present in the stratum corneum, which is markedly different from what is observed in most other membranes. The specific ceramides present in the stratum corneum are unusual and very diverse. Walter Holleran and colleagues will discuss the origin and importance of this diversity in detail in a review in this series. However, it should be noted that linoleate is present in the acylceramides and that in essential fatty acid deficiency oleate replaces linoleate, resulting in marked abnormalities in cutaneous permeability barrier function associated with an abnormal appearance of the extracellular lipid membranes (8–11). These observations indicate that essential fatty acids are required for the normal structure and permeability barrier function of the stratum corneum. The free fatty acids in human stratum corneum are predominantly straight chained, with 22 and 24 carbon chain lengths being the most abundant (7). Although cholesterol is the major sterol in stratum corneum, cholesterol sulfate is a minor sterol metabolite that plays a key role in regulating desquamation (this will be discussed in detail by Peter Elias and colleagues in another review in this series) (12, 13). The synthesis of cholesterol sulfate in the epidermis is catalyzed by the enzyme cholesterol sulfotransferase. Cholesterol sulfotransferase activity increases with keratinocyte differentiation, and recent studies have shown that SULT2B1b is the isoform that accounts for the cholesterol sulfotransferase activity in the epidermis (14–16). For information on the organization of lipids in the stratum corneum, a recent review by Bouwstra and Ponec (17) provides a comprehensive state-of-the-art update.

JLR: HOW ARE THE LIPIDS DELIVERED TO THE EXTRACELLULAR SPACES OF THE STRATUM CORNEUM?

KRF: The lipid is secreted from keratinocytes in lamellar bodies, which are ovoid, 0.2 × 0.3 μm, membrane bilayer-encircled secretory organelles that are unique to the epidermis (18) (**Fig. 1**). These lamellar bodies are not present in the undifferentiated basal layer of the epidermis, but they begin to appear as keratinocytes differentiate and are first observed in the upper stratum spinosum layer of the epidermis, with increasing numbers found in the stratum granulosum (18). These lamellar bodies contain phospholipids, glucosylceramides, sphingomyelin, and cholesterol (18). In addition, numerous enzymes, including lipid hydrolases such as β glucocerebrosidase, acidic sphingomyelinase, secretory phospholipase A_2, and neutral lipases, and proteases such as chemotryptic enzymes (kallikreins) and cathepsins, are localized to lamellar bodies (18). Moreover, recent studies have shown that antimicrobial peptides, such as human β-defensin 2 and the cathelicidin LL-37, are also present in lamellar bodies (18).

JLR: DO THE LIPIDS IN THE EXTRACELLULAR LIPID MEMBRANES IN THE STRATUM CORNEUM DIFFER FROM THE LIPIDS PACKAGED INTO LAMELLAR BODIES?

KRF: Yes. The lipids in the lamellar bodies are precursors of the stratum corneum extracellular lipids. After secretion, these lamellar body-derived lipids are further metabolized in the stratum corneum extracellular spaces by enzymes that are cosecreted in lamellar bodies (18–22). Specifically, β-glucocerebrosidase converts glucosylceramides into ceramides (23, 24), acidic sphingomyelinase converts sphingomyelin into ceramides (25, 26), and phospholipases convert phospholipids into free fatty acids and glycerol (27, 28). Both Gaucher's disease, caused by a deficiency in β-glucocerebrosidase, and Niemann-Pick disease, caused by a deficiency in acidic sphingomyelinase, lead to defects in the extracellular lipid membranes and abnormal permeability barrier function that result from the impaired conversion of lipid precursors into ceramides (23, 26). Walter Holleran and colleagues will discuss in greater detail the extracellular processing of sphingolipids in the stratum corneum in their review. Of note, disruption of the permeability barrier produces an increase in β-glucocerebrosidase activity and mRNA levels in the epidermis (29). Similarly, disruption of the permeability barrier also increases acidic sphingomylinase activity in the epidermis (25). Thus, the activities of the two key enzymes that are required for the extracellular metabolism of lamellar body lipids to the lipid species that form the lamellar membranes are enhanced after permeability barrier disruption. Additionally, inhibition of phospholipase A_2 activity, which blocks the conversion of phospholipids to free fatty acids, also leads to defects in the structure of the extracellular lipid membranes and permeability barrier homeostasis (27, 28). There are several different isoforms of phospholipase A_2 expressed in the epidermis, and which specific isoforms are important for the extracellular catabolism of phospholipids to fatty acids in the stratum corneum remains to be determined (30, 31). Finally, the cholesterol sulfate in the stratum corneum is metabolized by the lamellar body-derived enzyme, steroid sulfatase, to cholesterol [see the review by Peter Elias and colleagues (32) for a detailed discussion of the important role of the steroid sulfatase-mediated breakdown of cholesterol sulfate in regulating corneocyte desquamation].

JLR: DOES THIS EXTRACELLULAR PROCESSING OF LIPIDS HAVE OTHER IMPORTANT EFFECTS IN ADDITION TO PROVIDING THE LIPIDS REQUIRED FOR THE FORMATION OF THE EXTRACELLULAR LIPID MEMBRANES THAT MEDIATE PERMEABILITY BARRIER FUNCTION?

KRF: Yes. In fact, a number of key stratum corneum functions are derived in part from this extracellular processing of lipids. The glycerol that is formed by the breakdown of phospholipids by phospholipases plays a role in the stratum corneum as a water-holding agent, which helps to keep the stratum corneum hydrated. Hydration is

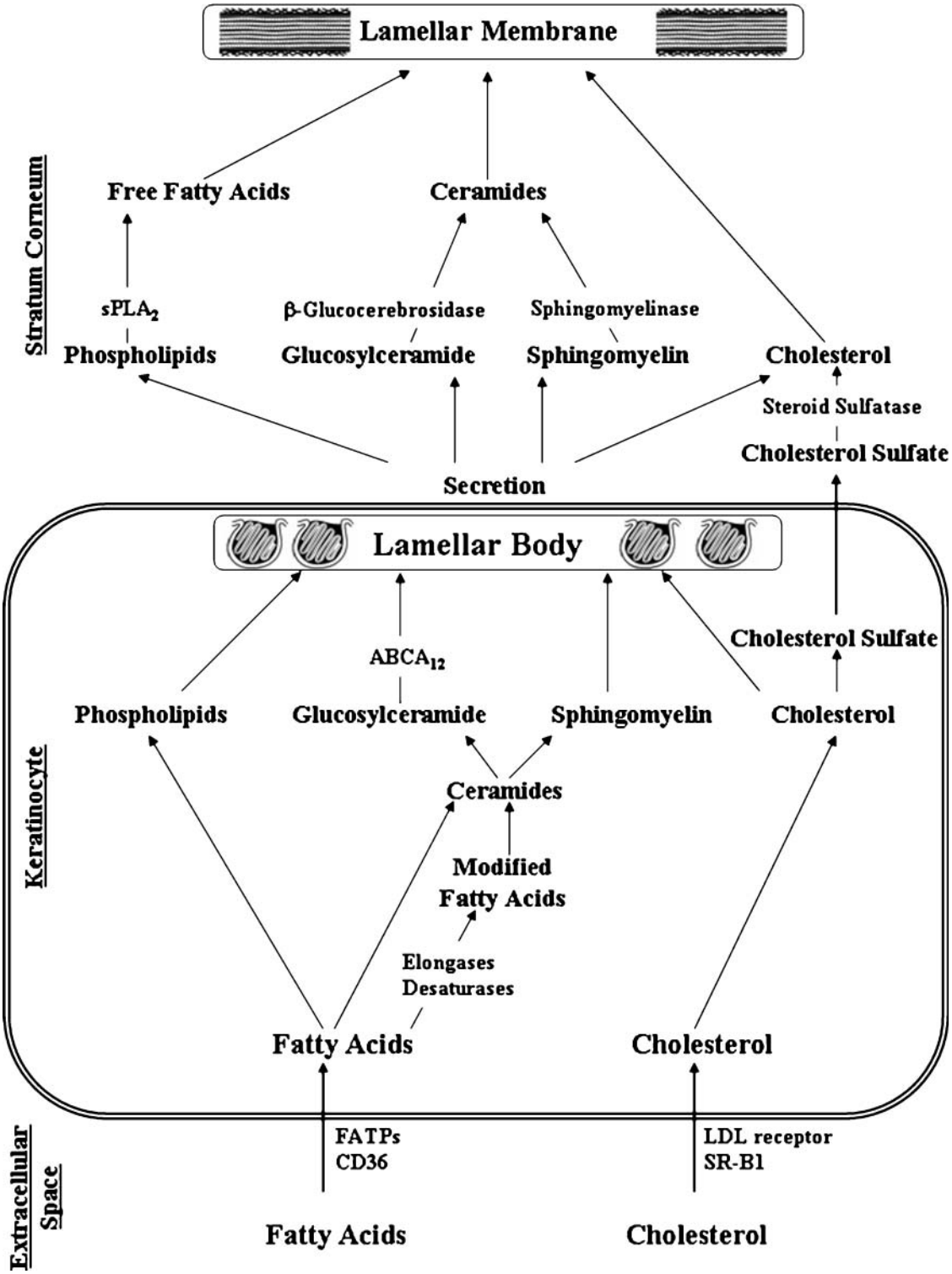

Fig. 1. Pathways for the formation of the extracellular lamellar lipid membranes that provide for the permeability barrier.

crucial for a smooth and flexible skin, and changes in hydration status signal several downstream responses, including epidermal DNA synthesis and catabolism of filaggrin into deiminated carboxylic acid metabolites (33–37).

The free fatty acids that are formed by phospholipid breakdown contribute to the acidification of the stratum corneum (38, 39). The pH of the outer stratum corneum and skin surface in humans and animals ranges from 5 to 5.5 (40). This acidic environment is very important, as it regulates the activity of many of the enzymes in the stratum corneum (40). For example, the activities of both β-glucocerebrosidase and acidic sphingomyelinase are optimal at or below pH 5.5, which is very similar to the pH of the stratum corneum. Conversely, many of the proteases

in the stratum corneum have a pH optimum of 7 or higher; therefore, their activities are decreased at the usual stratum corneum pH of 5.5. If the pH of the stratum corneum is increased, the activities of β-glucocerebrosidase and acidic sphingomyelinase are reduced and the extracellular processing of glucosylceramides and sphingomyelins to ceramides is impaired, leading to abnormalities in the structure of the extracellular lipid membranes and decreased permeability barrier function (4, 41–43). Furthermore, increases in stratum corneum pH stimulate protease activity, resulting in increased corneocyte desquamation (4, 41, 42). In newborns, the pH of the stratum corneum is increased, which could explain the decreased permeability barrier homeostasis and epidermal fragility that is observed during the neonatal period (4). Similarly, many cutaneous inflammatory disorders also are associated with increases in stratum corneum pH, which could adversely affect enzyme activity in the stratum corneum, resulting in a decrease in permeability barrier function and stratum corneum integrity and cohesion (40). Finally, the breakdown of cholesterol sulfate to cholesterol by the enzyme steroid sulfatase plays an important role in regulating desquamation (12, 13, 32). Steroid sulfatase deficiency results in recessive X-linked ichthyosis, which will be discussed in detail in the review by Peter Elias and colleagues (12, 13, 32). Additionally, cholesterol sulfate stimulates keratinocyte differentiation, adversely affects permeability barrier function, and inhibits cholesterol synthesis and HMG-CoA reductase activity in keratinocytes (44–48).

JLR: IS ANYTHING KNOWN ABOUT HOW LAMELLAR BODIES ARE FORMED?

KRF: The structural proteins that constitute the lamellar bodies have not yet been identified, and the details of lamellar body formation are not well understood. The incorporation of the lipid hydrolases and proteases into lamellar bodies requires the prior or concurrent delivery of lipid to the lamellar bodies (49). If lipids are deficient, the enzymes that are characteristically found in lamellar bodies are not transported from the Golgi to the lamellar bodies (49). Recent studies have shown that ABCA12, a member of the ABC family of transporters, is required for lamellar body formation (50, 51). Mutations in ABCA12 result in the failure to form normal lamellar bodies and extracellular lipid membranes (50, 51). Severe mutations in ABCA12 are associated with harlequin ichthyosis, a disease that is often fatal in childhood, whereas milder partial loss-of-function mutations in ABCA12 are associated with a less severe phenotype of lamellar ichthyosis type 2 (these disorders will be discussed in greater detail in the review by Peter Elias and coworkers) (50–54).

JLR: WHAT REGULATES LAMELLAR BODY SECRETION?

KRF: Acute disruption of the permeability barrier by mechanical forces (i.e., sequential tape stripping), solvents (i.e., acetone), or detergents (i.e., SDS) initiates a homeostatic repair response that results in the rapid recovery of permeability barrier function (55, 56). The first step in this repair response is the rapid secretion (within minutes) of the contents of the lamellar bodies from the outer stratum granulosum cells, resulting in a marked decrease in the number of lamellar bodies in stratum granulosum cells (50–80% of preexisting lamellar bodies are secreted) (57). Newly formed lamellar bodies begin to reappear in the stratum granulosum cells, and accelerated secretion continues until permeability barrier function returns toward normal (57). If one artificially restores permeability barrier function to normal by application of an impermeable membrane, one can inhibit the further secretion of lamellar bodies (57).

JLR: HOW DO THE STRATUM GRANULOSUM CELLS KNOW THAT THE PERMEABILITY BARRIER IS DISTURBED AND THAT IT IS TIME TO SECRETE LAMELLAR BODIES AND INITIATE THE HOMEOSTATIC REPAIR PROGRAM?

KRF: Within the epidermis, there is a calcium gradient with high levels of extracellular calcium in the upper epidermis surrounding the stratum granulosum cells (58, 59). Immediately after barrier disruption, the increased water movement through the compromised stratum corneum carries calcium outward toward the skin surface, resulting in a reduction in the calcium concentration surrounding the stratum granulosum cells (60–62). This change in calcium concentration appears to be the primary signal inducing lamellar body secretion. If one prevents the reduction in calcium levels by providing exogenous calcium, lamellar body secretion does not occur and permeability barrier repair is not initiated (60–62). Conversely, if one decreases the calcium surrounding the stratum granulosum cells without disrupting the permeability barrier by either iontophoresis or sonophoresis, lamellar body secretion is stimulated (63, 64). It is likely that potassium and other ions also play a role in this signaling process (65–67). In addition, other nonionic signals generated in the stratum corneum and by keratinocytes may also influence the repair response (for review, see Ref. 68). For example, cytokines such as interleukin-1α (IL-1α) are stored at high concentrations in the stratum corneum and are rapidly released after barrier disruption (69–71). Mice deficient in IL-1, IL-6, and tumor necrosis factor-α signaling have a delay in permeability barrier repair after acute barrier disruption, indicating a role for these cytokines in regulating permeability barrier homeostasis (25, 72, 73).

JLR: WHERE DO THE LIPIDS IN THE LAMELLAR BODIES COME FROM? FOR EXAMPLE, WHAT IS THE SOURCE OF LAMELLAR BODY CHOLESTEROL?

KRF: The epidermis on a weight basis is a very active site of cholesterol synthesis (74). Moreover, after acute barrier

disruption, there is a rapid and marked increase in epidermal cholesterol synthesis (75). The increase in cholesterol synthesis is associated with an increase in the activity, protein, and mRNA levels of HMG-CoA reductase, a key enzyme in the cholesterol biosynthetic pathway (76–78). Furthermore, after acute barrier disruption, a marked increase in the percentage of HMG-CoA reductase in the active dephosphorylated form is observed (77). Increased enzyme activation is observed as early as 15 min after acute permeability barrier disruption, and the degree of disruption required to activate the enzyme is less than that required to increase enzyme mass. The increase in HMG-CoA reductase activity occurs in both the upper and lower epidermis (79). Additionally, mRNA levels of other key enzymes in the cholesterol synthetic pathway, including HMG-CoA synthase, farnesyl diphosphate synthase, and squalene synthase, also increase after acute barrier disruption (80). Preliminary studies by our laboratory have suggested that the active forms of sterol-regulatory element binding protein-1 (SREBP-1) and SREBP-2 increase after barrier disruption, which could explain the concordant increase in the enzymes of the cholesterol synthetic pathway.

Evidence that disruption of the permeability barrier signals the increase in cholesterol synthesis is demonstrated by experiments in which an artificial permeability barrier is provided by occlusion with an impermeable membrane. Under these conditions, the increase in epidermal cholesterol synthesis and the increase in mRNA levels of the cholesterol synthetic enzymes are inhibited (75, 77, 80). Most importantly, if one inhibits the increase in epidermal cholesterol synthesis by topical application of statins, which inhibit HMG-CoA reductase activity and decrease cholesterol synthesis, the recovery of permeability barrier function is delayed (81). The initial wave of lamellar body secretion occurs, but the reappearance of lamellar bodies is delayed and those organelles that do appear have an abnormal internal structure. These abnormalities can be reversed by topical treatment with either cholesterol, the final product of the synthetic pathway, or mevalonate, the product formed by HMG-CoA reductase, indicating that these defects are not attributable to nonspecific effects of the topical application of statins (81). Of note, mice with a deficiency of 3β-hydroxysterol-Δ24, the enzyme that catalyzes the conversion of desmosterol to cholesterol, have abundant desmosterol but no cholesterol in the epidermis. These animals die within a few hours after birth from an impaired cutaneous permeability, providing additional evidence for the importance of cholesterol for normal permeability barrier function (82). Together, these results demonstrate an important role for epidermal cholesterol synthesis in permeability barrier homeostasis.

JLR: IS FATTY ACID SYNTHESIS IN THE EPIDERMIS ALSO IMPORTANT FOR BARRIER REPAIR?

KRF: The epidermis is also a very active site of fatty acid synthesis, and disruption of the permeability barrier results in a rapid and marked increase in fatty acid synthesis (74, 83). Barrier disruption increases the activities and mRNA levels of both of the key enzymes required for de novo fatty acid synthesis, acetyl-CoA carboxylase and fatty acid synthase (80, 84). The increase in acetyl-CoA carboxylase and fatty acid synthase induced by permeability barrier disruption is likely attributable to an increase in the activation of SREBPs. Once again, occlusion with an impermeable membrane that restores permeability barrier function prevents the increase in fatty acid synthesis and the increase in the expression of acetyl-CoA carboxylase and fatty acid synthase (80, 83, 84). Moreover, after acute barrier disruption, inhibition of fatty acid synthesis by the topical application of the acetyl-CoA carboxylase inhibitor, 5-(tetradecyloxy)-2-furancarboxylic acid (TOFA), delays the recovery of permeability barrier function (85). The initial wave of lamellar body secretion occurs normally, but the ability of the epidermis to synthesize new lamellar bodies is impaired and those lamellar bodies that are formed display abnormal lamellar membranes. These abnormalities in barrier repair and lamellar body formation can be reversed by topical treatment with free fatty acids, indicating that these defects are not the nonspecific effects of TOFA (85). These results demonstrate an important role for epidermal de novo fatty acid synthesis in permeability barrier homeostasis.

JLR: IS THERE ANY EVIDENCE THAT THE ELONGATION OF FATTY ACIDS IS IMPORTANT FOR PERMEABILITY BARRIER HOMEOSTASIS?

KRF: Relatively few studies have examined this issue, and the effect of permeability barrier disruption on the expression of the enzymes involved in the elongation of fatty acids has not yet been examined. Of note, animals deficient in ELOVL4 (for elongation of very long chain fatty acid-4) have a severely compromised permeability barrier and die soon after birth (86–89). These animals have deficient lamellar body contents and a paucity of lamellar membranes in the stratum corneum, which would account for the permeability barrier abnormality (89). Lipid analysis revealed a global deficiency of very long chain fatty acids in the epidermis and the absence of ω-*O*-acylceramides, which are key components of the extracellular lipid membranes of the stratum corneum (see the review by Walter Holleran and colleagues for additional information regarding the role of specific ceramides in permeability barrier homeostasis) (87–89). These observations demonstrate the importance of ELOVL4 in generating at least one of the lipids required for normal permeability barrier homeostasis. ELOV3 knockout mice also have a defective permeability barrier and abnormalities in stratum corneum structure, but because this enzyme is predominantly expressed in sebaceous glands and has only minimal expression in keratinocytes, it is currently hypothesized that the defects in stratum corneum structure and function are secondary effects (90).

JLR: IS DESATURATION OF FATTY ACIDS IMPORTANT FOR PERMEABILITY BARRIER HOMEOSTASIS?

KRF: The effects of permeability barrier disruption on the expression of enzymes that desaturate fatty acids have not been examined. Studies have shown that animals that are deficient in SCD2 (for stearoyl-CoA desaturase 2) have a defective permeability barrier, and many die soon after birth (91). The barrier defect is associated with a decrease in lamellar body contents and a decrease in lamellar membranes in the stratum corneum (91). In the SCD2-deficient mice, the content of linoleic acid in the acylceramide fraction was markedly reduced with increased linoleic acid in phospholipids, suggesting alterations in the partitioning of linoleic acid (91). Given the important role of acylceramides in permeability barrier function, the reduction of acylceramides containing linoleic acid could account for the observed barrier abnormalities. Of note is that ~30% of the animals survive, and in these animals SCD1 appears to compensate for the absence of SCD2 (91). However, in animals deficient in SCD1 (asebia mice), there are no abnormalities in permeability barrier homeostasis (SCD1-deficient mice have a sebaceous gland defect that will be discussed in Diane Thiboutot's review in this series) (92). The absence of defects in permeability barrier function in asebia mice that have marked abnormalities in sebaceous glands and the presence of normal permeability barrier function in areas of human skin with a paucity of sebaceous glands indicate that the lipids produced by sebaceous glands are not essential for permeability barrier homeostasis (92, 93). However, stratum corneum hydration is decreased in asebia mice that are deficient in sebaceous glands and in areas of human skin with a decreased number of sebaceous glands (92, 93). The triglycerides in sebaceous lipids are metabolized by lipases to free fatty acids and glycerol, and a decrease in glycerol in areas with reduced sebaceous gland activity leads to a decrease in stratum corneum hydration (92, 93).

JLR: ARE THERE FATTY ACID BINDING PROTEINS IN KERATINOCYTES?

KRF: Yes. Epidermal fatty acid binding protein (E-FABP) is expressed in keratinocytes (E-FABP has also been called C-FABP in rats, MAL 1 in mice, and PA-FABP in humans) (94–97). The amount of E-FABP increases with keratinocyte differentiation, and immunohistochemistry studies have demonstrated that the intensity of staining is greatest in the upper epidermis (96, 98, 99). The expression of brain, liver, and heart FABP is not usually detected in the epidermis (100, 101). Acute disruption of the permeability barrier induces E-FABP expression, and this increase can be prevented by covering with a vapor-permeable membrane (102). Additionally, inflammatory disorders, including psoriasis, are associated with increased E-FABP levels in the epidermis (95, 97, 98). In animals deficient in E-FABP, basal transepidermal water loss is lower than in wild-type animals, indicating better barrier function (100, 101). After acute barrier disruption, the return of barrier function to normal follows very similar kinetics to those observed in wild-type animals, indicating that a deficiency in E-FABP does not markedly impair normal permeability barrier homeostasis (100, 101). Of note, though, is that heart FABP is expressed in the epidermis of E-FABP knockout mice (usually not detectable in wild-type mice), and it is possible that this increase in heart FABP compensates for the absence of E-FABP (100, 101).

JLR: THE FATTY ACIDS PRODUCED IN THE EPIDERMIS WILL SERVE AS PRECURSORS FOR BOTH PHOSPHOLIPIDS AND CERAMIDES. WHAT IS KNOWN ABOUT THE SYNTHESIS OF PHOSPHOLIPIDS IN THE EPIDERMIS?

KRF: Although phospholipids are essential constituents of lamellar bodies, little is known about the regulation of the enzymes of phospholipid synthesis in the epidermis. Recent studies in our laboratory have focused on several of the enzymes involved in phospholipid synthesis (103). AGPAT (for 1-acyl-*sn*-glycerol-3-phosphate acyltransferase) catalyzes the acylation of lysophosphatidic acid to form phosphatidic acid, the major precursor of all glycerolipids. The expression pattern of AGPAT isoforms is unique, with relatively high constitutive expression of AGPAT 3, 4, and 5 but low constitutive expression of AGPAT 1 and 2 in murine epidermis (103). Localization studies indicated that all five isoforms of AGPAT were expressed in all nucleated layers of the epidermis (103). Moreover, acute permeability barrier disruption rapidly increased AGPAT 1, 2, and 3 mRNA levels, and this increase was sustained for at least 24 h (103). In parallel with the increase in mRNA levels, an increase in AGPAT activity also occurred (103). Additionally, the increase in AGPAT expression could be partially reversed by artificial barrier restoration by occlusion with an impermeable membrane, indicating that the expression of AGPATs is linked to permeability barrier requirements (103). In contrast, mitochondrial *sn*-glycerol-3-phosphate acyltransferase expression did not change after permeability barrier disruption (103).

JLR: ARE THERE OTHER PATHWAYS OF FATTY ACID METABOLISM THAT PLAY A ROLE IN PERMEABILITY BARRIER FUNCTION?

KRF: The LOX (for lipoxygenase) pathway in the epidermis plays a role in epidermal differentiation and hence permeability barrier function (104). Mutations in either 12*R*-LOX or eLOX-3 are associated with autosomal recessive congenital ichthyosis (these disorders will be discussed in detail in the review by Peter Elias) (105–107). Both 12*R*-LOX and eLOX-3 are localized to the differentiated stratum granulosum layer of the epidermis and convert arachidonic acid to hepoxilin- and trioxilin-like compounds that are believed to play a role in regulating keratinocyte

differentiation (105, 108–111). Moreover, very recent studies have shown that the creation of 12*R*-LOX-deficient mice results in a severe impairment in barrier function, with the mice dying soon after birth from a defective barrier (108). Abnormalities were not observed in the extracellular lipid lamellar membranes that mediate barrier function, and the levels of total fatty acids, cholesterol, and ceramides were not different from those in wild-type mice (108). However, in the protein-bound ceramide fraction that is covalently bound to the cornified envelope, there were alterations in the distribution of ceramide species, which might account for the permeability barrier abnormality (108). How metabolites of the LOX pathway are linked with epidermal differentiation and permeability barrier formation remains to be elucidated.

JLR: WHAT IS KNOWN ABOUT THE ROLE OF PERMEABILITY BARRIER FUNCTION IN REGULATING CERAMIDE SYNTHESIS IN THE EPIDERMIS?

KRF: Acute barrier disruption stimulates sphingolipid synthesis in the epidermis, and this increase in synthesis occurs in both the lower and upper epidermal layers (112, 113). However, in contrast to cholesterol and fatty acid synthesis, the increase in sphingolipid synthesis is delayed, first occurring at 6 h after barrier disruption (112). Additionally, the activity and mRNA levels of serine palmitoyl transferase, the first enzyme in the sphingolipid pathway, increase after barrier disruption (80, 112, 113). Occlusion with an impermeable membrane can inhibit the increase in sphingolipid synthesis and the increased expression of serine palmitoyl transferase, demonstrating the link with permeability barrier function (112, 113). Most importantly, the topical application of β-chloro-L-alanine, an inhibitor of serine-palmitoyl transferase activity, slowed permeability barrier recovery at the late time points and reduced the number of lamellar bodies in stratum granulosum cells and sphingolipids in the stratum corneum (114). This inhibition was overridden by coapplications of ceramides, indicating that the delay in repair was not attributable to the nonspecific toxicity of β-chloro-L-alanine (114). These studies demonstrate a key role for epidermal ceramide synthesis in the latter phase of permeability barrier repair.

JLR: ARE THESE CERAMIDES MODIFIED?

KRF: As noted above, glucosylceramides are the key ceramide constituent of lamellar bodies. Glucosylceramides are synthesized from ceramides by the enzyme, glucosylceramide synthase (UDP-glucose:ceramide glucosyltransferase). Under basal conditions, glucosylceramide synthase activity is localized predominantly in the outer epidermis (115, 116). Surprisingly, disruption of the permeability does not alter glucosylceramide synthase activity (115). However, topical treatment with an inhibitor of glucosylceramide synthase activity, P4 (D-1-threo-1-phenyl-2-hexadecanoylamino-3-pyrrolidino-1-propanol), delays barrier recovery after acute disruption (115). These results demonstrate that glucosylceramides are essential for permeability barrier homeostasis but that baseline epidermal glucosylceramide synthase activity appears sufficient to accommodate acute challenges to the barrier. Recent studies have confirmed the importance of glucosylceramide synthase for permeability barrier homeostasis. Mice with an epidermis-specific deficiency of glucosylceramide synthase have marked abnormalities in permeability barrier function and die soon after birth (117). Not unexpectedly, they have abnormalities in both lamellar body and stratum corneum structure (117).

JLR: IS TRIGLYCERIDE SYNTHESIS IMPORTANT FOR PERMEABILITY BARRIER FUNCTION?

KRF: Triglycerides are synthesized in the epidermis, but their role in permeability barrier homeostasis is poorly defined. Diacylglycerol acyltransferase (DGAT2) is expressed in the epidermis, whereas the expression of DGAT1 is barely detectable (118). DGAT2 knockout mice have abnormalities in permeability barrier function, which contribute to their demise soon after birth (118). The number of lamellar bodies is normal, but the internal content of the lamellar bodies and the quantity of lamellar membranes in the extracellular space of the stratum corneum are greatly reduced (118). However, it is unclear whether these abnormalities in cutaneous function are attributable to the absence of DGAT2 in the epidermis. When the skin of DGAT2 mice was transplanted to normal mice, epidermal permeability barrier function normalized, suggesting that the defects in permeability barrier function were not simply the result of the absence of DGAT2 in the epidermis (118).

JLR: ARE THERE ANY CLINICAL ABNORMALITIES THAT OCCUR SECONDARY TO DECREASED LIPID SYNTHESIS IN THE EPIDERMIS?

KRF: In the elderly, permeability barrier function, measured by transepidermal water loss, is normal or even better than normal at baseline (5). However, after acute permeability barrier disruption, both aged mice and humans (>75 years of age) have a delay in permeability barrier recovery associated with a decrease in lamellar body secretion and extracellular lipids in the stratum corneum (5). A decrease in both cholesterol synthesis and the activity of HMG-CoA reductase was seen in the aged animals in the basal state, and the usual stimulation of cholesterol synthesis and HMG-CoA reductase activity that is induced by acute permeability barrier disruption was blunted (119). Moreover, topical treatment with either cholesterol or mevalonate markedly improved permeability barrier homeostasis in aged animals (119, 120). These results demonstrate that aging results in a decrease in epidermal cholesterol synthesis, which negatively affects permeability barrier homeostasis.

Additionally, treatment with either topical or systemic glucocorticoids decreases epidermal lipid synthesis, resulting in abnormalities is permeability barrier homeostasis (121). Decreases in cholesterol, fatty acid, and ceramide synthesis were seen in the epidermis of animals treated with glucocorticoids and in human keratinocyte cultures incubated with glucocorticoids (121). The abnormality in permeability barrier homeostasis induced by glucocorticoids was corrected by topical treatment with a mixture of stratum corneum lipids (121). It should be recognized that glucocorticoid levels may be increased by a variety of different circumstances; hence, many different and diverse clinical conditions could result in decreases in epidermal lipid synthesis and abnormalities in permeability barrier homeostasis. For example, it has been shown that psychological stress in both mice and humans results in impaired permeability barrier homeostasis (122–125). Studies have further shown that in psychologically stressed animals, epidermal lipid synthesis is decreased, leading to decreased lamellar body formation (126). These abnormalities could be prevented by inhibiting either glucocorticoid action with RU-486 or glucocorticoid production with antalarmin, a corticotropin-releasing hormone receptor antagonist (127). Additionally, the abnormalities in permeability barrier homeostasis in psychologically stressed animals could be improved by treatment with topical lipids (126).

JLR: ARE THE RELATIVE QUANTITIES OF THE KEY LIPIDS IMPORTANT?

KRF: It is clear that cholesterol, ceramides, and fatty acids are required for the formation of lamellar bodies in keratinocytes. When one topically applies a lipid mixture containing equimolar concentrations of all three essential lipids, permeability barrier recovery after acute disruption is normal (128–130). In contrast, topical application of any one or two of the three key lipids to acutely perturbed skin actually results in a delay in permeability barrier repair associated with abnormal-appearing lamellar bodies (128–130). Both complete and incomplete mixtures of the three key lipids rapidly traverse the stratum corneum and are taken up by stratum granulosum cells, thereby markedly altering the molar distribution of lipids, leading to abnormalities in the formation of lamellar bodies (128–130). Along similar lines, chronic topical treatment with statins also results in abnormalities in lamellar body structure and permeability barrier homeostasis (57, 131). However, this is not attributable to a deficiency in cholesterol content, as cholesterol synthesis is normal as a result of the marked upregulation of HMG-CoA reductase (131). Rather, fatty acid synthesis is also markedly stimulated, which leads to an excess of fatty acids that alters the structure of lamellar bodies (57, 131). Thus, to synthesize lamellar bodies, the key lipids must be present in appropriate distributions, and an excess or deficiency of a particular lipid can disturb lamellar body formation.

JLR: ARE EXTRACUTANEOUSLY DERIVED LIPIDS IMPORTANT FOR PERMEABILITY BARRIER HOMEOSTASIS?

KRF: A number of lines of evidence suggest that extracutaneous lipids make a significant contribution to maintaining permeability barrier homeostasis. First, in the inhibitor experiments described above, despite a marked inhibition of lipid synthesis (e.g., topical statin treatment acutely inhibited cholesterol synthesis by >90%), the inhibition of permeability barrier recovery is relatively modest (81, 85, 114). This discrepancy suggests that alternative sources of lipid are available for the formation of lamellar bodies and the regeneration of stratum corneum lipid membranes. Second, studies in humans and animals have shown that systemically administered labeled cholesterol and fatty acids are delivered to the epidermis (75, 83, 132, 133). Third, essential fatty acids are present in the stratum corneum in large quantities and are required for the maintenance of a competent barrier (8–11). By definition, these essential fatty acids are obtained only from dietary sources. Fourth, plant sterols, which are of dietary origin, are present on the skin surface (132, 134, 135). Fifth, the epidermis lacks Δ6 and Δ5 desaturase activity and therefore must obtain arachidonic acid from extraepidermal sites (136, 137). Sixth, plant-derived fatty acids accumulate in the epidermis in certain disease states, such as Refsum's disease (138). Lastly, studies have shown that adding glucosylceramides to the diet can improve permeability barrier function (139). Together, these observations indicate that extracutaneous sources contribute to the epidermal lipid pool, but the precise contribution has not been determined.

JLR: ARE LIPOPROTEIN RECEPTORS PRESENT ON KERATINOCYTES?

KRF: Undifferentiated keratinocytes in culture have LDL receptors, but with differentiation the LDL receptors are no longer present on the plasma membranes of keratinocytes (140–142). In agreement with the in vitro studies, in vivo studies have demonstrated that LDL receptors are present only on the basal cells of normal murine and human epidermis (i.e., undifferentiated cells) (143, 144). However, in hyperplastic disorders with associated permeability barrier abnormalities, such as essential fatty acid deficiency or psoriasis, LDL receptors are expressed in the more differentiated stratum spinosum and stratum granulosum (144). Moreover, acute permeability barrier disruption induces an increase in LDL receptor mRNA and protein levels in the epidermis, and this increase can be inhibited by occlusion with an impermeable membrane that restores permeability barrier function (76). In unpublished studies, we have not observed a defect in permeability barrier homeostasis in LDL receptor knockout mice, indicating that the LDL receptor is not essential for the formation and maintenance of a normal permeability barrier. The other lipoprotein receptor ex-

pressed in keratinocytes is scavenger receptor class B type I (SR-BI). SR-BI is present in cultured human keratinocytes, and calcium-induced differentiation markedly decreases SR-BI levels (145). SR-BI mRNA is also expressed in murine epidermis, and SR-BI mRNA levels increase by 50% after acute barrier disruption (145). Additionally, using immunofluorescence, we demonstrated that SR-BI is present in human epidermis, predominantly in the basal layer, and increases after barrier disruption (145). The increase is completely blocked by occlusion with an impermeable membrane, indicating that the increase in epidermal SR-BI expression is regulated by permeability barrier requirements (145). The precise role of SR-BI in permeability barrier homeostasis remains to be determined. SR-BI could facilitate the uptake of cholesterol from HDL particles.

JLR: ARE THE APOLIPOPROTEINS THAT INTERACT WITH LIPOPROTEIN RECEPTORS PRODUCED IN THE EPIDERMIS?

KRF: The best studied is apolipoprotein E. Studies have shown that apolipoprotein E is synthesized by keratinocytes in culture and in vivo in the epidermis (76, 146, 147). In fact, human epidermal skin grafts transplanted onto mice result in the appearance of human apolipoprotein E in the serum, demonstrating that the production of apolipoprotein E in the skin may result in the systemic delivery of apolipoprotein E (148). The expression of apolipoprotein E in the epidermis is specified by a unique 1.0 kb enhancer domain located 1.7 kb downstream of the apolipoprotein E gene (149). Deletion of this enhancer resulted in the lack of expression of apolipoprotein E in the epidermis. Epidermal apolipoprotein E mRNA levels are increased by ~2-fold after acute disruption of the permeability barrier (76). In unpublished studies, we have not noted any alteration in permeability barrier homeostasis in apolipoprotein E knockout mice. In addition to apolipoprotein E, studies have shown that apolipoprotein A-II and serum amyloid A, a protein that can associate with HDL, are made by epidermal cells (150, 151). Of note is the fact that apolipoprotein A-I is made by chicken and carp epidermis but does not appear to be made in mammalian epidermis (152, 153).

The role of these apolipoproteins in epidermal biology remains to be determined. One can speculate that they could play a role in the movement of lipids between cells in the epidermis. The outer epidermal stratum granulosum cells require large quantities of lipids for lamellar body formation, and the lower epidermal basal cells synthesize and take up lipids from the circulation. The apolipoproteins and lipoprotein receptors could facilitate the movement of lipid between epidermal cells. In support of this concept are studies demonstrating that LCAT is made by the basal cells of the epidermis (154). LCAT mediates the conversion of cholesterol to cholesteryl esters in lipoprotein particles, which allows for the efficient removal of cholesterol from cells. In addition, recent studies by our laboratory have shown that ABCA1 is made in both the upper and lower epidermis, and acute disruption of the permeability barrier results in the downregulation of ABCA1 expression in both the upper and lower epidermis (155). This decrease in ABCA1 may reflect a reduction in free cellular cholesterol and a decrease in the conversion of cholesterol to oxysterols, activators of liver X receptor (LXR). Similar to other cells, ABCA1 expression is stimulated by LXR activators in keratinocytes, and an increase in cellular cholesterol activates LXR but a decrease in cellular cholesterol decreases the activation of LXR (155).

JLR: ARE TRANSPORTERS FOR THE UPTAKE OF FATTY ACIDS PRESENT IN THE EPIDERMIS?

KRF: In cultured keratinocytes, studies have shown that fatty acid uptake is mediated by a transport system that is temperature-sensitive, has saturable kinetics, and is decreased by trypsin treatment (156, 157). Additionally, fatty acid uptake in keratinocytes demonstrated a higher specificity for linoleic acid and arachidonic acid than for oleic acid, indicating a preference for fatty acids that must be obtained from extraepidermal sources (157). Recent studies in our and other laboratories have shown that FATP1 (for fatty acid transport protein 1), -3, -4, and -6 along with CD36 (a fatty acid transporter) are expressed in murine epidermis (158–160). After permeability barrier disruption, there was an increase in FATP1 and -6 and CD36 (158, 160). Additionally, studies have shown that permeability barrier disruption increases CD36 mRNA levels and that this increase can be blocked by occlusion with an impermeable membrane (158). Of note is that mice with spontaneous mutations in FATP4 or certain targeted disruptions of FATP4 display a restrictive dermopathy and a markedly defective permeability barrier function, which leads to death soon after birth (161, 162). Notably, transgenic mice that overexpress FATP4 only in the epidermis can rescue mice with a spontaneous mutation in FATP4 (163).

This result, together with the results seen with a targeted disruption of FATP4, indicates that it is the absence of FATP4 in the epidermis that causes the phenotypic changes, not the alterations in fatty acid metabolism in other tissues. Additionally, studies in mice with a temporally controlled disruption of FATP4 in the epidermis have demonstrated a cutaneous phenotype with defective permeability barrier function, but the phenotype was not nearly as severe as that seen in neonates (164). The explanation for the milder phenotype in adult animals could be compensation by other FATPs. As noted above, studies in adult mice have shown that several FATPs are present in the epidermis, including FATP1, -3, -4, and -6 (160). However, studies of embryonic expression at day 18.5 revealed that FATP1 was not expressed in epidermis, whereas the expression of FATP4 was relatively increased compared with the expression in adult epidermis (160). Thus, it is possible that newborn animals are more susceptible to the

absence of FATP4, whereas in adult mice the other FATPs can partially compensate for the deficiency of FATP4. In contrast, CD36 knockout mice and humans with a deficiency of CD36 do not have an apparent skin phenotype (165, 166). These studies demonstrate the potentially important role of fatty acid transporters in the epidermis.

JLR: EARLIER, YOU POINTED OUT THAT THE STRATUM CORNEUM IS COMPOSED OF CORNEOCYTES AND EXTRACELLULAR LIPIDS. IS THE FORMATION OF THESE TWO COMPARTMENTS COORDINATED?

KRF: As readers of this journal know very well, there are a variety of cellular sensors that monitor intracellular lipid levels and regulate the expression of genes. Several nuclear hormone liposensors, including peroxisome proliferator-activated receptor α (PPARα), PPARβ/Δ, PPARγ, and LXR-α and -β, are expressed in keratinocytes (167–169). Studies by our laboratory and others have shown that activation of PPARs and LXRs has major effects on epidermal/keratinocyte function. First, the addition of PPAR/LXR ligands to cultured human keratinocytes and the topical application of PPAR/LXR ligands to murine skin results in the increased expression of keratinocyte differentiation-related proteins, such as involucrin, loricrin, profilaggrin, and transglutaminase 1, which would stimulate cornified envelope formation (167, 170–177). Second, PPAR/LXR ligands are anti-inflammatory, decreasing the inflammation seen in response to phorbol 12-myristate-13-acetate treatment, a model of irritant contact dermatitis (176–179). Third, PPAR/LXR ligands increase cholesterol sulfotransferase activity, which would increase the synthesis of cholesterol sulfate (180). Finally, topical treatment of murine skin with PPAR/LXR ligands improves permeability barrier homeostasis, resulting in an acceleration of barrier recovery after acute disruption (174–177).

Associated with this improvement in permeability barrier homeostasis are increases in *a*) epidermal cholesterol, fatty acid, and sphingolipid synthesis, *b*) lamellar body number and secretion, and *c*) β-glucocerebrosidase activity, all of which could contribute to the enhanced barrier homeostasis (181, 182). Furthermore, recent studies have shown that PPAR/LXR activation increases the expression of ABCA12, a transporter required for the transport of lipids into lamellar bodies (183). Thus, we postulate that as the lipids that are required for the formation of lamellar bodies accumulate in keratinocytes, the increase in fatty acids and their metabolites would activate PPARs and the increase in oxidized cholesterol would activate LXRs. The activation of these nuclear hormone receptors would in turn stimulate the expression of genes required for corneocyte formation (e.g., involucrin, loricrin, filaggrin, and transglutaminase 1). In addition, activation of these nuclear hormone receptors would also stimulate the formation and packaging of lipids required for the formation of the extracellular lipid membranes. Thus, activation of PPARs and LXRs could provide a mechanism to coordinate the formation of the corneocytes and extracellular lipid membranes that constitute the stratum corneum.

JLR: CAN ONE USE TOPICAL LIPIDS TO IMPROVE PERMEABILITY BARRIER HOMEOSTASIS IN DAMAGED OR DISEASED SKIN?

KRF: Yes. Treatment with topical lipids can be divided into two approaches. First, one can use nonphysiological lipids such as petrolatum (i.e., Vaseline), lanolin, beeswax, etc. These lipids do not enter the lamellar body secretory pathway but rather fill the extracellular spaces of the stratum corneum with hydrophobic nonlamellar lipid that inhibits the movement of water and electrolytes (184). Treatment with these nonphysiological lipids can very rapidly, but only partially, restore permeability barrier function toward normal (185). A disadvantage of nonphysiological lipids is that they also can inhibit the normal permeability barrier repair mechanisms; thus, the underlying abnormality is not corrected (185). The second approach is to use lipids or precursors of the lipids that are normally present in lamellar bodies. Studies have shown that appropriate molar mixes of lipids that contain cholesterol, ceramides, and fatty acids can improve permeability barrier homeostasis (128–130). In contrast to nonphysiological lipids, these lipids are transported across the stratum corneum into the stratum granulosum cells, where they mix with the endogenous pool of lipids (128–130). Hence, it is important that the appropriate mixture of lipids be used, because as noted above, if incomplete or misbalanced mixtures of lipids are used, lamellar body contents are altered and permeability barrier homeostasis can be affected negatively (128–130, 185).

In certain disease or developmental states, in which a particular lipid class is decreased, a mixture of physiological lipids in which the missing lipid is dominant is most beneficial. For example, in aged animals, in which cholesterol synthesis is decreased to a greater degree than other lipid classes, studies have shown that topical treatment with cholesterol alone or cholesterol-dominant lipid mixtures improves permeability homeostasis, whereas fatty acid-dominant mixtures actually impede permeability barrier homeostasis (120). Similarly, in atopic dermatitis, a ceramide-dominant mixture is beneficial (186). One disadvantage of the use of physiological lipid mixtures is that in clinical conditions in which the lamellar body secretory system is malfunctioning (e.g., after ultraviolet or X irradiation or in very premature infants), physiological lipids cannot be incorporated into lamellar bodies; therefore, they cannot accelerate the movement of lipids to the extracellular spaces of the stratum corneum (26, 187–190). In some circumstances, a mixture of physiological and nonphysiological lipids may be ideal, because the action of physiological lipids is delayed, whereas nonphysiological lipids, such as petrolatum, provide an immediate partial restoration of the barrier.

JLR: DR. FEINGOLD, ANY CLOSING THOUGHTS?

KRF: So often in biology and medicine, we focus on the harmful effects of lipids, such as atherosclerosis and obesity. However, with regard to the epidermis, they provide the crucial ingredients that allow us to form a permeability barrier to the movement of water and electrolytes through the stratum corneum. While I have tried to discuss some of what is known about the role of lipids in the formation of this complex stratum corneum lamellar membrane that mediates permeability barrier function, it should be obvious to the reader that much work remains to be done to fully understand the formation and regulation of the epidermal permeability barrier.

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