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Pathogenesis-based therapies in ichthyoses

Joey E. Lai-Cheong^{*}, Peter M. Elias[†], and Amy S. Paller[‡]

^{*}St John's Institute of Dermatology, King's College London, London, United Kingdom

[†]Dermatology Service, Veterans Affairs Medical Center and Department of Dermatology, University of California, San Francisco, California

[‡]Department of Dermatology, Feinberg School of Medicine, Chicago, Illinois

Abstract

During the past 20 years, tremendous progress has been made in our understanding of the molecular basis of many genetic skin conditions. The translation of these laboratory findings into effective therapies for affected individuals has been slow, however, in large part due to the risk of carcinogenesis from random viral genomic integration and the lack of efficacy of topically applied genetic material and most proteins. As intervention at the gene level still appears remote for most genetic disorders, increased knowledge about the cellular and biochemical pathogenesis of disease allows specific targeting of pathways with existing and/or novel drugs and molecules. In contrast to the requirement for personalization of most gene-based approaches, pathogenesis-based therapy is pathway specific, and in theory, it should have broader applicability. In this chapter, we provide an overview of the pathoetiology of the various types of ichthyoses and demonstrate how a pathogenesis-based approach can potentially lead to innovative treatments for these conditions. Notably, this strategy has been successfully validated for the treatment of the rare X-linked dominant condition, CHILD syndrome, in which topical applications of cholesterol and lovastatin together to affected skin resulted in marked improvement of the skin phenotype.

Keywords

ceramides; cholesterol; fatty acids; ichthyosis; lanosterol; pathogenesis

Introduction

The ichthyoses consist of a genetically heterogeneous group of conditions in which there is a deregulation of cornification (1,2). The skin is characterized by widespread scaling associated with inflammation and blistering in some subtypes. Ichthyotic skin displays a defect in the epidermal permeability barrier and the severity of the ichthyosis in turn reflects the degree of barrier dysfunction (3). Barrier impermeability depends on the presence of an extracellular lipid bilayer containing the correct composition of cholesterol, ceramides, and free fatty acids (3). Thus, defects in the synthesis or secretion of these molecules can result in either the upstream accumulation of potentially toxic metabolites, and/or deficiency of

downstream end-products of importance for cell function, resulting in a dysfunctional epidermis and the formation of ichthyotic skin (4).

Current management of ichthyosis is mainly directed toward scale reduction, using topical treatments such as urea or lactic acid-based emollients, and/or keratolytics (2,5). And in severe cases, oral retinoids, such as acitretin, isotretinoin, and alitretinoin, may be used (6,7). However, these approaches all exhibit an inherent flaw, as the development of ichthyosis reflects a “best attempt” by the metabolically compromised epidermis to generate a functional epidermal permeability barrier (2). Our greater understanding of the pathomechanisms leading to many of the ichthyoses has paved the way for innovative therapeutic approaches in the management of ichthyosis. Novel treatments, involving gene or protein therapy, unfortunately remain remote given the widespread nature of the disease, difficulties in transcutaneous drug delivery, the large number of potentially painful injections, and the long-term risks of viral transduction involved in gene correction (5), notwithstanding ethical and governmental regulatory concerns (8). A more practical alternate approach would be to use a pathway-based strategy for these disorders. For instance, in syndromic lipid metabolic disorders, the cutaneous and extra-cutaneous features result from either a deficiency of the pathway product, and/or an accumulation of upstream toxic metabolites (3,9). Therefore, in inherited disorders of distal cholesterol metabolism, a logical therapeutic strategy would be to treat extracutaneous disease features with systemic coadministration of cholesterol and statins (10,11). This approach, however, could be hampered by first-pass metabolism of statins and intrahepatic incorporation of cholesterol into lipoprotein particles. To circumvent this problem, a topical strategy could be used, allowing direct access to the skin, and with sufficient absorption, perhaps to the extracutaneous tissues as well.

Pathogenesis of multisystem cholesterol biosynthetic disorders

Cholesterol is a key component of the epidermal lipid bilayer along with ceramides and fatty acids. The synthesis of cholesterol is a complex process involving several key intermediate steps, one of which is the conversion of lanosterol to cholesterol, also known as distal cholesterol metabolism. Abnormal biosynthesis of cholesterol from lanosterol can result in eight different syndromes, of which seven have an ichthyotic phenotype. These include lathosterolosis, CHILD (congenital hemi-dysplasia, ichthyosis and limb defects) syndrome, CHH (Conradi–Hünemann–Happle) syndrome, SC4MOL deficiency, XLI (X-linked ichthyosis), desmosterolosis, and SLOS (Smith–Lemli–Opitz) syndrome (12–19). The ichthyosis can range from severe, such as in CHILD syndrome, SC4MOL deficiency, and lathosterolosis, to moderately severe as in CHH and XLI, and finally mild to inapparent in SLOS and desmosterolosis. Lanosterol is a key intermediate sterol molecule and its conversion to cholesterol involves 19 reactions that are catalyzed by enzymes associated with the endoplasmic reticulum. These enzymatic steps include the reduction of 7, 14, and 24 double bonds from lanosterol, the removal of methyl groups at positions C4 α , C4 β , and C14, and the isomerization of the 8(9) double bond to 7(8), followed by desaturation at the 5 position to generate cholesterol. The pathogenesis of the ichthyoses in the inborn errors of distal cholesterol metabolism can largely be attributed to a deficiency of cholesterol required to form and maintain cell membrane, associated with an accumulation of toxic

sterol precursors (20–22). In addition, the formation of sterol metabolites that downregulate cholesterol synthesis (23), alter hedgehog signaling (24,25), and/or accelerate the degradation of HMG CoA reductase (26) could also contribute to disease pathogenesis. Finally, vitamin D deficiency could also worsen the disease phenotype, as 1,25(OH)₂ vitamin D3 is a potent regulator of epidermal differentiation and proliferation.

CHH or CDPX2 and CHILD syndromes

Conradi–Hünemann–Happle syndrome or X-linked dominant

chondrodysplasia punctata type 2—(CHH or CDPX2) (OMIM #302960) is caused by pathogenic mutations in the gene encoding the emopamil-binding protein (EBP) that catalyzes the conversion of 8(9)-cholestenol to lathosterol. CHH is characterized by linear ichthyosis that can spontaneously resolve chondrodysplasia punctata, cataracts, and short stature in affected females (27–30). In the X-linked dominant *CHILD syndrome* (OMIM #308050), reduced-function mutations in either the NAD(P)H steroid dehydrogenase-like (*NSDHL*) or occasionally the *EBP* gene (29,31) result in failure to remove the C-4 methyl group from lanosterol (Fig. 1). The skin in *CHILD syndrome* consists of unilateral circumscribed linear plaques topped by prominent wax-like scales (25). In both disorders, the involved skin sites conform to regions in which the mutant X-chromosome predominates (32,33).

SLOS syndrome, desmosterolosis, lathosterolosis, and SC4MOL deficiency

Although ichthyosis is not clinically apparent in *SLOS syndrome* (OMIM #270400) (7-dehydrocholesterol reductase (*DHCR7*) deficiency), both ultraviolet B-mediated photosensitivity (34,35) and a propensity to develop eczema (R. Elias and R. Steiner, personal communication) commonly occur. SLOS has an incidence of ~1 in 6–10,000 with over 120 different loss-of-function mutations reported in the *DHCR7* gene (35). *DHCR7* deficiency impairs both desmosterol (8-DHC) and 7-dehydrocholesterol (7-DHC) metabolism (23,36,37), resulting in elevated 7-DHC and 8-DHC blood levels, with proportionate reduction in serum cholesterol (13,14,16,17,30,31,35,38,39). *Lathosterolosis* (OMIM #607330) has not been described in the United States, but in the several European patients in whom this condition has been reported, prominent ichthyosis was a feature (15,40–42). In the United States, two individuals have been reported with *desmosterolosis* (OMIM #602398) caused by reduced-function mutations in the gene encoding 24-dehydrocholesterol reductase (*DHCR24*). These individuals display developmental and neurological anomalies with minimal ichthyosis (18,43).

XLI

The pathogenesis of XLI (OMIM #308100) is by far the most understood among the ichthyoses. XLI occurs as a result of steroid sulfatase (SSase) deficiency, leading to an accumulation of cholesterol sulfate (CSO₄) in the outer epidermis (44–46), erythrocyte cell membranes (44,46), and lipoprotein fractions of plasma (46). Whereas CSO₄ levels normally comprise ~1% of lipid mass in the stratum corneum (47,48), in XLI, CSO₄ contents can reach ~10–12% (49). Although the hydrolysis of CSO₄ generates some of the cholesterol required for the barrier, CSO₄ is also a potent inhibitor of HMG CoA reductase,

a key enzyme involved in cholesterol synthesis, thus further reducing cholesterol levels in XLI (49). The accumulation of CSO₄ coupled with cholesterol deficiency disrupts lamellar membrane architecture, accounting for the barrier abnormality in XLI (50,51) (Fig. 2).

Pathogenesis-based therapy in CHILD syndrome

In all of the lipid metabolic disorders, blockade of metabolite production alone, which can be temporarily effective (52), cannot usually be used as monotherapy for the cutaneous phenotype, because the end-products of these pathways (cholesterol, ceramides, and free fatty acids) are all required to prevent the development of a permeability barrier defect, which in turn would stimulate hyperproliferation, leading to an ichthyotic phenotype (Fig. 3). In 2011, Paller and coworkers reported the successful treatment of two unrelated patients with CHILD syndrome, an X-linked dominant disorder of distal cholesterol metabolism resulting from mutations in *NSDHL* gene (5,29) (Fig. 4). This gene encodes a member of the enzyme complex that removes the C-4 methyl group from lanosterol. Mutations in the *NSDHL* gene prevent the post-lanosterol generation of cholesterol but concurrently lead to accumulation of upstream, potentially toxic metabolites. Histologically, skin biopsies from individuals with CHILD syndrome show marked hyperkeratosis and acanthosis with an absent granular layer and dermal foam cells (5). Ultrastructurally, severe alterations in the epidermal lipid secretory system are present. These include premature fusion of individual organelles into intracellular multivesicular bodies which are incompletely secreted (5). Furthermore, the stratum corneum extracellular matrix displays a reduced amount of secreted lamellar material interspersed with abundant non-lamellar vesicles. In the study reported by Paller and coworkers, topical applications of cholesterol alone were ineffective, but applications of 2% cholesterol and 2% lovastatin resulted in reduced inflammation, skin thickening, and scaling in two patients with CHILD syndrome as early as 4–6 weeks following initiation of treatment (5). By 6 months, the treated skin had largely normalized at a clinical, histological, and ultrastructural level. Both patients tolerated the treatment with no systemic side effects. Although the primary rationale for provision of the pathway product (cholesterol) is to avoid epidermal dysfunction due to lipid deficiency (Fig. 3), co-provision of cholesterol could also be beneficial by further downregulating HMG CoA reductase activity secondary to negative feedback regulation. Another cholesterol-metabolic skin condition that could benefit from statin/cholesterol combination is CHH syndrome presenting with bone defects and patterned ichthyosis without lateralization (5).

Pathogenesis of other lipid metabolic disorders and possible therapeutic interventions

The successful validation of the pathogenesis-based approach, using topical cholesterol and lovastatin in CHILD syndrome, provides proof of principle that this strategy could theoretically be utilized not only for other disorders of distal cholesterol metabolism, but also in other disorders of lipid metabolism resulting from defects in either fatty acid or ceramide biosynthesis. Below are examples in which topical lipids or lipid-soluble products could theoretically be of benefit to affected individuals.

Sjogren-Larsson syndrome (SLS)

SLS (OMIM #270200) is a rare autosomal recessive disorder of fatty acid metabolism characterized by pruritic ichthyosis, spastic diplegia or tetraplegia, glistening white retinal dots, and mental retardation (53). It results from pathogenic mutations in the fatty aldehyde dehydrogenase (*FALDH*) gene leading to profound deficiency in the activity of FALDH (53). There is consequently both an accumulation of cytotoxic metabolites, coupled with a deficiency of free fatty acids, resulting in ichthyosis (9,54). These pathogenetic data therefore predict that SLS could potentially be treated with topical free fatty acids plus either a topical acetylCoA carboxylase or fatty acid synthase inhibitor.

Neutral lipid storage disease with ichthyosis (NLSDI)

NLSDI (OMIM #275630), also known as Chanarin-Dorfman syndrome, is a rare autosomal recessive disorder characterized by ichthyosis and mild neurological abnormalities (3). It is caused by mutations in the *ABHD5* gene that encodes a lipid hydrolase (55). This enzyme co-activates ATGL, a newly identified lipase that in turn hydrolyzes triacylglycerol (TAG) into diacylglycerides (DAG) for phospholipid and free fatty acid production. In NLSDI, there is accumulation of cytosolic TAG, but a lack of phospholipids and free fatty acids, an important component of the epidermal lipid bilayer. Although there is accumulation of TAG in NLSDI, acylceramide (acylCer) deficiency has recently been implicated to be responsible for development of the cutaneous disease (54), suggesting that the ichthyosis may respond to replacement with topical acylCer.

Refsum disease (RD)

RD (OMIM #266500) is an autosomal recessive disorder characterized by ichthyosis, peripheral neuropathy, and retinitis pigmentosa (56–58). It results from mutations in the *PHYH* gene that encodes phytanoyl-CoA-hydroxylase, a key enzyme that is involved in phytanic acid alpha oxidation (57). As a result, in RD there is an accumulation of phytanic acid, a C20-branched chain fatty acid, in blood and other tissues (58). This increase in phytanic acid leads to the replacement of other fatty acids, such as linoleic and arachidonic acids, leading to essential fatty acid deficiency. In this condition, there is an absence of the corneocyte lipid envelope (CLE), suggesting that either plant-derived, branched fatty acids cannot be utilized for acylCer production (59), or that the resultant acylCer cannot be utilized as a substrate for the de-esterifying enzyme that generates ω -OH-Cer for CLE formation. Therefore, the cutaneous features of RD could theoretically be treated with free fatty acids and/or acylCer, with or without a topical inhibitor of DAG/TAG synthesis, although treatment of the neurological and the systemic features would still require dietary intervention (59,60).

Autosomal recessive congenital ichthyosis (ARCI)

Some patients with *ARCI* have *ABCA12* missense mutations resulting in reduced but not absent glucosylceramide (GlcCer) transport into nascent lamellar bodies (61,62). This suggests that topical application of cell-permeant Cer, along with a topical liver X receptor (LXR) or peroxisome proliferator-activated receptor (PPAR) β/δ activator, should benefit

ARCI patients with residual ABCA12 expression, as recent studies have shown that both exogenous Cer and LXR/PPAR β/δ activators upregulate ABCA12 expression (63).

On the other hand, in patients with *Harlequin ichthyosis*, a non-syndromic but life-threatening recessive disorder of cornification, ABCA12 expression is absent (64). Hence, lipid replacement treatment with topical GlcCer could be beneficial.

Finally, in ARCI due to either *eLOX3* or *12RLOX* mutations, there is a failure to oxygenate ω -acyl linoleic acid in acylCer resulting in impaired de-esterification of ω -OH-Cer and a failure to covalently bind ω -OH-Cer to the external face of the cornified envelope (65). Therefore, it should be possible in theory to treat these patients with topical application of ω -OH-Cer.

Neuronopathic (type II) Gaucher disease (GD)

In *neuronopathic (type II)* GD (OMIM #230900), which is due to loss-of-function mutations in β -glucocerebrosidase (β -GlcCer'ase), enzyme replacement at a cost of over \$25,000/year is the current standard of therapy. The cutaneous phenotype in GD type II reflects both an accumulation of glucosylCer, with a corresponding reduction of ceramide production (66). Hence, the cutaneous phenotype, and perhaps the neurological features of GD type II patients, could benefit in theory from treatment with a GC synthase inhibitor and topical ceramide.

Pathogenesis-based therapy in Netherton syndrome (NS)

NS (OMIM #256500) is a rare autosomal recessive genodermatosis characterized by widespread skin inflammation, scaling, and hair shaft defects (67). Affected individuals with NS have allergic tendencies including atopic dermatitis and highly elevated serum IgE levels (68). Although not a true ichthyosis, NS is a scaling disorder caused by pathogenic mutations in the *serine protease inhibitor Kazal-type 5 (SPINK5)* gene that encodes the lymphoepithelial Kazal type-related inhibitor (LEKTI) (67). LEKTI is a serine protease inhibitor that counteracts with other proteases to regulate skin barrier homeostasis and inflammatory responses in the skin (69). A better understanding of the biology of LEKTI and its role in skin inflammation has led to the development of potentially useful treatments for this genetic disorder. As a consequence of LEKTI deficiency in NS, kallikreins 5 and 7 (KLK5, KLK7) activity becomes unrestrained leading to accelerated degradation of desmoglein 1 and stimulation of inflammation through both pro-inflammatory cytokine activation and proteinase-activated receptor 2 (PAR2) signaling. Activated PAR2 signaling leads to the production of pro-inflammatory molecules, and KLK5 can stimulate Th2 cytokines via stimulation of thymic stromal lymphopoietin (TSLP). In 2011, a significant clinical improvement was reported in NS by targeting the kallikrein 5-proteinase-activated receptor 2-thymic stromal lymphopoietin (KLK5-PAR2-TSLP) pathway using infliximab (68). TSLP and tumor necrosis factor alpha (TNF α) have been shown to be overexpressed in LEKTI-deficient skin of NS patients and in *SPINK5*-null mice as a result of unrestricted activity of epidermal proteases, including kallikreins (70,71). This leads to activation of PAR2 signaling and subsequent NF- κ B activation and TSLP expression (71). TSLP can induce an atopic response in mice and its expression can also be increased by TNF α and

interleukin 1 (72–74). Based on these patho-immunologic findings, a therapeutic approach to reduce the skin inflammation in NS would be to selectively target these molecules implicated in inflammation (68). In the present study, a single patient with severe NS and recurrent inflammatory flares unresponsive to dapsone and topical steroids, tacrolimus, and pimecrolimus was recruited for infusions of infliximab, which was administered at a dose of 5 mg/kg at weeks 0, 2, and 6 and subsequently every month (68). At baseline, the patient's keratinocytes exhibited a 15-fold increase in TNF α expression compared with normal control keratinocytes. Clinical improvement was noted after the second infusion, and after the 12th infusion the skin was clear of inflammatory lesions although no change in the degree of ichthyosis, xerosis, and serum IgE levels was noted. The treatment was well tolerated during the 2-year follow-up period. At a molecular level, a fourfold reduction in TSLP was noted in both lesional and non-lesional skin 1 year after therapy and remained reduced after 2 years. Of note, however, the level of TNF α was not reduced because infliximab is a neutralizing antibody and is therefore expected to downregulate TNF α target genes. An important point to note is that this strategy has benefited the patient by reducing the severe skin inflammation, but it had little impact on her xerosis and ichthyosis.

In addition, the amino acid sequences of the most of the LEKTI polypeptides have recently been delineated and the most effective LEKTI fragments against kallikreins (KLK5, KLK7, and KLK14) implicated in desquamation have been identified (69). These findings lead to the possibility of developing topical delivery of bioactive LEKTI fragments to treat the skin inflammation in NS by fine-tuning the epidermal serine protease activity (69,75). Finally, another approach would be to develop small molecules that could also potentially be used to target the desquamation-related kallikreins (75).

Conclusion and future considerations

The identification of cellular and biochemical processes that lead to ichthyosis in inherited disorders of lipid metabolism provides us with a different therapeutic approach using topical lipids and/or lipid-soluble products that exploit not only the unique accessibility of the skin but also the lipophilic property of the stratum corneum. The recent successful utilization of topical lovastatin and cholesterol combination in CHILD syndrome provides proof of concept that a pathogenesis or pathway-driven approach is effective and is a completely different strategy to the way individuals with severe ichthyoses are managed. Future topically applied strategies for other forms of ichthyosis could include: (i) oxygenated O-linoleoyl- ω -OH-ceramide for ARCI patients with 12R-lipoxygenase deficiency (ARCI) (76), (ii) acylCer for NLSOI (54), (iii) GlcCer synthase inhibition with ceramide replacement for type 2 GD (66), (iv) inhibitors of serine proteases (69) or the KLK5-PAR2-TSLP pathway for NS (68), and (v) filaggrin or agents that upregulate residual filaggrin expression for monoallelic ichthyosis vulgaris (and atopic dermatitis) (77).

Pathogenesis-based therapy possesses several inherent advantages in that it is: (i) mechanism specific for each disorder; (ii) safe, as natural lipids and/or approved drugs are often utilized; and (iii) relatively inexpensive, allowing wide utilization. Importantly, however, pathogenesis-based therapy requires the availability of therapy to supplement,

block the accumulation of toxic metabolites, or compensate for a deficiency, and may be ineffective if multiple downstream pathways contribute to disease pathogenesis.

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FIG 1.

Enzymatic stages in distal cholesterol metabolism and associated clinical disorders.

Syndromic disorders occur with mutations in 8 of the 10 post-lanosterol steps in cholesterol synthesis (***bold/italics***), and ichthyosis occurs in 7 of these diseases (**bold/underline**). *Lethal during neonatal period.

FIG 2.

Pathogenesis of X-linked ichthyosis (XLI). CSO_4 potentially inhibits HMG CoA reductase, further reducing cholesterol levels in XLI. The accumulation of CSO_4 coupled with cholesterol deficiency disrupts the lamellar membrane architecture and accounts for the barrier abnormality.

FIG 3.

Pathogenesis-based therapy for inherited disorders of distal cholesterol metabolism. The consequence of mutations downstream of the lanosterol pathway will lead an accumulation of toxic metabolites as well as a reduction in cholesterol synthesis. Thus treatment with topical cholesterol or topical proximal enzyme inhibitor such as lovastatin alone will not be sufficient for phenotypic improvement. Thus, combining topical cholesterol and topical proximal enzyme inhibitor will not only prevent the accumulation of toxic metabolite but also provide the cholesterol to the epidermal lipid bilayer and improve the phenotype.

FIG 4. Successful use of pathogenesis-based therapy using topical cholesterol and lovastatin in CHILD syndrome. Marked reduction in scaling and erythema was noted in two individuals with CHILD syndrome after 6 weeks of therapy with topical cholesterol and simvastatin. (Reprinted with permission from Paller et al. (5))