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Pathogenesis of the cutaneous phenotype in inherited disorders of cholesterol metabolism

Therapeutic implications for topical treatment of these disorders

Peter M. Elias,[1,*] Debra Crumrine,[1] Amy Paller,[2] Marina Rodriguez-Martin[3] and Mary L. Williams[1]

[1]Dermatology Service; Department of Veterans Affairs Medical Center and Dermatology; University of California, San Francisco; San Francisco, CA USA; [2]Departments of Dermatology and Pediatrics; The Feinberg School of Medicine; Northwestern University, Chicago, IL USA; [3]Dermatology Service; Hospital Universitario de Canarias; University of La Laguna; Tenerife, Spain

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Abbreviations: CHH, conradi-hünermann-happle syndrome; CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects syndrome; CDPX2, X-linked chondrodysplasia punctata type 2; CSO_4, cholesterol sulfate; DHCR7, 7-dehydrocholesterol reductase; EI, epidermolytic ichthyosis; EBP, emopamil-binding protein; HI, harlequin ichthyosis; IFAP, ichthyosis follicularis, patricia and photophobia syndrome; LB, lamellar bodies; L/NL, lamellar/non-lamellar; NS, netherton syndrome; SC, stratum corneum; SLOS, smith-lemli-opitz syndrome; SLS, sjögren-larsson syndrome; SSase, steroid sulfatase; XLI, X-linked ichthyosis

Molecular geneticists tend to conceptualize disease pathogenesis from the mutated gene outward, an approach that does not take into account the impact of barrier requirements in determining disease phenotype. An 'outside-to-inside' perspective has provided quite different explanations for the ichthyoses, including several of the disorders of distal cholesterol metabolism. Elucidation of responsible pathogenic mechanisms also is pointing to appropriate, pathogenesis (pathway)-based therapeutic strategies. In the case of the lipid metabolic disorders, it takes full advantage of new molecular, genetic and cellular pathogenesis information to correct or bypass the metabolic abnormality. This approach fully exploits the unique accessibility of the skin to a topical approach. Moreover, since it will utilize topical lipids and lipid-soluble, and often generic, lipid-soluble drugs, these treatments should be readily transported across the stratum corneum. If successful, this approach could initiate an entirely new departure for the therapy of the ichthyoses. Finally, because these agents are relatively safe and inexpensive, this form of treatment has the potential to be widely-deployed, even in the developing world.

Introduction

Current treatment of the ichthyoses remains symptomatic, and largely directed towards reducing the scaling component of these disorders. Yet, such therapy of the ichthyoses is often irrational, because removal of excess scale can interfere with homeostatic responses that allow patients to survive in a harsh, terrestrial environment. Moreover, the favored alternative, corrective gene therapy, though seductive in concept, remains a distant dream, impeded by: (1) difficulties in transcutaneous drug delivery; (2) enormous costs of the required 'designer gene' approach; (3) discomfort of intracutaneous injections; and (4) unknown, long-term risks of transfection with viral vectors.

All ichthyoses, including inherited syndromic disorders of distal cholesterol metabolism, display a permeability barrier abnormality, with the severity of the clinical phenotype paralleling the prominence of the barrier abnormality (reviewed in ref. 1–3). In our research, we have assumed that the cutaneous phenotype represents a best attempt by a metabolically-compromised epidermis to generate a competent permeability barrier in the desiccating, terrestrial environment (op. cit.). While "normal" epidermis mounts a vigorous, metabolic response in response to a compromised barrier that rapidly restores function,[4-6] "ichthyotic" epidermis only partially succeeds in normalizing function.[1-3] As a result, the clinical phenotype reflects the negative consequences of the genetic mutation for epidermal function, coupled with the epidermis' impaired, homeostatic response. Thus, unraveling the cellular and biochemical mechanisms that account for the barrier abnormality provides an explanation for the pathogenesis of the cutaneous phenotypes (reviewed in ref. 2, 3 and 7), and it could point to potentially-novel, pathway-based therapies. In disorders due to impaired cholesterol synthesis, evidence to date suggests that the clinical phenotype in most cases reflects either accumulation of toxic metabolites and/or deficiency of pathway end-product.[8] Moreover, in all of the lipid-metabolic disorders, whether due to metabolite accumulation, pathway product

*Correspondence to: Peter M. Elias; Email: eliasp@derm.ucsf.edu
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Table 1. Pathogenic mechanisms and potentially diagnostic features in disorders of distal cholesterol metabolism

Disorders	Keratohyalin/ Keratins	Lamellar body formation/ Contents	Lamellar body exocytosis	Post-secretary lipid processing	Lamellar bilayers	Cornified envelopes	Corneodes-mosomes	Corneocyte lipid envelope
Cholesterol and Isoprenoid Metabolism								
CHH/ CHILD[7,29]	Normal/Normal	***Abnormal contents***	***Impaired***	***Delayed***	***L/Non-L-PS***	Normal	Normal	Normal
XLI[17]	Normal/Normal	***Normal***	Normal	Normal	***L/Non-L-PS***	Normal	***Persist***	Normal

*Bolded and italicized features are particularly helpful in differential diagnosis.

deficiency, or both, lamellar/non-lamellar (L/NL) phase separation within the lamellar bilayers accounts, at least in part, for the barrier abnormality (examples of pathogenic mechanisms for disorders of distal cholesterol metabolism are shown in **Table 1**).

We typically assess four different, functional end-points; i.e., TEWL, pH, hydration and stratum corneum (SC) integrity, which separately or together can impact permeability barrier function. For example, a less cohesive SC, which often is due to an elevated pH of SC, increases proteolytic degradation of corneodesmosomes, which results in a poor quality SC. A high pH also activates serine proteases, which degrade lipid processing enzymes. Finally, the pH-driven increase also activates pro-inflammatory cytokines, such as IL-1α and IL-1β, further aggravating barrier function while provoking inflammation. By measuring multiple functional, structural and biochemical parameters and their structural/biochemical basis, we have been able to assemble a pathogenic composite for each disease. Together, this approach has identified key pathophysiologic abnormalities (e.g., metabolite accumulation and/or product depletion) in these disorders, which in turn could point to the most-promising, potential, pathogenic-based therapeutic interventions (see below).

Pathogenesis of Multisystem, Cholesterol Biosynthetic Disorders

Nine enzymatic steps are required to generate cholesterol from lanosterol, with the further generation of cholesterol sulfate from cholesterol comprising a tenth step (**Fig. 1**). While syndromic disorders, with a variety of developmental malformations, have been reported in seven of these diseases,[9-13] an abnormal cutaneous phenotype has been described in only six, i.e., lathosterolosis, desmosterolosis, Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects (CHILD) syndrome, Conradi-Hünermann-Happle syndrome (CHH) or X-linked chondrodysplasia punctata type 2 (CDPX2), SC4MOL deficiency[14-16] and X-linked ichthyosis (XLI).[17] The pathogenesis of the ichthyosiform dermatosis (and likely the extracutaneous abnormalities) in all of the inborn errors of distal cholesterol metabolism can be variously attributed to either: deficiency of cholesterol in cell membranes and/or toxic effects of accumulated sterol precursors with resulting functional alterations.[18,19] Sterol precursors can only partially substitute for cholesterol in the formation of SC lamellar membranes, and cholesterol is one of the three key SC lipids (along with ceramides and free fatty acids) required to form lamellar membranes (reviewed in ref. 20). Additional, downstream pathogenic mechanisms whereby sterol metabolites could contribute to disease pathogenesis include: (1) formation of oxysterol metabolites that either downregulate cholesterol synthesis or activate the liver X receptor;[21] (2) altered hedgehog pathway signaling (HOX normally is tethered onto cell membranes via a cholesterol moiety);[22,23] and/or (3) deficient peroxisomal function, as we have described in both CHH, CHILD patients and in the 'bare patches' mouse model,[24-28] which displays *Nsdhl* mutations that mimic CHILD syndrome[29,30] (further information about our work on the pathogenesis of CHILD syndrome, CHH and XLI is provided below); and (4) sterol metabolite-accelerated degradation of HMGCoA reductase.[31]

While ichthyosis is not clinically apparent in *Smith-Lemli-Opitz syndrome* (SLOS) (OMIM #270400) [7-dehydrocholesterol reductase (DHCR7) deficiency], both photosensitivity and a propensity to develop eczema are common[32] (Drs. Rosalind Elias and R. Steiner, personal communication). DHCR7 deficiency impairs both desmosterol and 7-dehydrocholesterol metabolism,[20,21,33] resulting in elevated 7-DHC and 8-DHC blood levels, with proportionate, phenotype-dependent reductions in serum cholesterol,[9-13,24,32,34,35] alterations that are mimicked in *Dhcr7*$^{-/-}$ *and* $^{+/-}$ mice,[36] and in mice with a knock-in of the human T93M mutation.[37] SLOS is fairly common (predicted incidence of ≈1:10,000),[8] with over 120 different *DHCR7* mutations identified to date.[32]

Although the PI is unaware of lathosterolosis cases in the US, several patients have been described in Europe, and all have prominent ichthyosis. Moreover, a mouse model of lathosterolosis (*Sc5d*$^{-/-}$ and $^{+/-}$) is available,[15] which should allow assessment of pathogenic mechanisms in this disorder (see below). Furthermore, a US kindred[38] and several additional patients in Europe[14] have been described with desmosterolosis, a disorder that displays prominent congenital anomalies, but minimal evidence of skin abnormalities. Finally, a prominent skin phenotype has been described in two patients with SC4MOL deficiency, who present with a severe ichthyosiform dermatosis and psoriasiform features.[16]

Conradi-Hünermann-Happle Syndrome (CHH) or *X-linked dominant chondrodysplasia punctata type 2* (CDPX2) (OMIM #302960) exhibits linear bands of scaling or follicular spikes in a morphogenic pattern (i.e., along the lines of Blaschko), and generalized erythroderma, most prominently in neonates. Involved skin sites conform to regions in which the mutant X-chromosome predominates.[39,40] The cutaneous features of CHH and CHILD

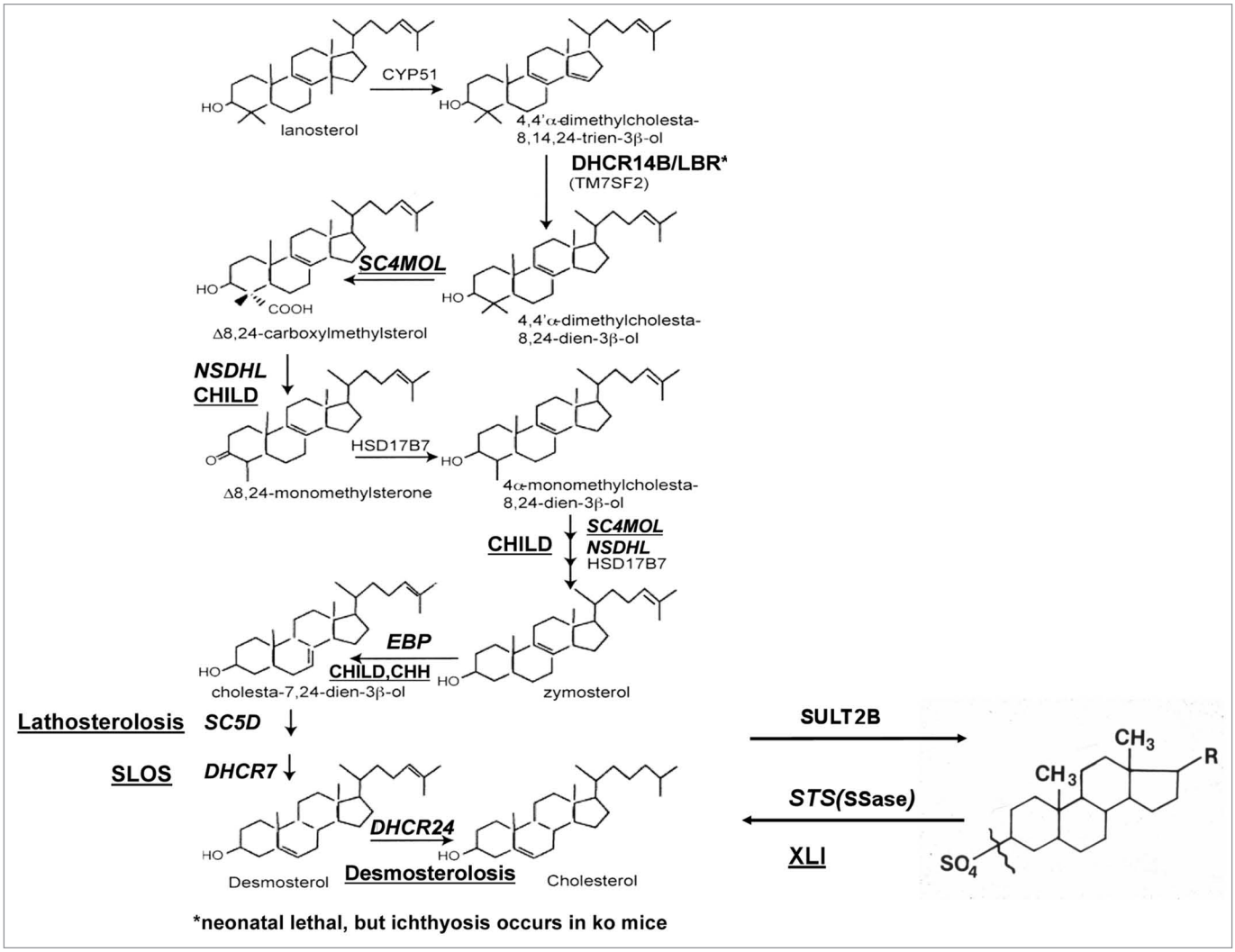

Figure 1. Enzymatic stages in distal cholesterol metabolites and their associated clinical disorders. Syndromic disorders occur with mutations in 7 of the 9 post-lanosterol steps in late cholesterol synthesis (indicated by bold/italics). A prominent cutaneous phenotype (ichthyosis) occurs in 6 of these diseases (indicated by bold/italics & underline).

syndrome can improve after infancy,[40] due to diminished viability of keratinocytes bearing the mutant X chromosome.[29] The cutaneous phenotype in CHILD syndrome (OMIM #308050), however, differs in its distribution from CHH; i.e., it is strictly unilateral, including both skeletal defects and internal organ involvement. Skin lesions are circumscribed plaques, surmounted by prominent wax-like scales, which typically involve flectures.[23]

CHH is caused by mutations in *EBP* (emopamil-binding protein) that encodes 3β-hydroxysterol-Δ^8, Δ^7-isomerase, which catalyzes the conversion of 8(9)-cholestenol to lathostero1,[34,41,42] resulting in diagnostic elevations in serum 8-dehydrocholesterol and 8(9) cholesterol.[43] Mutations in *NSDHL*, which encodes a member of the enzyme complex that removes the C-4 methyl group from lanosterol, underlie CHILD syndrome. However, CHILD syndrome can also be caused by mutations in *EBP*[9,43] (**Fig. 1**). Given the close proximity of the sites of metabolic blockade, the presence of some phenotypic overlap between CHILD and CHH is not surprising (reviewed in ref. 9). Availability of mouse models of CHH and CHILD syndrome[8] should allow for an assessment of the mechanistic basis for the cutaneous phenotype in CHH and CHILD syndrome, and for preclinical evaluation of potential therapies for these patients.

Both the density of lamellar bodies (LB) and LB secretion appear normal in CHH, but organelle contents are abnormal, displaying vesicular inclusions. Moreover, newly-secreted material fails to disburse at the stratum granulosum-SC interface.[7] Furthermore, these electron-lucent vesicles persist as discrete spheres after secretion at the stratum granulosum-SC interface. Importantly, maturation of lamellar bilayers is delayed, and bilayer membranes with normal morphology are displaced by extensive areas of lamellar/non-lamellar phase separation (**Table 1**).[29] Yet, the morphology of clinically-affected skin sites in CHILD syndrome is even more dramatically abnormal than that in CHH. Although LB form normally, they display almost no internal lamellae, and they fuse into intracellular multivesicular bodies,

which then are largely (but incompletely) secreted.[7] Nevertheless, the SC displays a huge expansion of the extracellular matrix, which is filled with interspersed lamellar and non-lamellar material.[7] Together, these features predict a severe barrier abnormality in both CHILD and CHH.

Recessive X-linked ichthyosis (XLI). The pathogenesis of XLI is better known than for any of the other ichthyoses. As a result of steroid sulfatase (SSase) deficiency in XLI, cholesterol sulfate (CSO_4) accumulates in the outer epidermis,[44-46] in erythrocyte cell membranes,[45,47] as well as in both the LDL (β-lipoprotein) and pre-LDL fractions of plasma.[45] But CSO_4 levels in epidermis are an order of magnitude higher than are levels in blood,[45,47] likely explaining the prominence of epidermal vs. other organ involvement in XLI.[48] Normally, CSO_4 levels decline to about 1% of lipid mass in the outer SC, through ongoing hydrolysis during SC transit.[49,50] In contrast, the SC in XLI typically contains 10–12% cholesterol sulfate (by dry weight).[48] Hydrolysis of CSO_4 generates some of the cholesterol required for the barrier, while conversely, CSO_4 itself is a potent inhibitor of HMGCoA reductase, further reducing cholesterol levels in XLI.[48] Although SSase is secreted from lamellar bodies (like other lipid hydrolases that process barrier lipid precursors into their own hydrophobic products), CSO_4 is delivered to the SC interstices by its extreme amphiphilicity, which allows it to diffuse readily across cell membranes;[51] i.e., in the absence of a lipid milieu within corneocytes, cholesterol sulfate likely partitions preferentially into the highly hydrophobic, extracellular domains of the stratum corneum. Accumulation of CSO_4, coupled with cholesterol depletion, provokes lamellar/non-lamellar phase separation,[17] accounting for the barrier abnormality in XLI.[52]

Recent Studies in Relevant Animal Models

Insig-2 (Epi-insig) DKO mice. The Brown and Goldstein group recently published relevant work on another animal model with aberrant cholesterol synthesis; i.e., epidermal-localized *Insig-1* mice with an additional germ-line deletion of *Insig-2* (Epi-*Insig*) DKO mice.[53] This model mimics the syndromic human disorder, Ichthyosis Follicularis, Atrichia and Photophobia (IFAP) syndrome (OMIM #308205). Deletion of these intracellular proteins allows migration of SREBP from the endoplasmic reticulum to the Golgi apparatus followed by translocation to the nucleus, where these SREBPs excessively stimulate several genes involved in cholesterol synthesis. As a result, both sterol metabolites and cholesterol accumulate in the skin. Pertinently, these mice respond to treatment with topical simvastatin, which simultaneously normalizes both metabolite production and cholesterol levels in epidermis.[53] This recent work, coupled with preliminary evidence of efficacy with topical lovastatin plus cholesterol in CHILD syndrome,[54] provides evidence that metabolite accumulation in the epidermis can be toxic; and conversely, that blockade of metabolite production (and normalization of cholesterol levels) could be beneficial for these disorders.

Mouse models of SLOS. While SLOS patients display a minimal skin phenotype, *Dhcr7*$^{+/-}$ mice display prominent ichthyosis, with neonatal lethality due to a putative permeability barrier abnormality.[36] More pertinent to SLOS patients, who display residual enzyme function, our still-unpublished preliminary studies in *Dhcr7*$^{+/-}$ mice (with S. Patel) demonstrate epidermal structural abnormalities in both lamellar body contents and lamellar bilayer organization, predictive of a barrier abnormality in SLOS patients with comparable reductions in enzyme activity. These mice also display serum 7DHC and cholesterol levels that are comparable to patients with moderate SLOS due to partial loss-of-function mutations.[36] One relatively-common mutation in SLOS (*T93M*) has been recapitulated in a transgenic 'knock-in' mouse model.[37,55] While their skin phenotype has not yet been assessed, this model should also be useful to assess both pathogenic mechanisms and preclinical therapeutic studies.

Mouse models of CHH, CHILD, desmosterolosis and lathosterolosis. We also have recently begun to assess a potential animal model of desmosterolosis. Like *Dhcr7*$^{-/-}$ mice, *Dhcr24*$^{-/-}$ mice are neonatal lethal, apparently due to a failure of epidermal development in utero, but possibly also due to a barrier defect.[56,57] In contrast, *Dhcr24*$^{+/-}$ mice survive, and like *Dhcr7*$^{+/-}$ mice, they show structural evidence of a skin barrier abnormality. While the Bpa, Stri and Tattered strains closely mimic varying severities of CHH and CHILD syndromes, one of these animal models is not a pure analogue of human disease; i.e., the *Sc5d*$^{-/-}$ mouse, but partial loss-of-function in the *Sc5d*$^{+/-}$ could reflect comparable reductions in enzyme function in lathosterolosis. Thus, this model could also be useful to assess pathogenic mechanisms and potential therapies for lathosterolosis.

Therapeutic Implications

Current therapy of the ichthyoses is largely aimed at scale removal; i.e., it is purely symptomatic. Not only is this form of therapy relatively ineffective, it often can be counterproductive; e.g., by removing 'excess' stratum corneum (SC), symptomatic therapy can do more harm than good (='therapeutic paradox') as seen with: (1) retinoids in the treatment of Netherton syndrome (NS),[58] and sometimes in epidermolytic ichthyosis (EI);[59] (2) excessive absorption of salicylates, lactic acid or immunosuppressive molecules in NS;[58] and (3) worsening of the permeability barrier after alpha-hydroxyacid applications, accentuating fluid and electrolyte abnormalities in HI, NS, EI and other disorders.[58] While localized gene therapy has shown promise in focal conditions, such as pachyonychia congenital,[60] generalized skin involvement in most of the ichthyoses makes topical gene therapy impractical. Moreover, this approach can be limited by pain from injections,[60] unknown risks for viral vector-induced neoplasia, and the high cost of 'designer gene' replacement, which together render gene therapy largely impractical for this diverse group of disorders, and certainly unattainable for patients in the developing world.

Very recently, we proposed a novel, pathogenesis-based approach to the treatment of ichthyosis in disorders of distal cholesterol metabolism;[54] i.e., provision of pathway product plus blockade of metabolite production, exploiting this new understanding of disease pathogenesis (**Fig. 2**). If metabolite accumulation appears to account for the cutaneous phenotype,

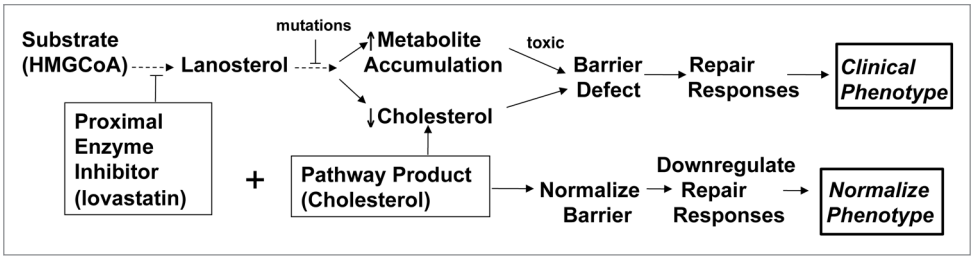

Figure 2. Pathogenesis-based therapy for disorders of distal cholesterol metabolites: Bases for improvement in clinical studies.

Table 2. Pathogenesis and pathway-based therapy of inherited disorders of distal cholesterol metabolism

Metabolic category	Inheritance pattern (Incidence)	Affected protein (*gene*)	Normal function	Amenable to Pathogenesis-based treatment	Proposed therapy
CHH (CDPX2)	x-linked dominant (rare)	delta(8)-delta(7) sterol isomerase emopamil-binding protein (*EBP*)	Distal cholesterol synthesis	**Very Likely (but can be self-resolving)**	**HMGCoA reductase inhibitor + cholesterol**
CHILD syndrome	x-linked dominant (very rare)	NAD(P)H steroid dehydrogenase-like protein (*NSDHL*)	Same	**Yes (Shown)**	**Same (cholesterol alone ineffective)**
SLOS	Recessive (fairly common)	7-dehydroreductase (*DHCR7*)	Same	**Very Likely**	**Same**
SC4MOL	Recessive (very rare)	Sterol-C4-methyl oxidase (*SC4MOL*)	Same	**Very Likely**	**Same**
Lathosterolosis (No known US cases)	Recessive (very rare)	Lathosterol-5-desaturase (*Sc5d*)	Same	**Very likely**	**Same**
Desmosterolosis	Recessive (very rare)	24-dehydroreductase (*DHCR24*)	Same	**Very likely**	**Same**
X-linked ichthyosis	X-linked recessive (fairly common)	Steroid sulfatase (*STS*)	Desulfation of cholesterol sulfate	**Very Likely**	**HMGCoA reductase or SULT2B inhibitor + cholesterol**

it would seem reasonable to deploy a proximal enzyme inhibitor [e.g., of HMGCoA reductase (lovastatin)] to reduce levels of potentially-toxic metabolites. In addition, provision of the pathway product (cholesterol) to avoid epidermal dysfunction due to cholesterol deficiency could also be beneficial by further downregulating (negative feed-back) of HMGCoA reductase activity. Then, this new information about disease pathogenesis has the potential to be deployed rapidly into topical therapy for patients with rare inherited disorders of distal cholesterol metabolism (**Table 2**). Another not-so-rare, inherited disorder of distal cholesterol metabolism, X-linked ichthyosis (XLI), occurs in 1:2,000–6,000 males. Our studies over several years already have shown that disease pathogenesis in XLI also reflects both metabolite (CSO_4) accumulation and end-product (cholesterol) deficiency (see also above).[17,46,48] Pertinently, topical cholesterol alone in our experience is not effective in XLI, but the ichthyosis in XLI could be treatable with either a topical statin or a sulfotransferase inhibitor (plus cholesterol). It must be emphasized that blockade of metabolite production alone, though it could be temporarily useful, cannot be utilized as monotherapy for the cutaneous phenotype in these disorders, because the end-product of this pathway (i.e., cholesterol) is required to prevent development of a permeability barrier abnormality (topical statins provoke a barrier abnormality with ichthyosiform changes in normal mouse skin).[61,62]

In very preliminary studies, we have treated two patients with one of the rare disorders of distal cholesterol metabolism (CHILD syndrome) [Drs. Amy Paller (Northwestern University) and Marina Rodriquez-Martin (Canary Islands Univ Hospital)—point mutation in G83Dp Gly83 Asp in *NSHDL*, and nonsense mutation (c.317C>A; p.S106x) in *NSHDL*, respectively]. Notably, these patients failed to improve with topical cholesterol alone, but both responded to dual treatment with cholesterol plus lovastatin.[54] Both excessive scale and epidermal hyperplasia diminished greatly, and one patient displayed improved mobility of underlying extremities by 6–8 weeks of treatment. In principal, this approach bridges the two poles of symptomatic vs. curative (i.e., gene) therapy. It also displays the following inherent advantages: (1) it is disease-targeted and mechanism-based specificity; (2) it is inherent safe; (3) it is relatively low-cost; and (4) most-importantly, it exploits the accessibility of skin to assess efficacy, as well as providing the opportunity to assess the mechanisms responsible for positive outcomes.

Yet, topical pathogenesis-based therapy is not curative, and even if successful, it would need to be utilized for the duration of the patient's lifetime. Moreover, despite knowledge of disease pathogenesis, it is possible that such mechanism-targeted

therapies may not always be effective, if multiple downstream pathways contribute to disease pathogenesis. However, since these patients' skin displays higher than normal water permeability, both the inhibitors and lipid end-products should be readily bioavailable. If either the drug or the lipid end-product fails to be delivered (suggested by a failure to respond to either pathway product or pathway product ± inhibitor), it is possible that co-applications of inhibitor and lipid product together could interfere with absorption of one or both.

Finally and importantly, it is possible that there will be benefits for the extracutaneous features of one or more of these disorders. In the case of disorders of distal cholesterol metabolism, the transdermal approach has the potential to deliver statins and cholesterol to extracutaneous tissues prior to hepatic first-pass metabolism, offering the tantalizing prospect that topical therapy could improve the extracutaneous manifestations in one or more of these disorders. It is highly likely that the cutaneous phenotype reflects pathogenic mechanisms that also are on-going in extracutaneous tissues, successful pathogenesis-based therapy for the ichthyoses could point to comparable approach(es) to treat/prevent the extracutaneous manifestations of these disorders.

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