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Review

Formation and functions of the corneocyte lipid envelope (CLE)☆

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ABSTRACT

Corneocytes in mammalian stratum corneum are surrounded by a monolayer of covalently bound ω-OH-ceramides that form the corneocyte (-bound) lipid envelope (CLE). We review here the structure, composition, and possible functions of this structure, with insights provided by inherited and acquired disorders of lipid metabolism. This article is part of a Special Issue entitled The Important Role of Lipids in the Epidermis and their Role in the Formation and Maintenance of the Cutaneous Barrier. Guest Editors: Kenneth R. Feingold and Peter Elias.

1. Structure and composition of the CLE

Concurrent with epidermal terminal differentiation, the plasma membrane of granular (SG) cells disappears, paralleled by the formation of cornified envelope (CE) and its associated, external membrane monolayer, the corneocyte-bound lipid envelope (CLE) (Fig. 1). Both the origin and the function of this structure are still uncertain, but the recent identification of inherited and acquired disorders of lipid metabolism that impact this structure is providing new insights into the pathway leading to its formation, as well as to its putative functions.

The CLE is comprised of a monolayer of unusually long-chain, ω-acylated-hydroxy-ceramides (ω-OH-Cer; OS, or ω-OH-acyl-sphingosine), with lesser amounts of omega-hydroxy-fatty acids (ω-OH-FA), bound covalently primarily to glutamate residues in involucrin, located within the external portion of the cornified envelope (Fig. 1) [1–3]. Studies in Gaucher's disease, type II, as well as in saposin-deficient transgenic mice show that the CLE initially is enriched in omega-hydroxy-glucosylceramides [ω-OH-(glucosyl)Cer], which subsequently are deglucosylated to ω-OH-Cer [4] (also see Sandhoff's article, in this issue) (Fig. 1). Of the five known isoforms of ceramidase, two (alkaline and acidic) are present in the stratum corneum (SC) [5–8]. While the alkaline form is present at low levels throughout the SC, the acidic isoform localizes in close proximity to the CLE [9]. Because of its localization, activity of the acidic isoform likely dominates the generation of ω-OH-FA. Yet, the low levels of free sphingoid bases in normal SC show that most of the covalently bound ω-OH-Cer remains intact even in the outer layers of normal SC (Table 1) (see also Loiseau et al.'s paper, J Dermatol Sci In Press 2013).

2. Formation of the CLE

It has been suggested that fusion of the limiting membrane of lamellar bodies generates the CLE, concurrent with exocytosis of these organelles at the apical plasma membrane of the outermost SG cells [10] (Fig. 1). By implication then, the limiting envelope of lamellar bodies would have to be enriched in ω-OH-(glucosyl)Cer, rather than the expected phospholipid-dominant composition of the limiting membrane of virtually all other cellular organelles. Support for this hypothesis comes

Abbreviations: acylCer, acylceramides; CE, cornified envelope; CLE, corneocyte-bound lipid envelope; EFAD, essential fatty acid deficiency; (F)FFA, (free) fatty acids; HI, Harlequin ichthyosis; NLSDI, neutral lipid storage disease with ichthyosis; ω-OH-Cer, omega-hydroxy-ceramides; ω-OH-FA, omega-hydroxy-fatty acids; ω-OH-(glucosyl)Cer, omega-hydroxy-glucosylceramides; RD, Refsum disease; SC, stratum corneum; SG, stratum granulosum

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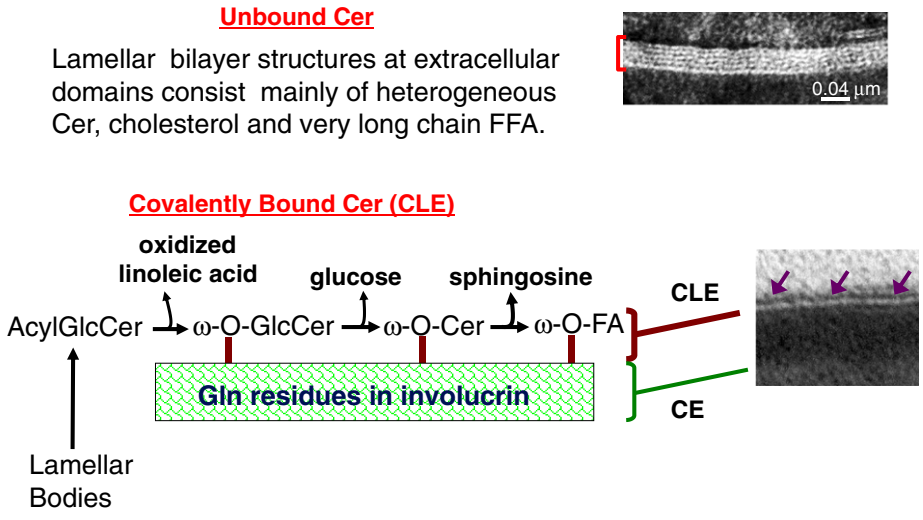

Fig. 1. Model of Bound and Unbound Ceramides in Stratum Corneum Extracellular Domains.

from the recessively inherited ichthyosis, Harlequin ichthyosis, attributable to loss-of-function mutations in the transmembrane lipid transporter, ABCA12 [11,12] (see article by Akiyama et al., in this issue). Although lack of this transporter results in a failure to deliver (glucosylCer) into nascent lamellar bodies [12], *forme fruste* organelles, with little or no internal lamellar contents, continue to be formed in large numbers, and presumably continue to be secreted in HI [10]. Despite a diminution of secreted lamellar membrane contents, a normal-appearing CLE appears external to the CE in this recessively inherited disorder (Fig. 2B vs. A), effectively ruling out lamellar body contents as the source of the CLE. But either fusion of these abortive lamellar bodies into the apical plasma membrane of the outermost cells of the SG, or insertion of other membrane fragments could account for the generation of the CLE [10]. Definitive proof of this mechanism will not be possible until biochemical analyses of both the bound lipids, as well as the composition of the limiting membrane of LBs are performed in HI.

Nonetheless, it is still most widely accepted that the CLE is generated from a smaller pool of secreted extracellular acyl-(glucosyl)Cer. Hydrolysis of the omega-acyl linoleate moiety by an as-yet-uncharacterized, extracellular lipase would then generate a pool of ω-OH-(glucosyl)Cer that form the CLE (Fig. 1). With ultrastructural cytochemistry, lamellar bodies normally appear loaded with acidic lipase activity, which further appears to be secreted into the extracellular spaces of the SC (Fig. 3). This sequence parallels the secretion of other lamellar body-derived lipid and protein contents, including glucosylceramides. Since lamellar bodies contain little or no triglycerides [13], it has been unclear what the role of this abundant extracellular lipase activity could be. It now seems plausible that this secreted lipase activity within the SC extracellular domains could account for the hydrolysis of ω-esterified (oxidized) linoleic acid from acylCer, generating the ω-OH-Cer destined for covalent binding to the external face of the CE (Fig. 4).

Table 1
Covalently bound ω-OH-Cer content declines in EFAD mouse epidermis.

	CLE-ω-OH-Cer* (μg/mg dry epidermis)	CLE content** (% of normal mouse)
Normal	1.88 ± 0.12	100.0 ± 13.0
EFAD	0.82 ± 0.07***	49.7 ± 10.5***

Legend:
* Covalently bound lipids were isolated, and the resultant Cer fractions were quantitated by HPTLC-scanning densitometry, as described in [1].
** Using randomly-obtained electron micrographs (n = 10), CLE content was determined as the percent of the overall inter-desmosomal corneocyte-surface covered by CLE, as described by Behne et al. [30].
*** $P < 0.01$ vs. normal control mice.

3. Pathways leading to the formation of the CLE: Insights from inherited and acquired metabolic disorders

While the pathway that leads to ceramide and acylCer formation is now well characterized (see articles by R. Sandhoff and K. Sandhoff, in this issue), the biochemical sequence leading to acylCer and ω-OH-Cer formation remained uncertain until relatively recently. Issues such as: i) How are the unusually long-chained ω-acylated FA generated? ii) How does a subset of acylCer acquire a specific class of FFA; i.e., linoleic acid, for purposes of ω-esterification? iii) How does the putative lipase or transferase that generates ω-OH-Cer target the oxidized linoleate moiety in acylCer? Recent studies in a group of recessively inherited and acquired disorders are helping to provide answers to questions such as these.

Two key steps are involved in ω-OH-Cer formation. An epidermis-unique isoform of the ELOV family, ELOVL4, generates the very-long chain N-acyl groups [14], while a cytochrome P450 isoform, CYP4F22, generates the ω-OH-Cer [15,16]. While loss of ELOVL4 appears to be lethal in neonates, deficiency in CYP4F22 leads to a form of non-syndromic autosomal recessive ichthyosis [17]. We have shown that the CLE is absent in the recessive disorder, neutral lipid storage disease with ichthyosis (NLSDI or Chanarin–Dorfman syndrome) [14] (Fig. 2C). The cause of NLSDI is loss of function mutations in CGI-58, a co-factor that is required for the activation of a subset of acidic lipases which recognize linoleic acid-enriched triglycerides (Fig. 4). CGI-58 is also a co-factor for ATGL in adipose tissue, but ATGL ko mice lack skin features, while loss of CGI-58 results in a syndromic form of ichthyosis [18,19] (see article by R. Zechner et al., in this issue). Together, these studies suggest that a pool of linoleate-enriched triglycerides transfers this EFA to previously synthesized ω-OH-(glucosyl)Cer, generating ω-acyl-(glucosyl) ceramides (Figs. 1 & 4).

Similarly, the CLE and bound ceramides are almost entirely absent in another recessively inherited subgroup of ichthyoses, attributable to loss-of-function mutations in either the 12R lipoxygenase (12R-LOX) or epidermal lipoxygenase 3 (eLOX3) (Fig. 2E) [20,21] (see also article by P. Krieg, in this issue). While mice with a transgenic knock-out of 12R-LOX display a prominent barrier abnormality, whether a CLE is present or absent in these mice was not noted. Subsequently, Alan

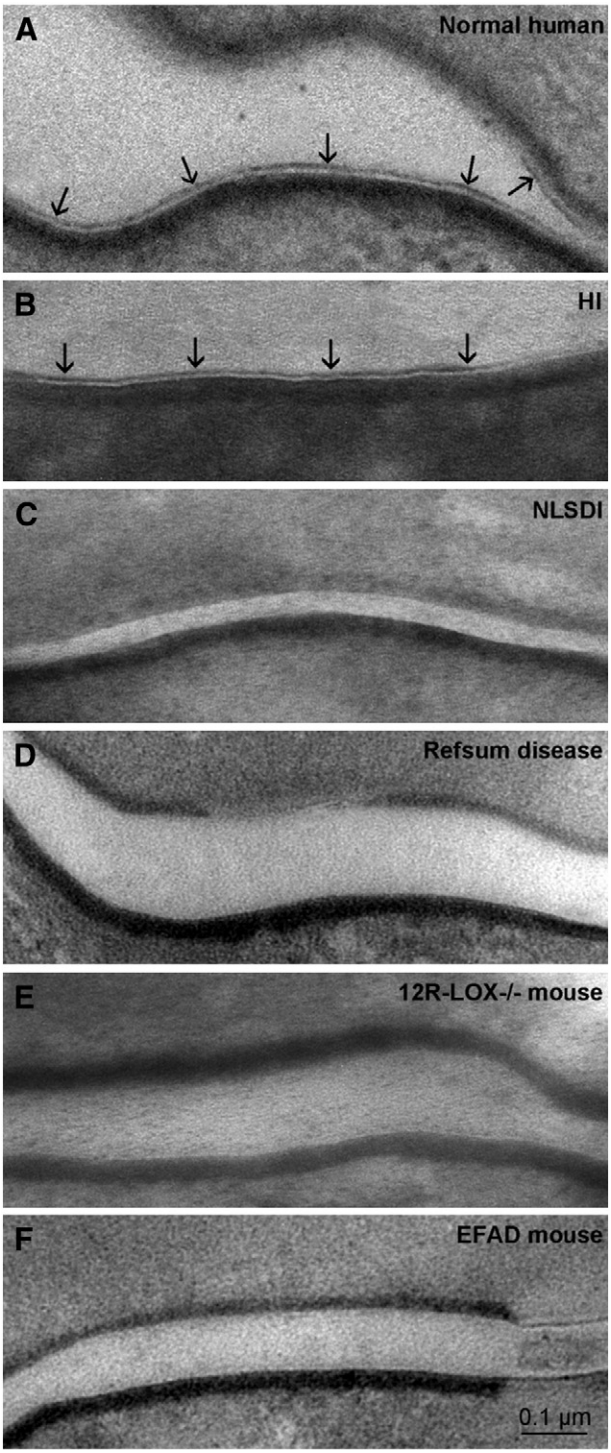

Fig. 2. CLE in Normal and Diseased Skin (see text for abbreviations).

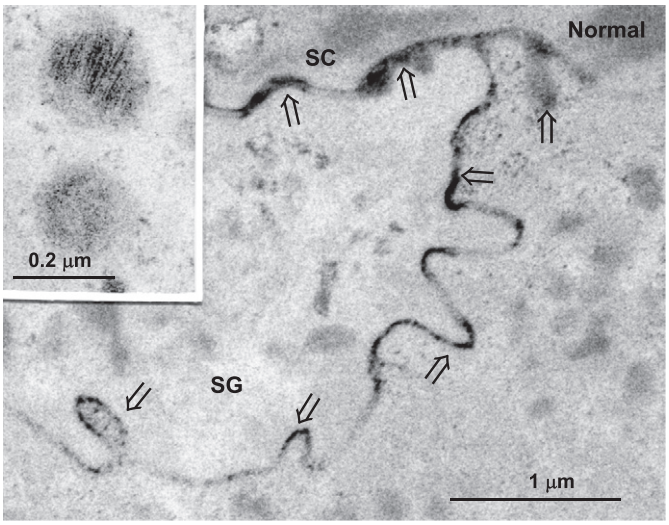

Fig. 3. Normal human epidermis: Lipase activity is restricted to lamellar bodies (inset), and after secretion, within the extracellular spaces (open arrows). Methods for assessing upon localization on an ultrastructural level are cited in [24].

Brash's laboratory at Vanderbilt University showed that these two ALOX enzymes, which localize solely to keratinizing epithelia, sequentially oxidize the linoleate moiety of acylCer [22,23] Oxidized linoleate then becomes the substrate for the putative extracellular lipase that generates ω-OH-(glucosyl)Cer that becomes covalently bound to the CE (Fig. 4) (further details of this biochemical sequence can be found in an article from Brash's group, in this issue). Accordingly, the CLE and bound Cer are largely absent in 12R-Lox$^{-/-}$ transgenic mice (Fig. 2E) [22]. Together, these studies clearly demonstrate that oxidation of the omega-esterified linoleic acid moiety is a prerequisite for CLE formation. Finally, the release of ω-OH-Cer is paralleled by the liberation of linoleate products, such as hepoxilin and trioxilin that have putative pro-barrier signaling functions in the epidermis [24,25] (see also A. Brash's article, in this issue).

Ultrastructural studies show that the CLE is either absent, partially formed, or loosely attached to the CE in the exceedingly rare, neurocutaneous disorder, Refsum disease (RD) [26] (Fig. 2D), which is due to loss of function mutations in phytanic acid oxidase, a peroxisomal enzyme that metabolizes unsaturated, branched-chain fatty acids normally found in plant-derived glycerolipids into species that can be more readily eliminated. In the absence of this oxidase, these abnormal free fatty acids likely replace some of the usual acylated fatty acids found in membrane lipids, producing often severe, multisystem abnormalities [27]. While biochemical data are still lacking, the ultrastructural abnormalities suggest that unmetabolized phytanic acid incorporates into the triglyceride pool, competing with the linoleic acid that normally incorporates into the triglyceride pool that contributes to CLE formation (Fig. 4). It seems reasonable to assume that these plant-derived fatty acids would not serve as an appropriate substrate for either the ALOXs or the putative lipase/transferase that generates ω-OH-(glucosyl)Cer, explaining the reduced CLE in this disorder.

Finally, in still unpublished work, we have shown that dietary essential fatty acid deficiency (EFAD) leads to reduced CLE formation (Fig. 2F), which is paralleled by a marked reduction in bound ω-OH-Cer (Table 1; see also [28]). In EFAD, omega esterified linoleate is replaced by oleic acid [29], which cannot serve as a substrate for the ALOXs. As in RD, it is doubtful that the oleate moiety in ω-OH-(glucosyl)Cer would be an appropriate substrate for the lipase/transferase catalytic step that leads to the formation of the CLE (Fig. 4). While it has been suggested that substitution of oleate for linoleate in acylCer comprises the molecular defect that accounts for the barrier abnormality in EFAD [29], it is possible that failure to generate a CLE instead provokes the barrier abnormality.

Together, these inherited disorders have provided important insights into the pathway that leads to formation of the CLE. Needless to say, each of these disorders is accompanied by profound functional abnormalities, but to what extent dysfunction can be attributed to loss of the CLE vs. parallel abnormalities in extracellular lamellar bilayers is uncertain, because structures other than the CLE are impacted in each of these disorders.

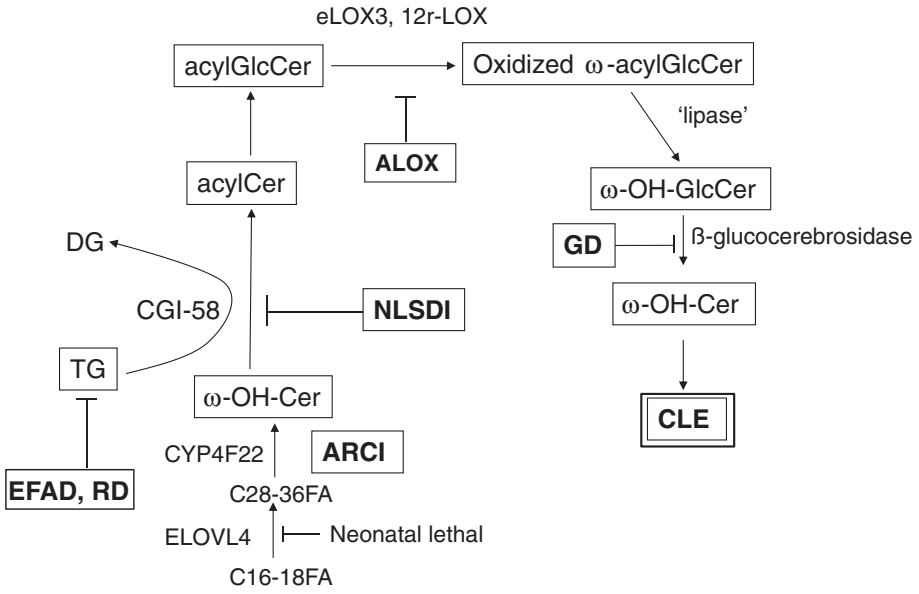

Fig. 4. Pathways leading to CLE formation: Key insights from inherited and acquired lipid metabolic disorders are highlighted (see text for further details).

4. What is the function of the CLE?

While the functional implications of the above metabolic sequence are still emerging, it seems likely that ω-OH-(glucosyl)Cer resist ceramidases, allowing the persistence of this monolayer, unchanged at least during the initial stages of corneocyte maturation [4] (Fig. 1). This would allow the CLE to function as a scaffold for the organization of the extracellular lamellar bilayers, as needed for barrier function [28,30].

Alternatively, it has been suggested that the CLE contributes to the cohesion of the SC [3]. The basis for this assertion lies in the observation that exhaustive lipid solvent extraction, while removing all of the lamellar bilayers, induces the collapse and firm attachment of corneocytes to one another, rather than separating them [1,3]. Yet, whether the CLE serves this function under normal conditions, when the lamellar bilayers are present, remains uncertain.

Finally, the CLE could also function as a semi-permeable membrane that could allow the free transmembrane passage of water, while restricting the loss of larger hygroscopic molecules, such as filaggrin breakdown products, out of the corneocyte [9]. Then, after deglucosylation of ω-OH-(glucosyl)Cer, the CLE becomes vulnerable to attack by one or both of the two ceramidase isoforms, known to be present in SC [5,8]. We demonstrated a large amount of acidic ceramidase activity in close proximity to the CLE, as well as the extracellular lamellar bilayers within the mid- to outer SC by in situ zymography [9]. The subsequent replacement of some ω-OH-(glucosyl)Cer by ω-OH-FFA would render the CLE less effective as a semi-permeable membrane, eventually allowing the parallel loss of water and the hygroscopic contents out of corneocytes in the SC. Should this feature become more prominent, it could have clinical consequences. Indeed, accelerated degradation of the CLE, indicated by a higher ratio of omega-hydroxy-fatty acids to omega-hydroxy-ceramides, is an overlooked, but potentially important feature of atopic dermatitis [31] (see related article by Elias et al., in this issue). Indeed, atopic dermatitis is often complicated by colonization with bacteria that secrete ceramidase [32], and/or activation of endogenous ceramidase activity [33]. Either mechanism could contribute to the xerosis that is such a prominent feature of atopic dermatitis. Specifically, the dry skin of atopics can be attributed not only to the reduced generation of hygroscopic breakdown products of filaggrin, but also to an accelerated leakage of these materials out of corneocytes.

5. Conclusion

While the function(s) of the CLE remain uncertain, its structure, composition, and pathways leading to its formation are in the process of being clarified through insights provided by both inherited and acquired disorders of lipid metabolism.

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