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Pathogenesis of permeability barrier abnormalities in the ichthyoses: inherited disorders of lipid metabolism

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Abstract

Many of the ichthyoses are associated with inherited disorders of lipid metabolism. These disorders have provided unique models to dissect physiologic processes in normal epidermis and the pathophysiology of more common scaling conditions. In most of these disorders, a permeability barrier abnormality "drives" pathophysiology through stimulation of epidermal hyperplasia. Among primary abnormalities of nonpolar lipid metabolism, triglyceride accumulation in neutral lipid storage disease as a result of a lipase mutation provokes a barrier abnormality via lamellar/nonlamellar phase separation within the extracellular matrix of the stratum corneum (SC). Similar mechanisms account for the barrier abnormalities (and subsequent ichthyosis) in inherited disorders of polar lipid metabolism. For example, in recessive X-linked ichthyosis (RXLI), cholesterol sulfate (CSO_4) accumulation also produces a permeability barrier defect through lamellar/nonlamellar phase separation. However, in RXLI, the desquamation abnormality is in part attributable to the plurifunctional roles of CSO_4 as a regulator of both epidermal differentiation and corneodesmosome degradation. Phase separation also occurs in type II Gaucher disease (GD; from accumulation of glucosylceramides as a result of to β-glucocerebrosidase deficiency). Finally, failure to assemble both lipids and desquamatory enzymes into nascent epidermal lamellar bodies (LBs) accounts for both the permeability barrier and desquamation abnormalities in Harlequin ichthyosis (HI). The barrier abnormality provokes the clinical phenotype in these disorders not only by stimulating epidermal proliferation, but also by inducing inflammation.

Supplementary key words

ATP binding cassette transporter 12; arachidonate lipoxygenase; barrier function; epidermal lipids; harlequin ichthyosis; neutral lipid storage disease; recessive X-linked ichthyosis; stratum corneum; transepidermal water loss

> One thing is certain. The sequencing of the genome will soon look like the easiest thing that biologists ever did. …what the genes actually do—constitutes the real code of living systems. To crack that code will take centuries, but getting there will be more than half the fun.

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—Melvin Konner, “Weaving Life’s Pattern,” Nature 418: 279, 2002

Many of the ichthyoses are associated with inherited disorders of lipid metabolism. These disorders have provided unique models to dissect physiologic processes in normal epidermis and the pathophysiology of more common scaling conditions. In most of these disorders, a permeability barrier abnormality “drives” pathophysiology through the stimulation of epidermal hyperplasia. Among primary abnormalities of nonpolar lipid metabolism, triglyceride accumulation in neutral lipid storage disease as a result of a lipase mutation provokes a barrier abnormality via lamellar/nonlamellar phase separation within the extracellular matrix of the stratum corneum (SC). Similar mechanisms account for the barrier abnormalities (and subsequent ichthyosis) in inherited disorders of polar lipid metabolism. For example, in recessive X-linked ichthyosis (RXLI), cholesterol sulfate (CSO_4) accumulation also produces a permeability barrier defect through lamellar/nonlamellar phase separation. However, in RXLI, the desquamation abnormality is in part attributable to the plurifunctional roles of CSO_4 as a regulator of both epidermal differentiation and corneodesmosome degradation (2). Phase separation also occurs in type II Gaucher disease (GD; from the accumulation of glucosylceramides as a result of β-glucocerebrosidase deficiency) (3). Finally, failure to assemble both lipids and desquamatory enzymes into nascent epidermal lamellar bodies (LBs) accounts for both the permeability barrier and desquamation abnormalities in harlequin ichthyosis (HI). The barrier abnormality provokes the clinical phenotype in these disorders not only by stimulating epidermal proliferation but also by inducing inflammation.

RATIONALE

The ichthyoses are rare scaling disorders (disorders of cornification) in which a large number of unrelated inherited disorders result is excessive visible scale (4–8). All of these disorders display a prominent permeability barrier abnormality, associated with abnormalities in the architecture of lamellar membranes in the extracellular spaces of the SC, where the barrier resides. Abnormal membrane structure can result directly from abnormalities in lipid metabolism (9–13) (to be discussed in this review) or indirectly from primary abnormalities in the corneocyte that either impede lipid secretion or alter scaffold function (discussed only briefly in this review; see Ref. 13). Initial pathogenic studies classified the inherited ichthyoses as either abnormalities in the structural proteins of the corneocyte “bricks” or as resulting from inborn errors of lipid metabolism (the “mortar”) (11,12). This approach yielded two key insights: *1*) that disorders of lipid metabolism alone can alter the extracellular matrix sufficiently to provoke ichthyotic disorders; and *2*) that extracellular lipids contribute to the cohesive properties of normal SC (Table 1). However, it failed to illuminate the functional interdependence of the bricks and mortar components. Moreover, it also failed to predict the epidermal homeo-static responses that occur in response to altered SC function, in which the permeability barrier abnormality leads to epidermal hyperplasia and cytokine signaling of inflammation. This review focuses on the subcellular pathogenesis of ichthyoses as a result of disorders of lipid metabolism, using a function-driven model of disease.

ROLE OF THE PERMEABILITY BARRIER IN DISEASE PATHOGENESIS

All of the ichthyoses studied to date, whether primary disorders of lipid or protein metabolism, have demonstrated a permeability barrier abnormality (9,10,13). Because permeability barrier requirements generally drive metabolic responses in the underlying epidermis (15,16), the clinical phenotypes in the ichthyoses almost certainly reflect a best effort attempt by the epidermis to normalize barrier function (9). These metabolic responses to a flawed barrier, although only partially successful, usually suffice to allow survival in a dry, terrestrial environment. For example, in HI, in which few if any lipids are delivered to the SC interstices (17), the epidermis compensates as well as it can with an intense, hyperplastic response

(increased cell proliferation in response to a defective barrier) that generates multiple layers of corneocytes (the "make more cells" imperative) (9) (see below). Even in inherited disorders that affect the structural proteins of the corneocyte bricks, permeability barrier abnormalities result from downstream alterations in the extracellular, lipid-enriched matrix (14), although by divergent mechanisms. For example, transglutaminase 1 (TGM1)-negative lamellar ichthyosis (LI) and loricrin keratoderma represent disorders in which the primary enzyme and its principal substrate, respectively, which both are involved in the formation of the corneocyte, are affected. In both of these disorders, the cornified envelope is attenuated, resulting in an impaired corneocyte scaffold, leading, in turn, to fragmented and foreshortened lamellar membranes (18,19). These altered membranes lead to an impaired barrier caused by the leakage of water via the extracellular pathway. This link between a defective cornified envelope and the extracellular avenue of increased transepidermal water loss (TEWL) in both LI and loricrin keratoderma provides definitive proof that the corneocyte provides the scaffold necessary for the supramolecular organization of the lipid-enriched, extracellular matrix.

Alternatively, in epidermolytic hyperkeratosis, mutated keratins (either keratin 1 or 10) form abnormal, dominant-negative keratin pairs that disrupt the cytoskeleton, thereby impeding LB exocytosis (20). Once again, the barrier abnormality is provoked via a defect in the extracellular matrix (i.e., a reduction in secreted lipids) (20). Thus, in inherited disorders of corneocyte proteins of diverse etiology, the protein abnormality ultimately provokes a defect in the extracellular lamellar membranes (mortar) (18–20). This secondary defect in the extracellular matrix then allows accelerated, extracellular transcutaneous water movement (i.e., the permeability barrier abnormality), which drives epidermal hyperplasia, resulting in a thickened (ichthyotic) SC.

Finally, and pertinent for the inflammation that accompanies many of the ichthyoses, abnormal permeability barrier function inevitably stimulates signaling mechanisms that attempt to restore barrier function (21), but it also recruits downstream inflammation (i.e., another example of the "outside-inside" pathogenesis of inflammatory dermatoses) (21,22). Moreover, if this cytokine cascade is sustained, both epidermal hyperplasia with hyperkeratosis and inflammation develop (21,23), accounting for clinical features of the inflammatory ichthyoses.

DISORDERS OF NONPOLAR LIPID PROCESSING

Neutral lipid storage disease (Chanarin-Dorfman syndrome)

Neutral lipid storage disease with ichthyosis (NLSDI), or Chanarin-Dorfman syndrome [OMIM, Online Mendelian Inheritance in Man (OMIM) 275630], is a rare, recessive disorder often caused by mutations in a gene encoding for a putative lipid hydrolase, *ABHD5* (also known as *CGI-58*) (24–27), that leads to an accumulation of cytosolic triacylglycerides (TAGs). Although the presence of ichthyosis indicates an *ABHD5* mutation, kindreds with a lipid storage myopathy but no ichthyosis have been linked instead to mutations in desnutrin (*PNPLA2*, *ATGL*, or *TTS-22*), for which ABHD5 serves as a coactivator largely restricted to adipose tissue (28). C*GI-58/ABHD5* is located on chromosome 3p21; it has seven exons and is expressed in many tissues, including skin. Affected patients are almost all homozygous, although a few cases of compound hetero-zygosity have been reported. C*GI-58/ABHD5* encodes for a 349 amino acid protein that coactivates a newly identified lipase, ATGL, that hydrolyzes TAGs into diacylglycerides for phospholipid and free fatty acid production (29). However, the pathway that leads to cytosolic TAG accumulation in NLSDI has not been fully characterized. Labeling studies suggest that diacylglyceride is used for phospholipid synthesis, but excess substrate in NLSDI is stored in tissues as TAG (30,31). Whether the lack of lipase activity results in a lack of phospholipid loading into LBs is likely but not yet investigated (Fig. 1). Alternatively, the protein encoded by *CGI-58/ABHD5* may affect epoxide hydroxylation, but this remains to be confirmed experimentally (see below). One important consequence of

the lack of phospholipids would be a downstream deficiency of free fatty acids (in epidermis, all secreted phospholipids are hydrolyzed normally into a large pool of nonessential FFAs that is an important constituent of the extracellular lamellar bilayers in SC) (32).

TAG accumulation in cytosolic droplets in multiple tissues allows for the rapid clinical diagnosis of NLSDI by Oil Red O staining of frozen skin biopsies, which demonstrate diagnostic lipid droplets in both the epidermal basal layer and in appendageal epithelia (33), or by visual inspection of leukocytes on blood smears (33,34) (Table 2). Although the ichthyosiform phenotype in NLSDI is non-diagnostic, it most closely resembles the nonbullous congenital ichthyosiform erythroderma (CIE) variant of autosomal recessive congenital ichthyosis (ARCI; see below) (33,35). However, NLSDI patients also often experience pruritus, with or without atopic features (34,35), an erythrokeratoderma variabilis-like dermatosis (24), or a severe “oily” (seborrheic) type of ichthyosis (36).

Neutral lipid-positive storage vacuoles likely do not account for the ichthyosiform phenotype in NLSDI, because these large, cytosolic inclusions eventually become entombed within corneocytes, where they likely are unavailable to influence extracellular functions, such as permeability barrier homeostasis or desquamation. Moreover, comparable cytosolic lipid droplets occur as a nonspecific response to toxic insults, as in many hyperplastic dermatoses (37–41). More pertinent instead to disease phenotype in NLSDI could be amorphous, lipid microinclusions that occur within epidermal LBs (33). These organelle contents are secreted, along with normal-appearing lamellar membranes, at the stratum granulosum (SG)/SC interface (33). Accordingly, LBs normally encapsulate several types of lipase activity (42–44), including the coactivator encoded by *CGI-58/ABHD5* (26,45). Therefore, the enzyme mutation and the lipid microinclusions in NLSDI are likely linked to disease pathogenesis through their colocalization within LBs.

Barrier function, assessed as abnormalities in TEWL, is markedly abnormal in NLSDI, with basal TEWL levels up to 3-fold higher than in age-matched, normal controls (35). These levels are comparable to those reported for other ichthyoses with a similar phenotype, such as nonbullous CIE and TGM1-negative LI (46,47).

Recent studies suggest that it is the persistence of secreted, “unprocessed” TAG, coupled with decreased FFA caused by the lack of phospholipid precursors, that likely accounts for the permeability barrier abnormality in NLSDI (35). In normal epidermis, LBs are replete with lamellar membranes that show no evidence of nonlamellar discontinuities. After secretion, secreted lamellar contents transform into “mature” lamellar membrane structures that regulate permeability barrier homeostasis, which again fill the SC interstices (48). Thus, in normal human epidermis, a uniform lamellar phase that completely fills the SC interstices equates with permeability barrier competence (48). In NLSDI, LBs display lipid microinclusions that transform into electron-lucent, lipid-filled “clefts” after secretion (33). To delineate whether these clefts contain phase-separated (nonlamellar) lipid, we assessed tissue samples after ruthenium tetroxide postfixation, a method that allows for the visualization of hydrophobic lipid structures, such as the extracellular lamellar membranes (49), coupled with embedding in a lipid-retaining resin (LR White). Using this method, the clefts did not appear empty but rather filled with an amorphous, electron-dense material adjacent to arrays of lamellar membranes (35). Moreover, these new images provide additional insights into the pathogenesis of NLSDI, which can be ascribed to lamellar/nonlamellar phase separation within the SC interstices (Fig. 1). Phase separation occurs in lipid-based, membrane bilayers when the amount of nonpolar lipid exceeds the capability of this lipid to incorporate into polar lipid-based, lamellar membranes (50–52). These results suggest that ceramide (Cer)-based membrane bilayers of the SC interstices, like their phospholipid-based counterparts, display a limited capacity to incorporate non-polar species, such as triacylglycerols.

To assess whether an inhomogeneous extracellular matrix forms an inherently less effective permeability barrier than interstices that are uniformly replete with lamellar membranes, we perfused the SC of NLSDI with a water-soluble, electron-dense tracer, lanthanum nitrate. Whereas the interstices of normal human SC completely exclude water-soluble molecules, lanthanum permeates through nonlamellar domains in the extracellular spaces at all levels of the SC in NLSDI (35). In summary, these studies show that lamellar/nonlamellar phase separation underlies the permeability barrier abnormality in NLSDI.

ARCI

The ARCIs comprise a group of disorders of cornification with congenital presentation. On clinical, biochemical, and morphological grounds, it has long been recognized that this group is clinically heterogeneous, likely comprising multiple disease entities (53–56). Indeed, these patients reveal a remarkable diversity of underlying genetic mutations (57–65). Before this genetic diversity became known, the LI phenotype, with large dark, plate-like scaling, had been distinguished on clinical grounds from nonbullous congenital erythroderma (CIE or nonbullous CIE), with fine scaling involving flexural sites, and often with prominent erythema (54), but many intermediate phenotypes also have been described (5,6).

Although a functional barrier abnormality is present in all ARCI subtypes studied to date (19,46), structural and biochemical differences between the LI and the CIE phenotypes provided initial clues about the heterogeneity within this group of ichthyoses (54,56,66). The major distinguishing feature of the LI phenotype is abnormal cornified envelope cross-linking attributable to TGM1 deficiency, resulting in attenuated cornified envelopes (19). In contrast, the CIE phenotypes (in which cornified envelopes are normal) display prominent abnormalities in LBs and SC extracellular lamellar membranes. Although the number of LBs is increased in CIE, many of these organelles are smaller than normal and show abnormal internal organization (i.e., fragmented lipid lamellae), often giving them a vacuolated appearance (56). The SC of CIE individuals also retains large amounts of exogenous *n*-alkanes, whereas TAG and FFA levels decrease (54). Together, disorganized lamellar arrays and nonpolar nonlamellar/lamellar phase separation account for the barrier abnormality (56). However, in CIE, several variable ultrastructural features were observed only in subsets of patients. These variable findings include the following: *1*) an absence of electron-lucent lamellae; *2*) abnormal spacing and interruptions of lamellar structures; and *3*) intracellular lipid droplets and vesicular complexes, within both the SC and the SG (10,46,56,66,67). An alternative classification of the variable ultrastructural findings in ARCI is widely applied in Europe: type I is characterized by abundant lipid droplets within corneocytes; type II shows polygonal clefts within the SC; type III shows vesicular and membranous structures in the SG; and type IV is characterized by lentiform swollen areas within corneocytes and perinuclear accumulation of curved membranes in the SG (55,66). Because this classification preceded the use of ruthenium tetroxide to evaluate membrane structures, it is of limited utility.

Today, the variability of ARCI morphology can be explained by the genetic heterogeneity that is now becoming apparent, although some ultrastructural findings most likely reflect nonspecific sequelae of disturbed cornification. Subsequently, it became clear that newly discovered gene mutations do not always correlate well with or explain the observed clinical and morphological phenotypes (e.g., the LI phenotype is frequently, but not exclusively, caused by TGM1 deficiency). The same TGM1 mutation can cause both LI and CIE phenotypes, and the LI phenotype can result from mutations other than TGM1 (68–71).

Several of the newly discovered mutations causing ACRI govern the synthesis of enzymes directly involved in the production, transport, or assembly of lipid components of the SC (Table 1). In an intense, ongoing effort, detailed genotype-phenotype relationships, including structural correlations, are being established. Best studied for their consequences for the

epidermal permeability barrier are mutations in *ichthyin* on chromosome 5q33, which putatively encodes for a transmembrane receptor. By electron microscopy, the SG of patients with *ichthyin* mutations contains many empty or partially filled vacuolar and vesicular structures, which are thought to represent defective LB (71). In one study, 85% of patients with this morphologic pattern were found to have mutations in *ichthyin* (71). Because *ichthyin* mutations do not result in decreased mRNA levels, the responsible mutations likely alter the function, rather than the expression levels, of the putative receptor.

It has been proposed that the endogenous ligands for the putative ichthyin receptor are hydroxyepoxyalcohols (69), presumably generated in normal epidermis (72) and reportedly esterified at high rates into phospholipids (73). Epidermal hydroxyepoxyalcohols are metabolic products of 12*R*-lipoxygenase (LOX) and hydroperoxide isomerase (epoxyalcohol synthase) eLOX3 (74,75) (Fig. 2). Mutations in *ALOX12* (for arachidonate lipoxygenase) and *ALOXE3* on chromosome 17p13, which result in the complete loss of enzymatic activity as a result of abnormal protein folding, are relatively common (>10%) among patients with ARCI (60,61,70,76). Thus, these enzymes and the putative ichthyin receptor may function in concert along the same metabolic pathway, catabolizing leukotriene derivatives of arachidonic acid to hydroxyepoxyalcohol end products, specifically 12(*R*)-hepoxilin A3 and 12(*R*)-hydroperoxy-eicosatetraenoic acid (75,76) (Fig. 2). Additional evidence for the relevance of LOX deficiency for the permeability barrier derives from mouse models that display increased TEWL, resulting in death within 3–5 days after birth (77,78). Ultrastructural examination of the SC of these animals revealed vesicular structures in the upper SG cell layers that are comparable to the structural abnormalities in the SC of human ARCI subjects with *ichthyin* mutations. In mouse epidermis, these findings also correlate with an increase in protein-bound, ester-linked lipid species (77). Corneocytes isolated from LOX-deficient animals are more fragile and show abnormal filaggrin processing, features that have not yet been identified in affected human skin.

The initial transformation of arachidonic acid into epoxyalcohols and the downstream effects on the putative ichthyin receptor have been proposed to provide a framework for several intermediate metabolic steps that could, when disturbed, cause an ARCI phenotype and permeability barrier abnormalities (14,70) (Fig. 2). First, pedigrees with ARCI linked to the *ALOX12/ALOXE3* chromosomal region on 17p13 but lacking mutations in these genes indicate that there may be at least one additional gene in this region coding for a protein within the same pathway (70). Second, in other ARCI kindreds, mutations in cytochrome P450, family 4, subfamily F, polypeptide 22 (Cyp4F22) on chromosome 19p12 encode a putative fatty acid ω-hydroxylase and may perturb a late enzymatic event in the epoxyalcohol oxidation and hydroxylation cascade (79). Yet, information on SC structure and barrier function is lacking in these patients. Third, fatty aldehyde dehy-drogenase, which is deficient in Sjögren-Larsson syndrome (SLS) (see below), could have the ability to oxidize trioxilin products within the above pathway. However, the prominent central nervous system abnormalities that are present in SLS, but lacking in the ARCI phenotypes, indicate that the pathophysiological consequences of blockade at this step are broader in scope. Moreover, differences in the cutaneous phenotype of SLS (a “lichenified” rather than a “scaly” pattern accompanied by prominent pruritus) suggest that other substrates may be affected. Finally, *CGI-58/ABHD5*, which is mutated in neutral lipid storage disease (see above), has also been proposed to function as an epoxide hydroxylase in the same biochemical pathway (79). However, there is no reason to suspect that the activities of this lipase are restricted to these epoxide metabolites. Indeed, labeling studies suggest a broader effect on acyl-lipid metabolism (see above). Finally, although a unitary pathway hypothesis always is attractive (70), it should be recalled that mutations in disparate genes, such as TGM1 (see above), cause identical phenotypes. More likely is the hypothesis that any derangement of epidermal lipid metabolism can provoke an ichthyosiform phenotype. Finally, it still remains to be seen how many distinct clinical, morphological, and biochemical

disease subsets will be distinguished among these patients, or whether most will converge into a common phenotype.

Although a lack of peroxidated lipid metabolites may be the common pathogenetic basis in ARCI phenotypes that are not caused by TGM1 deficiency (Fig. 2), the mechanism whereby this abnormality provokes disease is unknown. The pathogenesis of the barrier abnormality could be related to essential fatty acid deficiency, in which a lack of substrate for the ω-esterification of Cers to acylceramide is known to provoke a barrier abnormality (80–83). Alternatively, some of the accumulating hydroxyepoxyalcohol substrates are potent and selective activators of peroxisome proliferator-activated receptor (PPAR) α (84), a ligand-activated nuclear hormone receptor with prodifferentiating and anti-inflammatory activity in the epidermis (85,86) (Fig. 2). In addition, Cyp4F22 activity also likely generates potent PPARα agonists, because it is a homolog of the leukotriene B2-ω-hydroxylase and ω-hydroxylation of other eicosanoids enhances PPAR-activating properties (79,87). Yet, the biological significance of this association remains unclear, because PPARα deficiency results only in transient developmental defects in fetal mouse epidermis (85), presumably as a result of redundancy in other epidermal nuclear hormone receptors. Finally, one or more of these metabolites could mobilize intracellular calcium, thereby altering permeability barrier homeostasis by downregulating LB secretion (88,89). This last possibility is consistent with the LB secretory defect that has been described in preliminary studies of this group of ichthyoses (e.g., *ichthyin* mutations; see above).

OTHER DISORDERS OF NONPOLAR LIPID METABOLISM

SLS

Several other primary disorders of nonpolar lipid metabolism display an ichthyotic phenotype with additional systemic abnormalities (Table 2). In at least one of these disorders, SLS, lamellar/nonlamellar phase separation could provoke both a barrier abnormality and the distinctive clinical phenotype. SLS is a recessively inherited disorder of the brain and skin, attributable to the accumulation of free and esterified long-chain aliphatic alcohols (90) as a result of defective peroxisomal oxidation of long-chain aliphatic alcohols. A variety of mutations in the *ALDH3A2* gene, encoding the microsomal enzyme fatty aldehyde dehydrogenase, have been described (91,92). Patients with SLS display a characteristic triad of mental retardation, spastic diplegia or quadradiplegia, and ichthyosis (91,93). The epidermal phenotype is quite characteristic, exhibiting a ridge or lichenified pattern with fine, brown desquamation and prominent pruritus, which may be caused by coaccumulation of the proinflammatory leukotriene metabolite, leukotriene B_4 (91,94). Although the pathogenesis of the putative barrier abnormality is still unknown, epidermal LB contents are abnormal (95) and extracellular lamellar bilayers exhibit structural abnormalities consistent with lamellar/nonlamellar phase separation (95,96).

Disorders of peroxisomal fatty acid metabolism

In two recessively inherited, nonpolar disorders of peroxisomal lipid metabolism, Refsum disease (RD) and rhizomelic chondrodysplasia punctata (RCDP; OMIM 21508), similar pathomechanisms to SLS could be operative[2] (Table 2). RD (OMIM 266500) is a rare disorder caused by a defect in the first step in peroxisomal β-oxidation of phytanic acid, a C16 saturated fatty acid with four additional methyl groups at C3, C7, C11, and C15 (96). This branched

[2]An additional pathomechanism could also be operative in CHILD (for congenital hemidysplasia with ichthyosiform erythroderma and limb defects) and Conradi-Hünermann syndromes; that is, an accumulation of distal sterol precursors (7-dehydrocholesterol/zymosterol) could result in lamellar membranes that are deficient in cholesterol. Cholesterol is one of the key lipids (with Cers and free fatty acids) that are required to form mature lamellar membranes, and such cholesterol-deficient membranes provide a suboptimal barrier (Ref. [1]; p. 74).

chain fatty acid is enriched in tissues of ruminant animals (97). Accumulation of phytanic acid, although characteristic of RD, is not pathogenic, because increased phytanic acid levels occur in other disorders of peroxisomal biogenesis, including SLS and RCDP (97). In RD, peroxisomal β-oxidation of phytanic acid is blocked by the presence of the methyl group at the 3-position. Mutations in the gene encoding phytanoyl-CoA hydroxylase (*PAHX*, *PHYH*) occur in up to 80% of RD patients (98), but some patients do not have *PAHX* mutations but rather mutations in peroxin 7 receptor (*PEX7*) (99). PEX7 mutations underlie the more severe phenotype, RCDP, in which severe skeletal defects predominate (99,100). A mild ichthyosiform phenotype, albeit poorly described, can also be present. In all RD cases, multisystem accumulation of phytols, predominantly phytanic acid, occurs, sometimes in millimolar concentrations (97). Severely affected patients can die in childhood, but most do not become symptomatic until adolescence, from a disease complex that includes retinitis pigmentosum, deafness, cerebellar ataxia, anosmia, and ichthyosis (98). The initial symptom is often night blindness, which can progress to blindness. Death usually results from cardiac arrhythmia, but these as well as other disease symptoms improve with the implementation of a phytol-free diet (97,98). The pathogenesis of the disease complex in RD could be explained in part by the high affinity of phytanic acid for the retinoid X receptor and PPARα (100,101). Although purely speculative, the symptoms of RD mimic several features of hypervitaminosis A, which include visual, neurological, and desquamatory abnormalities. In addition, phytanic acid can induce apoptosis in cardiac and neuronal cells and can mobilize Ca^{2+} from mitochondrial stores (97). The relative roles of these mechanisms in disease pathogenesis remain unknown.

Disorders of distal sterologenesis with ichthyosiform phenotypes

Two multisystem syndromes with ichthyosis, X-linked dominant chondrodysplasia punctata type 2 (CDPX2) (Conradi-Hünermann-Happle syndrome; OMIM 302960) and CHILD syndrome (OMIM 308050), are caused by mutations in genes encoding enzymes of the postsqualene cholesterol biosynthetic pathway. CDPX2 is caused by mutations in the *EBP* (for emopamil binding protein) gene that encodes 3β-hydroxysteroid-Δ^8,Δ^7-isomerase, catalyzing the conversion of 8(9)-cholestenol to lathostero1 (102,103), resulting in diagnostic deviations of the sterol precursors 8-dehydrocholesterol and 8(9)-cholestenol (104). Mutations either in EBP or in NAD(P)H steroid dehydrogenase-like protein, encoding a member of the enzyme complex that removes the C-4 methyl group in the next-most proximal step of the pathways, have been reported to underlie CHILD syndrome [104,105; D. K. Grange et al., cited in (106)]. Given the close approximation of the metabolic blockages, the striking phenotypic similarities and genetic overlap are not surprising (reviewed in Ref. 106). Both are X-dominant, proposed male-lethal traits associated with asymmetric skeletal malformations and a variety of other deficits. Cutaneous features in CDPX2, the more common of the two conditions, are most striking in the neonate, in which linear bands of scaling are distributed in a morphogenic pattern (the lines of Blaschko), postulated to conform to regions in which the mutant X chromosome is the active X (107,108), accompanied by a generalized erythroderma. The cutaneous features resolve after infancy, leaving atrophy (follicular atrophoderma and alopecia) and, in some instances, a mild ichthyosis on the extremities (108). Disease severity is dependent on both the specific mutations and the extent to which the mutant X chromosome is active in affected tissues (109–112). The resolution of the cutaneous phenotype presumably reflects the dilution of effects as a consequence of the diminished viability of keratinocytes bearing the mutant X (113). The cutaneous phenotype in CHILD syndrome differs in its distribution, which is typically limited to one side of the body (104,105). Resolution also occurs, but usually it is only partial. The skeletal defects and internal organ involvement are also restricted to the same, usually right, side.

The pathophysiologic basis for the ichthyosiform phenotype, like the manifestations of the syndromes, is unclear. The multisystem malformations that characterize disorders of postsqualene sterologenesis have been attributed to the following: *1*) deficiency of bulk cholesterol in membrane function; *2*) toxic effects of accumulated precursors; and/or *3*) developmental effects of altered Hedgehog pathway signaling (114). In skin, it seems likely that cholesterol deficiency per se is the major contributor, because a cutaneous phenotype does not occur in either Smith-Lemli-Opitz syndrome (OMIM 270400), attributable to 7-dehydrocholesterol reductase deficiency, or in hairless mice treated with the 7-hydrocholesterol inhibitor AY9944 (115). In contrast, blockade of the Δ24 reductase, converting desmosterol to cholesterol, through the inhibitors triparanol and 20,25-diazocholesterol, is associated with ichthyosis in both rodent models and human (115,116). It is likely, therefore, that 7-dehydrocholesterol, but not desmosterol, can substitute for cholesterol in the formation of SC lamellar membranes.

Before the identification of primary sterologenesis defects in CDPX2 and CHILD syndromes, these disorders were thought to be related to the peroxisomal biogenesis disorders. Deficient peroxisomal function in cultured fibroblasts has been described in both CDPX2 and CHILD syndromes (113,117–120) and in the murine homolog of EBP deficiency, the bare patches mouse (113), which displays cutaneous defects that, like the phenotype in CDPX2, resolve over time (113,121). The clinical phenotypes of the postsqualene sterologenesis and peroxisome biogenesis disorders bear some striking resemblances (121), including skeletal defects (chondrodysplasia punc-tata), central nervous system and/or hepatic involvement, and ichthyosis in the PEX7 disorders (rhizomelic chondrodysplasia punctata) and adult RD. Although their contribution to cellular cholesterol synthesis overall is unclear, the localization of the postsqualene enzymes in the sterol biosynthetic pathway to peroxisomes likely explains these phenotypic convergences.

DISORDERS OF POLAR LIPID PROCESSING

RXLI

Molecular genetics and biochemistry—RXLI is caused by null mutations in the gene encoding the microsomal enzyme, steroid sulfatase (SSase) (122,123). Because of its location on the distal tip of the short arm of the X chromosome (124–128), the *SSase* gene has been the subject of considerable research. The gene mutations/deletions in RXLI (129–133) provoke ichthyosiform skin changes, with occasional extracutaneous organ system involvement, as a result of contiguous gene syndromes (134–136).

SSase is a classic microsomal enzyme that further localizes to coated pits in the plasma membrane (137,138), where it hydrolyzes the 3β-sulfate esters from both CSO_4 and sulfated steroid hormones. In epidermis, SSase activity is low in the basal and spinous layers, whereas enzyme levels peak in the SG (10–20 times higher) and persist into the SC, where it is concentrated in membrane domains (2) (Fig. 3). In cytochemical studies, SSase activity localizes not only within the cytosol (i.e., microsomes) but also within LBs, and SSase is delivered to the interstices of the lower SC by LB secretion (2). Thus, SSase, like other lipid hydrolases that are involved in the extracellular processing of secreted polar lipids (48), uses the LB secretory system to reach sites where it participates in the regulation of permeability barrier homeostasis and desquamation.

As a result of enzyme deficiency in RXLI, CSO_4 accumulates in the epidermis (139–141), in erythrocyte cell membranes (140,142), and in the LDL (β-lipoprotein) fraction of plasma, where it produces diagnostic alterations in electrophoretic mobility (140,143). But CSO_4 levels in epidermis/SC are 1 order of magnitude higher than the levels in blood (140,142,144), likely explaining the prominence of skin versus other organ involvement in RXLI. Normally,

CSO_4 constitutes ~5% of the total lipid of human SG, declining to ~1% of lipid mass in the outer SC, through ongoing hydrolysis of CSO_4 by SSase during SC transit (145,146) (Fig. 3). However, as a result of absent SSase activity, the SC typically contains 10–12% CSO_4 (by dry weight) in RXLI (144). Like other SC lipids, CSO_4 is concentrated in the SC interstices, but in contrast to other barrier lipid precursors, it is not delivered by LB secretion (147). Rather, its mode of delivery to the SC interstices can be explained by its amphilicity, which allows it to diffuse readily across the cell membrane (148). Thus, in the absence of a lipid milieu within corneocytes, CSO_4 likely partitions preferentially to the highly hydrophobic, extracellular domains of the SC.

CSO_4 "cycle" and its regulatory significance—Because cholesterol sulfotransferase activity, which generates CSO_4, predominates in the lower nucleated cell layers of the epidermis, whereas SSase peaks in the outer epidermis, Epstein et al. (149) proposed that an "epidermal CSO_4" exists in the epidermis, in which cholesterol is first sulfated in the lower epidermis and then desulfated back to cholesterol in outer epidermal layers (Fig. 4). Disruption of this CSO_4 cycle accounts for both the abnormal desquamation and the permeability barrier abnormality in RXLI (see below).

Sulfation of cholesterol by cholesterol sulfotransferase is a step that is intimately linked to keratinization (150–152), including cornification in the epidermis (153–155). For example, CSO_4 levels are several orders of magnitude higher in keratinizing than in mucosal epithelia (150), and reversal of keratinization, through the induction of mucous metaplasia in keratinizing epithelia (e.g., by the application of exogenous retinoids), dramatically reduces tissue CSO_4 levels (156,157). Moreover, cholesterol sulfotransferase expression is linked to epidermal development in utero (158,159), and CSO_4 levels increase late in fetal development (160).

CSO_4 is a potent regulatory molecule in many extracutaneous tissues (161,162). For example, whereas retinoic acid inhibits cholesterol sulfotransferase expression, PPARα and liver X receptor activators stimulate its expression (163). CSO_4 stimulates epidermal differentiation by at least two related mechanisms (Fig. 4): *1*) it activates the η isoform of protein kinase C (164–166), which in turn stimulates the phosphorylation of differentiation-linked proteins, assessed as increased cornified envelope formation (167); and *2*) it is also a transcriptional regulator of proteins involved in cornified envelope formation, such as TGM1 and involucrin, operating through an activator protein-1 binding site in the promoter region (168,169). It is likely that these two mechanisms are linked, as shown in Fig. 4: protein kinase C activation by CSO_4 could phosphorylate activator protein-1, leading to enhanced transcriptional regulation of TGM1 and involucrin. Together, these observations provide an explanation for the biological significance of the CSO_4 cycle.

Basis for the permeability barrier abnormality in RXLI—Patients with RXLI display only a minimal basal barrier abnormality (170,171) but a pronounced delay in recovery kinetics after acute perturbations (171), suggesting that excess CSO_4 destabilizes permeability barrier homeostasis. To assess this hypothesis, we performed both in vitro and in vivo studies, showing, first, that CSO_4 fails to form eutectic mixtures with other SC lipids, with excess CSO_4 apparently segregating within nonlamellar domains in model lipid mixtures (51) and in diseased SC (52). Accordingly, ultrastructural images of SC in RXLI show frequent but focal nonlamellar domains, with disruption of the extracellular lamellae (2,172). Yet, the barrier abnormality could be attributable not only to excess CSO_4 but also to decreased cholesterol (the cholesterol content of the SC in RXLI is reduced by ~50%) (144), and a discrete decrease in cholesterol produces abnormal extracellular lamellar membranes (173). To varying extents, the decrease in cholesterol in RXLI could be caused by (Fig. 3) the following: *1*) reduced generation of cholesterol from CSO_4 as a result of the enzyme deficiency (172,174); and/or

2) CSO_4-mediated inhibition of HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis (174). CSO_4, like oxygenated sterols, is a potent inhibitor of cholesterol synthesis (174), consistent with the reduced levels of cholesterol in the SC of RXLI (144). Finally, CSO_4 inhibits the TGM1-mediated attachment of ω-hydroxyceramides to the cornified envelope in vitro, a step that forms the corneocyte lipid envelope (175). Yet, the cornified envelope/corneocyte-bound lipid envelope scaffold does not appear abnormal in RXLI (P. M. Elias et al., unpublished observations). Thus, the dominant mechanisms that account for the barrier abnormality in RXLI appear to be lamellar/nonlamellar phase separation of excess CSO_4 and reduced cholesterol content of the SC lamellar membranes (2).

Mechanisms proposed to cause abnormal desquamation in RXLI—Kinetic studies have demonstrated that the hyperkeratosis in RXLI reflects delayed desquamation (12,176). The basis for this classic, retention type of ichthyosis is the persistence of corneodesmosomes at all levels of the SC (cited in Ref. 2). Two key serine proteases, kallikrein (KLK) 7 [stratum corneum chymotryptic enzyme (SCCE)] and KLK5 [stratum corneum tryptic enzyme (SCTE)], are primary mediators of desquamation that degrade corneo-desmosomes in vitro (177). CSO_4 may increase SC retention through the known ability of this lipid to function as a serine protease inhibitor (2,12). Moreover, although the activities of these enzymes are restricted by the acidic pH of normal SC (SCCE and SCTE exhibit neutral pH optima), the pH of the SC in RXLI is even lower than that of normal SC (178). As a result, serine protease activity in RXLI is reduced below the levels in normal SC (2). An unrelated mechanism, which could contribute to increased SC cohesion in RXLI, posits that Ca^{2+}, if present in sufficient quantities, could stabilize highly anionic SO_4 groups (from the persistence of CSO_4) on adjacent lamellar bilayers (179). Indeed, CSO_4-containing lipo-somes aggregate avidly in the presence of calcium (180,181). Moreover, the lower SC in RXLI demonstrates abundant Ca^{2+} in extracellular domains, which preferentially localize along the external faces of opposing corneodesmosomes (2). Thus, the delayed degradation of corneodesmosomes in RXLI could be attributable in part to leakage of Ca^{2+} into the lower SC (caused by the barrier defect), with the formation of Ca^{2+} bridges between adjacent corneodesmosomes (2).

Sphingolipidoses

In its most severe form, the sphingolipidosis, type 2 GD can present with a neonatal “collodion baby” phenotype ichthyosis (182–184). Studies in patients, transgenic murine analogs, and inhibitor-based models have shown that substantial reductions in lysosomal β-glucocerebrosidase (EC 3.2.1.45) can provoke GD, a profound barrier abnormality (3,183); in contrast, diminished activity of another key Cer-generating enzyme, acidic sphingomyelinase, the causative enzyme of Niemann-Pick disease, although also provoking barrier abnormalities (4,185), rarely, if ever, causes ichthyosiform skin changes. The distinct cutaneous phenotypes may reflect the generation of the full spectrum of all nine human SC Cer species from glucosylceramides, whereas acidic sphingomyelinase generates only two SC Cers from corresponding sphingomyelin precursors (186). Cers constitute 50% of the extracellular lamellar membranes in SC; as such, they are absolutely required for normal barrier function (186). When β-glucocerebrosidase levels are very low (<90% of normal), ichthyotic signs can emerge (182–184,187), attributable to both hyperplasia consequent to a severe permeability barrier abnormality (188) and direct mitogenic activity of excess glucosylceramides (189) (Fig. 5). The persistence of glucosylceramides in extracellular lamellar membranes also imparts an “immature” appearance that is quite distinctive and potentially diagnostic of GD (3,187). Decreased Cer in relation to cholesterol and FFA in GD (185,188) also likely results again in lamellar/nonlamellar phase separation caused by altered molar ratios of the three key lipids, analogous to the effects of excess CSO_4 in RXLI (2) (see above). This conclusion is based upon the observation that topical Cers normalize barrier function in severe glucocerebrosidase deficiency (4), but the cause of the barrier abnormality in GD is more complex, because topical

Cers do not normalize barrier function in the face of enzymatic blockade (183). Hence, it is likely that both decreased Cers and excess glucosylceramides contribute to the barrier abnormality in GD (Fig. 5). The metabolic production and fate of epidermal Cer is the topic of a subsequent review in this series by Drs. W. Holleran and Y. Uchida.

FAILURE OF LB ASSEMBLY OR SECRETION

HI

HI is a rare, recessively inherited disorder that presents at birth with a thick, plate-like encasement of the entire skin surface that has life-threatening consequences. In neonates who survive the perinatal period, the plate-like encasement is shed, and the phenotype shifts to a severe ichthyosiform erythroderma (9,190). Transcutaneous water loss rates remain extremely high (47), explaining at least in part the prominent epidermal hyperplasia and hyperkeratosis that are presumably driven by the permeability barrier abnormality, as described above. The barrier defect in HI is a primary disorder of the LB secretory system (191). Specifically, LBs with replete lamellar contents are found only rarely in HI. Instead, the cytosol of the SG layer contains numerous, small vesicular structures (192), which presumably represent nascent LBs that lack internal contents. It is likely that these nascent organelles undergo exocytosis, because the cornified lipid envelope, a structure thought to derive from the fusion of LB with the plasma membrane, is normal in HI (192). Nevertheless, the extracellular spaces of the SC are largely devoid of lamellar membranes (192).

ABCs are a large group of proteins that mediate the transport of a variety of different substrates across cellular membranes. These proteins contain two transmembrane sequences and two ATP binding domains, which undergo conformational changes that facilitate first the binding and then the dissociation of attached lipids (193). To date, 48 ABC genes have been identified, which have been further divided into seven subfamilies, based on sequence homology and supramolecular organization of the nucleotide binding folds (194–197). The ABCA subfamily comprises 12 functional transporters that all mediate lipid transport (198), with the exception of one pseudogene (ABCA11). ABCA transporters function as components of highly specialized cellular lipid-transporting organelles in major physiological systems, in which defects cause severe inherited diseases in the cardiovascular, visual, and respiratory systems. Accordingly, gene mutations of ABCA proteins are linked to several recessive disorders of lipid metabolism, including ABCA1 [Tangier disease (156,157)], ABCA4 [Stargardt disease (158–160)], and surfactant deficiency in newborns, which has been linked to ABCA3 deficiency (161,162). Further study has revealed that ABCA3 regulates lipid transport into the LBs of alveolar type 2 cells (199,200).

ABCA12 is a recently characterized member of the ABC transporter superfamily, which serves as a putative transporter for glucosylceramides from the Golgi apparatus (201) into epidermal LBs. In HI [and in some cases of ARCI with a LI phenotype (202)], truncation or deletion mutations in both alleles of the gene that encodes ABCA12 (203) result in a failure to deliver newly synthesized glucosylceramides into nascent LBs (194,204). As a result, few if any lamellar lipids are delivered to the SC interstices (192), and as noted above, a profound barrier abnormality results (205). Recent studies in HI keratinocytes have demonstrated not only defective glucosylceramide transport into LBs but also that corrective transfer of the ABCA12 gene into HI keratinocytes restores normal glucosylceramide loading into LBs (194). In those HI patients with residual ABCA12 expression, it is possible that topical treatment with either PPARγ or PPARδ activators could be beneficial, because our recent studies show that these two nuclear hormone receptors upregulate ABCA12 expression in normal keratinocytes (198). Mutations in the lipid transporter *ABCA12* place HI into a disease spectrum with ARCI (202). Although in HI the genetic *ABCA12* abnormalities are truncations or deletions, the *ABCA12* mutations reported in ARCI to date have been solely missense mutations (202).

Because HI is characterized not only by a profound barrier abnormality but also by striking hyperkeratosis (thickening of the SC), the lipid transporter defect likely underlies the desquamation abnormality as well, but by an indirect mechanism. Because lipid delivery to LBs is required for the subsequent or concurrent importation of proteins into these organelles (206), it is likely that a failure of lipid delivery also impairs the delivery of hydrolytic enzymes to LBs in HI; therefore, little or no enzymes are delivered to the SC interstices (Fig. 6). Because an array of LB-derived proteases is required for normal desquamation (207–209), the failure of protease delivery could result in corneodesmosome retention, explaining (along with the intense hyperplastic response to the barrier abnormality) the extreme hyperkeratosis in neonates with HI.

Cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma syndrome

A noncongenital neurocutaneous syndrome with microcephaly, mental retardation, generalized ichthyosis, and palmoplantar keratoderma was recently ascribed to mutations in the *SNAP29* gene, encoding for the SNARE29 protein involved in intracellular vesicle fusion (210). Aside from normal-appearing LBs, the epidermis of these patients exhibits numerous vesicular structures of varying size in the SG and SC layers that contain glucosylceramide, KLK5, and KLK7 (210). As the SNARE proteins are known to mediate neuromediator secretion (211), *SNAP29* mutations could cause a permeability barrier abnormality by impairing LB secretion. The defect is possibly limited to a subset of LBs in the skin, explaining the selective enrichment of glucosylceramide, KLK5, and KLK7 in the retained vesicular structures seen by electron microscopy.

SYSTEMIC CONSEQUENCES OF BARRIER ABNORMALITIES IN THE ICHTHYOSES

The importance of calories lost through evaporation has been long recognized in the treatment of children with thermal burns and in premature infants who have immature skin barriers (212), but this factor has not been addressed previously in children with extensive inflammatory or genetic skin diseases. Short stature has been reported in some ichthyoses, such as Netherton syndrome (213), HI (214), and trichothiodystrophy (214–216), but growth failure is present at times in other forms of ichthyosis, suggesting that common pathogenic mechanism(s) could be operative. Although epidermal inflammation and hyperproliferation have been proposed to explain growth failure in adults with exfoliative erythroderma (217), negative nitrogen balance does not occur until losses exceed 17 g/m^2/day (218). Therefore, nutrient drain from a hyperplastic epidermis alone is unlikely to account for the growth failure in these children. Alternatively, recent studies have shown that caloric losses from an impaired permeability barrier is the most likely cause of growth failure in severe ichthyosis phenotypes (47). Because transcutaneous evaporation is necessarily accompanied by a loss of heat (0.58 kcal/ml) (219), excessive rates of TEWL can constitute a significant caloric drain. All of these pediatric subjects displayed impaired barrier function with a marked increase in TEWL rates, resulting in large daily volumes of evaporative water loss, but TEWL rates ranged widely among study patients, as may be expected in view of the genetic heterogeneity included under the umbrella term “ichthyosis” (220).

The number of kilocalories lost from daily total TEWL ranged from 84 to 1,015 kcal (8–42 kcal/kg/day, with a mean of 433 ± 272 kcal/day) in this cohort, in contrast to expected rates of 41 to 132 kcal/day for age-matched children with competent barriers. In patients with moderate to severe barrier abnormalities, the consequent caloric drain from heat evaporation appeared sufficient to account for growth failure. Moreover, and alternatively, evaporative caloric losses could be compounded by caloric expenditures from cutaneous hyperplasia, chronic inflammation, which would be expected to increase metabolic rates, and/or anorexia

accompanying systemic inflammation. Indeed, in the subject in whom resting energy expenditure was measured, it was 19% or higher than predicted; patients with the highest rates of TEWL also displayed the highest resting expenditure, suggesting that the severity of the barrier defect correlates with increased metabolic demands. Some patients were in positive caloric balance at the time of study, but they had dropped below normal growth patterns early in life (221). Hence, their current positive caloric balance likely reflected that they had now reached a steady state of growth, but they remained below normal body weights. A significant number of these patients were in negative energy balance, suggesting how precariously these patients maintain energy balance.

As noted above, both possession of the correct type and quantity of lipid and their organization into lamellar sheets are required for the formation of a competent barrier (222–224). Indeed, ultrastructural assessment of permeability barrier-related structures predicted the severity of the functional defect in ichthyosis patients with growth failure (47). The most severe barrier defects were observed in patients with HI and Netherton syndrome, and assessment of the LB secretory system and evaluation of cutaneous barrier function by measurement of TEWL correlated well with the magnitude of caloric drain from cutaneous water losses in these patients.

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Abbreviations

ALOX	arachidonate lipoxygenase
ARCI	autosomal recessive congenital ichthyosis
CDPX2	X-linked dominant chondrodysplasia punctata type 2
Cer	ceramide
CHILD	congenital hemidysplasia with ichthyosiform erythroderma and limb defects
CIE	congenital ichthyosiform erythroderma
CSO_4	cholesterol sulfate
GD	Gaucher disease
HI	harlequin ichthyosis
KLK	kallikrein
LB	lamellar body
LI	lamellar ichthyosis
LOX	12*R*-lipoxygenase
NLSDI	neutral lipid storage disease with ichthyosis
OMIM	Online Mendelian Inheritance in Man
PPAR	peroxisome proliferator-activated receptor
RCDP	rhizomelic chondrodysplasia punctata
RD	Refsum disease
RXLI	recessive X-linked ichthyosis

SSase	steroid sulfatase
SC	stratum corneum
SCCE	stratum corneum chymotryptic enzyme
SCTE	stratum corneum tryptic enzyme
SG	stratum granulosum
SLS	Sjögren-Larsson syndrome
TAG	triacylglyceride
TEWL	transepidermal water loss
TGM1	transglutaminase 1

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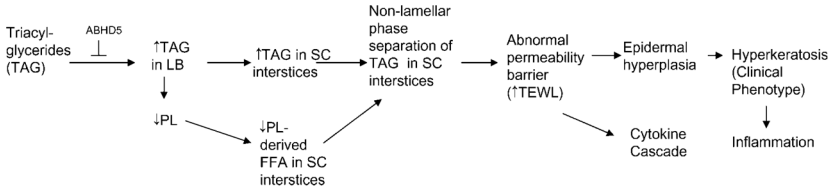

Fig. 1.

Proposed pathogenesis of neutral lipid storage disease. LB, lamellar body; PL, phospholipids; SC, stratum corneum; TAG, triacylglyceride; TEWL, transepidermal water loss.

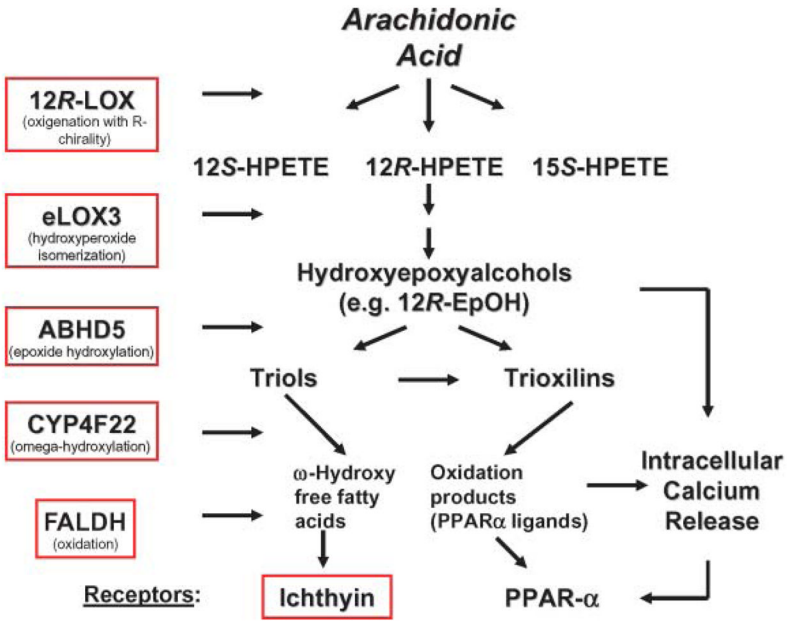

Fig. 2.

Potential disruptions in peroxidated lipid pathways in autosomal recessive congenital ichthyosis. CYP4F22, cytochrome P450, family 4, subfamily F, polypeptide 22; FALDH, fatty aldehyde dehydrogenase; PPAR, peroxisome proliferator-activated receptor; 12*R*-HPETE, 12 (*R*)-hydro-peroxyeicosatetraenoic acid; 12*R*-LOX, 12*R*-lipoxygenase.

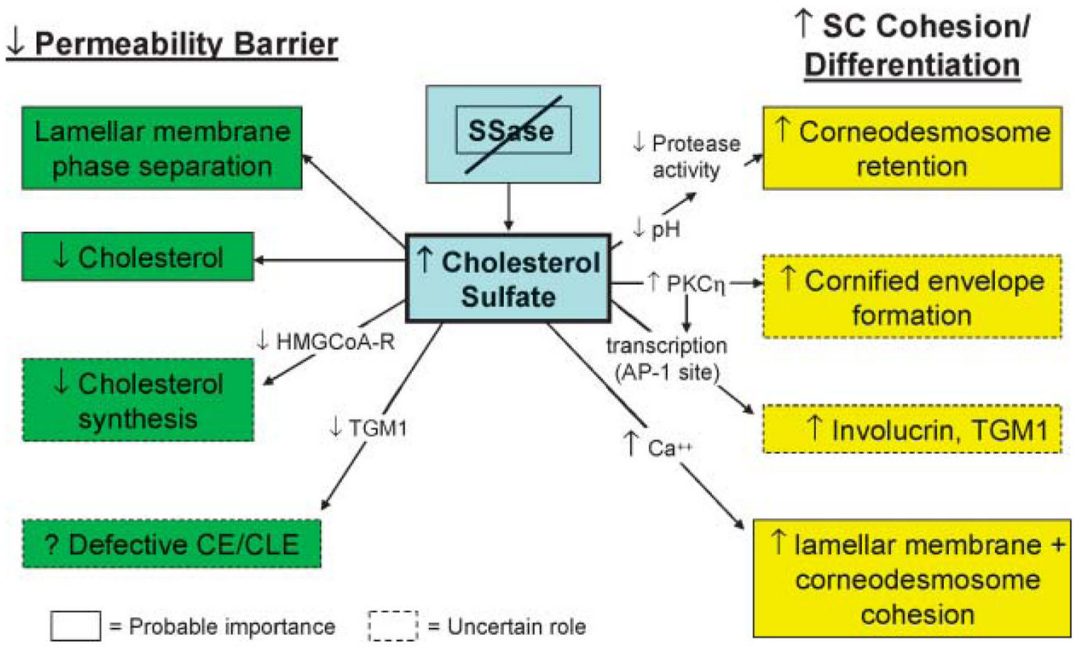

Fig. 3.

How steroid sulfatase (SSase) deficiency leads to recessive X-linked ichthyosis. CE, cornified envelope; CLE, cornified lipid envelope; PKC, protein kinase C; TGM1, transglutaminase 1.

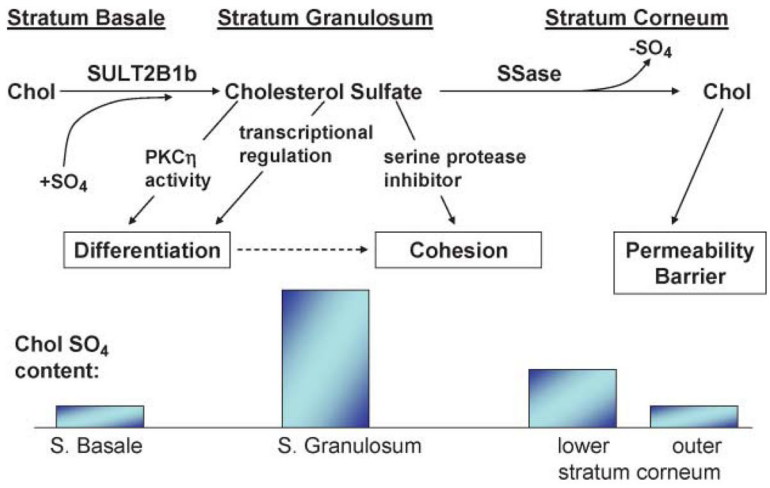

Fig. 4.

Consequences of the epidermal cholesterol sulfate cycle for normal skin. Chol, cholesterol; SULT2B1b, cholesterol sulfotransferase.

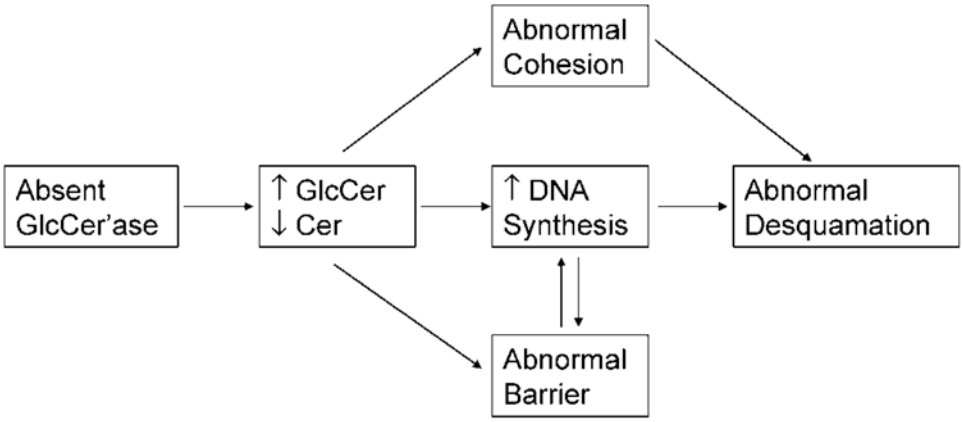

Fig. 5.
Potential pathogenic mechanisms in Gaucher disease. Cer, ceramide; GlcCer, glucocerebroside; GlcCer'ase, glucocerebrosidase.

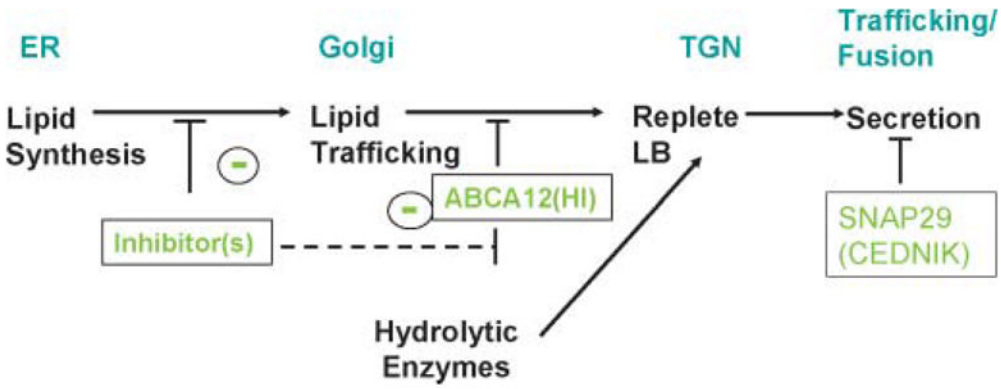

Fig. 6.

Protein delivery to lamellar bodies is dependent upon prior lipid deposition: sites of blockade in harlequin ichthyosis and cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma syndrome. ER, endoplasmic reticulum; TGN, *trans*-Golgi network.

TABLE 1

Inherited lipid metabolic disorders with ichthyosis

Metabolic Category	Inheritance Pattern	Multisystem	Affected Protein (Gene)	Normal Function
Fatty acid metabolism				
Refsum disease	Recessive	Yes	Phytanoyl-CoA hydroxylase (*PAHX, PHYH*); peroxin 7 receptor (*PEX7*)	α-Hydroxylation of branched chain FFA
Sjögren-Larsson syndrome	Recessive	Yes	Fatty aldehyde dehydrogenase (*ALDH3A2*)	Oxidation of fatty aldehydes to free fatty acids
Autosomal recessive congenital ichthyosis	Recessive	No	12*R*-Lipoxygenase (*ALOX12*)	? Oxygenation of arachidonic acid to12(*R*)-HPETE
	Recessive	No	Lipoxygenase-3 (*ALOXE3*)	? Hydroxyperoxide isomerization of 12(*R*)-HPETE to epoxyalcohol metabolites
	Recessive	No	Cytochrome P450 4F22(*CYP4F22, FLJ39501*)	? ω-Hydroxylation of trioxilins
	Recessive	No	Ichthyin (*ichthyin*)	? Receptor for hydroxyepoxyalcohol metabolites
Cholesterol metabolism				
Conradi-Hünermann syndrome	X-linked dominant	Yes	Δ^8, Δ^7-sterol isomerase emopamil binding protein (*EBP*)	Distal cholesterol synthetic pathway
CHILD syndrome	X-linked dominant	Yes	NAD(P)H steroid dehydrogenase-like protein (*NSDHL*)	Distal cholesterol synthetic pathway
X-linked ichthyosis	X-linked recessive	(Yes)	Ssase	Desulfate cholesterol sulfate
Sphingolipid metabolism				
GD type I	Recessive	Yes	β-Glucocerebrosidase (*GBA*)	Deglucosylated β-glucocerebrosidase
Niemann-Pick disease	Recessive	Yes	Acidic sphingomyelinase (*SMPD1*)	Generates ceramides from sphingomyelin
Triglyceride metabolism				
Neutral lipid storage disease	Recessive	Yes	CGI-58 acid lipase (*ABHD5*)	Generates diacylglycerides and FFAs from triacylglycerides
Lipid transporter				
Harlequin ichthyosis	Recessive	No	ATP binding cassette (*ABCA12*, truncation, deletion)	Transports glucosylceramides into LBs
Lamellar ichthyosis (some)	Recessive	No	ATP binding cassette (*ABCA12*, missense)	Same
CEDNIK syndrome	Recessive	Yes	Soluble *n*-ethylmaleimide-sensitive factor attachment protein receptor (*SNAP29*)	Facilitates exocytosis of LB contents

ALOX, arachidonate lipoxygenase; CEDNIK, cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma; CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; GD, Gaucher disease; LB, lamellar body; 12(*R*)-HPETE, 12(*R*)-hydroperoxyeicosa-tetraenoic acid; SSase, steroid sulfatase.

TABLE 2

Ichthyoses that have or could have lamellar phase separation as a basis for barrier abnormality

Disease	Enzymatic Defect	Barrier Dysfunction	Lamellar/Nonlamellar Phase Separation	Phase-Separated Lipid
Neutral lipid storage disease	Neutral lipid hydrolase (CGI-58)	Demonstrated (35)	Demonstrated (35)	Triglycerides
Recessive X-linked ichthyosis	SSase	Demonstrated (225)	Demonstrated (225)	Cholesterol sulfate
Refsum disease	Phytanoyl-CoA hydroxylase (PhyH); peroxin 7 receptor	Not assessed	Not assessed	Phytanic acid in all glycerolipids (226)
Sjögren-Larsson	Fatty aldehyde dehydrogenase	Not assessed	Demonstrated (227)	Not assessed
GD	β-Glucocerebrosidase	Demonstrated (228)	Demonstrated (228)	Glucosylceramides
CHILD syndrome	NAD(P)H 3β-hydroxysteroid dehydrogenase (NSDHL)	Not assessed	Not assessed	Not assessed
Niemann-Pick disease	Acidic sphingomyelinase	Demonstrated (14,229)	Demonstrated (229)	Not assessed