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SJÖGREN-LARSSON SYNDROME: MOLECULAR GENETICS AND BIOCHEMICAL PATHOGENESIS OF FATTY ALDEHYDE DEHYDROGENASE DEFICIENCY*

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Abstract

Sjögren-Larsson syndrome (SLS) is an inherited neurocutaneous disorder caused by mutations in the *ALDH3A2* gene that encodes fatty aldehyde dehydrogenase (FALDH), an enzyme that catalyzes the oxidation of fatty aldehyde to fatty acid. Affected patients display ichthyosis, mental retardation and spastic diplegia. More than 70 mutations in *ALDH3A2* have been discovered in SLS patients including amino acid substitutions, deletions, insertions and splicing errors. Most mutations are private, but several common mutations reflect founder effects, consanguinity or recurrent mutational events. FALDH oxidizes fatty aldehyde substrates arising from metabolism of fatty alcohols, leukotriene B₄, ether glycerolipids and other potential sources such as sphingolipids. The pathogenesis of the cutaneous and neurologic symptoms is thought to result from abnormal lipid accumulation in the membranes of skin and brain; the formation of aldehyde Schiff base adducts with amine-containing lipids or proteins; or defective eicosanoid metabolism. Therapeutic approaches are being developed to target specific metabolic defects associated with FALDH deficiency or to correct the genetic defect by gene transfer.

Keywords

ichthyosis; mental retardation; spastic diplegia; mutation; leukotriene; ω -oxidation; fatty aldehyde; fatty alcohol

INTRODUCTION

Fifty years ago, Sjögren reported a preliminary description of patients from northern Sweden with a distinctive combination of symptoms consisting of ichthyosis, mental retardation and spastic diplegia or tetraplegia [1]. One year later in a landmark monograph, Sjögren and Larsson extensively described the clinical findings of their 28 patients and established the autosomal recessive inheritance of the disease [2]. Patients with Sjögren-Larsson syndrome (SLS) were subsequently recognized in other geographic and ethnic populations around the world [3]. Three decades after its initial description, SLS was found to be an inborn error of lipid metabolism caused by deficiency of fatty aldehyde dehydrogenase (FALDH; EC

*This article is dedicated to the fiftieth anniversary of the initial description of Sjögren-Larsson syndrome and to the many researchers who have subsequently contributed to the understanding of this disease.

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1.2.1.48) [4;5]. Studies of SLS have subsequently become instrumental in elucidating the physiologic role of FALDH in normal metabolism and highlighting the importance of this enzyme in epidermal differentiation and the nervous system [6].

This minireview summarizes recent advances in the molecular genetics of FALDH deficiency and the biochemical pathogenesis of SLS. Previous descriptions of the clinical phenotype [2;3;6] and pathology [6] of this disease are still reasonably up-to-date.

CLINICAL FEATURES OF SLS

The clinical features of SLS develop during prenatal development and infancy. Pathologic skin involvement can be seen as early as 23 weeks gestation [8]. Patients tend to be born preterm [9]. The ichthyosis in SLS is usually present at birth and is the first symptom that brings the patient to medical attention. Most SLS patients are born without a collodion membrane covering their skin. The ichthyosis is generalized in distribution and is prominent in the flexure areas, nape of the neck, trunk and extremities [10] (Figure 1A-C). The central face tends to be spared. The skin is often mildly erythematous early in life and, unlike most other forms of ichthyosis, has a disturbing pruritic character. Neurologic symptoms and signs appear during the first year or two of life and consist of delay in reaching motor milestones due to spastic diplegia or much less commonly, spastic tetraplegia. Approximately one-half of the patients are non-ambulatory and most others require braces or crutches to walk [11]. Seizures occur in about 40% of patients. Cognitive deficits are equally divided among those with mild, moderate or profound retardation, but rare patients have been found with normal intellect [6]. Delayed speech and dysarthria are commonly seen. A distinctive ophthalmologic finding is the presence of retinal crystalline inclusions, so-called glistening white dots, surrounding the fovea [12;13] (Figure 1D). Although all SLS patients do not have the retinal inclusions, their presence is a pathognomonic feature for this neurocutaneous disease. Photophobia and myopia are also often present. Brain MRI reveals white matter disease and MR spectroscopy identifies an unusual lipid peak in myelin [14;15]. Most SLS patients live well into adulthood.

MOLECULAR GENETICS OF *ALDH3A2*

SLS is caused by mutations in the *ALDH3A2* gene that codes for FALDH [16]. The human *ALDH3A2* gene (formerly known as *FALDH* and *ALDH10*) is mapped to chromosome 17p11.2. The locus seems to have undergone an ancient duplication event generating a closely linked *ALDH3A1* gene coding for a cytosolic aldehyde dehydrogenase (ALDH) (Figure 2).

The human *ALDH3A2* gene is 31 kb long and consists of 11 exons that are numbered 1-10 with an additional exon (exon 9#x2019;) situated between exons 9 and 10 [17;18]. Alternative splicing of exon 9#x2019; results in the production of two transcripts, which encode protein isoforms that differ at their carboxy-terminal domains (Figure 2). The most abundant transcript is derived from splicing of exons 1-10 and produces a 485 amino acid protein. A minor transcript that accounts for less than 10% of the total FALDH mRNA is produced by splicing of exon 9#x2019; between exons 9 and 10, and encodes a variant protein isoform (FALDH_v) of 508 amino acids [17].

In addition to alternative splicing, three transcripts (2.0, 3.8 and 4 kb) that arise from utilization of distinct polyadenylation sites in the 3#x2019; untranslated region have been seen on Northern analysis [17]. The longer transcripts (3.8 and 4 kb) are more abundant in brain, heart, skeletal muscle and pancreas, whereas the liver has an excess of the shorter transcript.

The human *ALDH3A2* promoter lacks a TATA box and has multiple CpG islands. The transcription start site is at nucleotide -238 in relation to the translation initiation codon and there is a functional Sp1 binding site at 51 nucleotides further upstream [17]. An second transcription start site has been reported at nucleotide -195 [18]. In humans, Northern analyses indicate that the *ALDH3A2* gene is expressed in most tissues [17;18]. In mice, the minor transcript encoding FALDH_v generally mirrors the amount of the major protein isoform transcript, except for brain and testes where it is slightly more abundant [19]. FALDH enzyme activity is proportional to the amount of *ALDH3A2* mRNA. Enzyme activity is highest in liver and is considerably lower in intestine, stomach, kidney, lung, brain and skin.

ALDH3A2 gene expression is induced in rodent liver and white adipose tissue by insulin, and is decreased in diabetic animals [20]. Clofibrate, a ligand for the peroxisome proliferator activated receptor- α (PPAR α), increases *ALDH3A2* mRNA by several-fold in mouse liver [21].

***ALDH3A2* MUTATIONS AND SEQUENCE VARIATIONS IN SLS**

To date, more than 72 *ALDH3A2* mutations have been reported in SLS patients representing at least 121 families from around the world [22]. A variety of mutations have been identified including deletions, insertions, missense mutations, splicing defects and complex rearrangements. Most mutations are private, but several common mutations have been found in patients from Europe [23-28], the Mideast [26] and Brazil [29]. For example, the c.943C>T mutation is responsible for SLS in most of the Swedish patients [23;24] and a c.1297_1298delGA allele is carried by many other European patients [25]. *ALDH3A2* haplotype analysis using microsatellite markers or intragenic SNPs indicate that these two mutations are each associated with a single haplotype and their high frequency in the European SLS population probably represents founder effects and shared ancestry [26]. In contrast, several other common mutations (c.682C>T, c.551C>T, c.733G>A, c.798+1delG) each occur on multiple different haplotypes and probably originate from recurrent mutational events. Most of these nucleotide changes involve CpG dinucleotides, and may represent mutational hotspots in the gene. Approximately 55% of SLS patients are homozygous for their *ALDH3A2* allele [22].

Missense mutations account for the largest group of mutations (38%) found in *ALDH3A2* and result in amino acid substitutions that are scattered throughout the gene [22]. When expressed in FALDH-deficient hamster cells, most missense mutations encode FALDH proteins with little or no detectable catalytic activity [26]. A few mutant enzymes possess residual catalytic activity and appear to have altered kinetic properties and/or protein stability (Mousumi and Rizzo, unpublished data).

Twelve splice-site mutations have been identified in SLS patients and all have been shown to cause exon skipping or lead to utilization of cryptic splice sites [26]. Nucleotide deletions and insertions of various sizes have been found in the *ALDH3A2* gene. The largest reported deletion is 6kb and results in complete loss of exon 9 [27,28]. Several complex *ALDH3A2* alleles containing multiple nucleotide changes have also been seen [22].

All SLS patients with FALDH deficiency have been found to carry mutations in the *ALDH3A2* gene, but only one mutant allele could be identified in several patients after sequencing exons amplified from genomic DNA or mRNA [26,27]. Strategies used for mutation screening in SLS, however, have not examined the promoter region of the gene or most of the 3' untranslated DNA. No mutations have been found in exon 9' that uniquely codes for the FALDH_v protein isoform.

At least 15 intragenic polymorphisms, including SNPs, microsatellite TG repeats and insertions/deletions, have been detected in the *ALDH3A2* gene [22]. Most polymorphisms are intronic and are not known to affect gene expression. There are no common amino acid-altering polymorphisms in the *ALDH3A2* gene, but one silent polymorphism (c.1446A>T) involves codon 481 in exon 10 [27]. Four major intragenic *ALDH3A2* haplotypes have been identified using SNPs [26] and haplotype associations have been established for 56 of the known mutations [22].

It was hoped that identification of the mutations causing SLS would give insight into the basis for phenotypic variation in this disease. However, genotype-phenotype correlations in SLS are complicated by the mutational heterogeneity and paucity of patients with the same genotype. Siblings with SLS who have an identical *ALDH3A2* genotype tend to be similar in phenotypic severity, but they also share genetic background. The Swedish patients who carry an identical *ALDH3A2* allele seem to have a limited spectrum of phenotypic variation [2,7]. Nevertheless, significant variation in neurologic disease has been reported in a large Arab family with 6 affected siblings [30]. Among 9 Brazilian patients homozygous for c.1108-1G>C, there were some differences in the presence of pruritus, retinal glistening white dots and photophobia [29]. It would appear, therefore, that much of the clinical variation in SLS cannot be explained by the *ALDH3A2* genotype alone, and other genetic or environmental factors must come into play.

PROPERTIES OF THE FALDH PROTEIN

The FALDH protein is a member of a large ALDH family encoded by at least 19 distinct genes in man [31]. The enzymes differ according to subcellular localization, substrate specificities and protein sequence homology. The ALDHs have been traditionally grouped into 3 classes (1, 2 and 3). FALDH is a class-3 enzyme and has historically been called microsomal ALDH to distinguish it from cytosolic (class-1) and mitochondrial (class-2) isozymes.

FALDH has been purified from human liver [32], rat liver [33-35] and rabbit intestine [36]. Based on DNA analyses of the cloned genes, the human and rodent proteins share about 84% amino acid sequence identity. By analogy with other class-3 ALDHs, the enzyme is probably catalytically active only as a dimer comprised of two similar 54 Kd subunits. In human fibroblasts, FALDH consists of 4 distinct isoforms that are separable by isoelectric focusing of native enzyme, and all are catalytically deficient in SLS [37]. The molecular basis for this microheterogeneity is not known, but it may originate from dimer formation with different combinations of the FALDH and FALDH_v subunits and/or interaction with other cellular proteins. This also raises the possibility that the FALDH isoforms have functional specificity for certain substrates or metabolic pathways.

Subcellular density gradient fractionation studies indicate that human liver FALDH is located solely in the endoplasmic reticulum (ER) [32]. In rat liver, the enzyme is clearly microsomal, but immunoelectron microscopy using anti-FALDH antibodies has identified a cross-reacting protein in the outer mitochondrial membrane and peroxisomal membrane as well [38]. The rat enzyme is synthesized on free polysomes and subsequently inserted into the ER [39]. Deletion mutagenesis studies indicate that the carboxy-terminal 35 amino acid residues of the major FALDH isoform comprise a hydrophobic domain, which anchors the protein to the ER membrane, and is flanked by two short hydrophilic ER targeting sequences [40]. The catalytic portion of the protein faces the cytoplasm.

FALDH catalyzes the NAD-dependent oxidation of saturated and unsaturated aliphatic aldehydes ranging from 6- to 24-carbons long, although it has a clear preference for substrates with 16- to 20-carbons [32]. The enzyme also oxidizes branched-chain aliphatic

aldehydes, such as 2-methyl-undecanal; 3,7,11-methyl-dodecanal; phytal [41] and dihydrophytal [32]. Studies of SLS patients indicate that FALDH also acts on the ω -carbonyl group of the leukotriene B₄ (LTB₄) metabolite, 20-CHO-LTB₄ [42]. Retinal [32] and 4-hydroxy-2-nonenal [35], a product of lipid peroxidation, are not oxidized by the enzyme.

In addition to acting on free aldehyde substrates, FALDH interacts with fatty alcohol dehydrogenase to form a fatty alcohol: NAD oxidoreductase (FAO) enzyme complex that catalyzes the overall oxidation of fatty alcohol to fatty acid [43]. Consequently, patients with SLS are deficient in both FALDH and FAO activity [5]. The FAO complex has not been purified to homogeneity, but the two catalytic components from rabbit intestine FAO have been separated and subsequently reconstituted to restore the complete oxidation of fatty alcohol to fatty acid [44]. Kinetic studies of FALDH and FAO in human fibroblast homogenates suggest that, under normal conditions, fatty alcohol dehydrogenase activity is the rate-limiting step in the oxidation of fatty alcohol to fatty acid [5]. It would appear that the catalytic sites of the two enzymatic components are physically close and the aldehyde intermediate remains tightly bound to FAO [43]. The specific alcohol dehydrogenase(s) that comprises FAO is not known.

The 3-dimensional structure of FALDH is not established; however, a related class-3 cytosolic rat ALDH that shares 64% amino acid identity with human FALDH, but lacks its hydrophobic carboxy-terminal domain, has been crystallized [45]. The basic structure of this protein undoubtedly resembles that of FALDH and may provide a template for modeling the human protein.

BIOCHEMICAL ABNORMALITIES IN SLS

Studies of SLS have been essential for defining the biological role of FALDH. This enzyme functions in metabolism of several lipids that generate fatty aldehyde metabolites (Figure 3). As a component of FAO, FALDH is necessary for the oxidation of long-chain aliphatic aldehydes derived from fatty alcohol metabolism [4,5]. SLS patients, who lack FAO activity, have elevated 16- and 18-carbon alcohols in plasma and in their cultured skin fibroblasts [46]. Free fatty aldehydes are not easily detected in the cells or tissues, perhaps due to their highly reactive nature and propensity for forming covalent adducts with amino-containing molecules.

Cleavage of the alkyl group from 1-*O*-alkylglycerol lipids, such as plasmalogens and 1-*O*-alkyldiacylglycerol, generates long-chain aldehydes that are subsequently oxidized to fatty acids. Cultured fibroblasts and keratinocytes from SLS patients carry out the cleavage step normally, but have an impaired ability to oxidize the fatty aldehyde to fatty acid [47].

FALDH has recently been implicated in ω -oxidation of the eicosanoid, LTB₄ [42]. This lipid inflammatory mediator is synthesized from the 20-carbon fatty acid arachidonic acid (Figure 3). During its catabolism, LTB₄ undergoes initial ω -hydroxylation to 20-OH-LTB₄ and sequential ω -oxidation to 20-CHO-LTB₄ and 20-COOH-LTB₄. Leukocytes from SLS patients have a profound defect in catabolizing LTB₄, suggesting that FALDH is responsible for the 20-CHO-LTB₄ oxidative step [42]. SLS patients excrete large amounts of LTB₄ and 20-OH-LTB₄ in urine.

Oxidation of phytol to phytanic acid is deficient in SLS fibroblasts [41] (Figure 3). In addition, α -oxidation of phytanic acid generates pristanal, which is subsequently oxidized to pristanic acid. Recombinant human FALDH utilizes pristanal as substrate and SLS fibroblast homogenates are deficient in pristanal oxidation [48]. Despite these findings in cultured fibroblasts, SLS patients do not accumulate phytol or phytanic acid in plasma,

which raises the possibility that other tissue-specific aldehyde dehydrogenases are active *in vivo* to bypass the FALDH-dependent steps.

Additional potential substrates for FALDH include fatty aldehydes generated from metabolism of sphingolipids, isoprenoid alcohols and ω -hydroxy fatty acids other than 20-OH-LTB₄. In addition, certain biochemical abnormalities in SLS are probably indirectly related to the FALDH defect, such as deficiency of serum polyunsaturated fatty acids derived from delta-6 desaturase activity [49] and reduction of ceramides-1 and -6 in cutaneous scales from patients [50].

BIOCHEMICAL PATHOGENESIS OF SLS

Elucidation of the biochemical mechanisms responsible for symptoms in SLS is complicated by the involvement of FALDH in several lipid pathways, which are more or less prominent in skin and brain, and the lack of detailed lipid analyses of affected tissues. The pathogenic mechanisms almost certainly differ in the skin and nervous system. Nevertheless, it is likely that the biochemical pathogenesis of SLS originates from 1) accumulation of lipid substrates that cannot be metabolized by FALDH (or FAO), and/or their diversion into other metabolic products; or 2) deficiency of critical fatty acid products of FALDH.

Fatty aldehydes are obvious candidate lipids for causing the symptoms of SLS. Aliphatic aldehydes, such as the 16-carbon hexadecanal, are toxic to cultured fibroblasts and keratinocytes, and SLS cells are more susceptible to hexadecanal than normal [51,52]. Fatty aldehydes form covalent Schiff base adducts with primary amines of phosphatidylethanolamine, creating N-alkyl-phosphatidylethanolamine [51], which drastically alters the hydrophilic portion of the molecule and could affect membrane-dependent functions. Numerous other potential Schiff base targets exist, including the primary amino groups in certain amino-lipids, such as phosphatidylserine and sphingosine, and even protein lysine residues. In contrast to aldehydes, straight-chain fatty alcohols, such as octadecanol, appear to be much less harmful and there is no experimental evidence that they are directly pathogenic in SLS.

Cutaneous Pathogenesis

The biochemical mechanisms leading to ichthyosis in SLS are undoubtedly related to the pivotal role of lipid metabolism in epidermal differentiation [53]. The histopathology of the skin in SLS reveals striking hyperkeratosis, papillomatosis, acanthosis and a slight inflammatory infiltrate in the upper dermis [54]. These pathologic findings, however, are not specific to SLS. In most other forms of ichthyosis, disruption of the epidermal water barrier is a central mechanistic feature that leads to the dry, flaky appearance of the skin. The water barrier is critically dependent on the lipid composition of the membranes in the stratum corneum [55]. These membranes are initially synthesized and packaged into intracellular lamellar bodies in the keratinocytes of the granular layer [53]. The lamellar bodies subsequently fuse with the apical surface of the plasma membrane and extrude their membrane contents into the granular cell-stratum corneum boundary, where they are assembled into highly organized stacked membrane bilayers that attach to, and intercalate between, the dead corneocytes. In SLS skin, some lamellar bodies are misshapen or lack their normal membrane structures, but they appear to fuse with the apical plasma membrane normally [56,57]. Ultrastructural studies reveal abnormal lipid inclusions in the cytoplasm of the granular cells and in the stratum corneum, suggesting that the membranes have an altered lipid composition. In cultured SLS keratinocytes, fatty alcohols accumulate and are diverted into biosynthesis of wax esters and other lipids that are relatively unique to skin (Rizzo, Simon, Carney, unpublished data). These lipids may interfere with formation of lamellar body membranes in keratinocytes and result in abnormal stratum corneum

membranes. The consequent dysfunctional water barrier would cause increased proliferation of keratinocytes [10] and reactive hyperkeratosis.

An alternate mechanism for the ichthyosis in SLS has recently been proposed based on genetic linkage studies that identify a critical epidermal role for 12*R*-eicosanoid metabolites (hepoxilins and trioxilins) of arachidonic acid (see Figure 3). Hepoxilins exist as *R*- or *S*-isomers and have potent biological activities that are mediated via an intracellular G-coupled protein receptor [58,59]. The 12*R*-*LOX* and *eLOX3* genes code for two enzymes, 12*R*-lipoxygenase and a hydroperoxide isomerase (hepoxilin synthase), respectively, that act sequentially on arachidonic acid to synthesize the epoxyalcohol product (8*R*-hydroxy-11,12-epoxyeicosa-5*Z*,9*E*,14*Z*-trienoic acid) referred to as (*R*)-hepoxilin-A3 [abbreviated (*R*)-HXA3] [60]. Mutations in the 12*R*-*LOX* and *eLOX3* genes have recently been found in patients with ichthyosis, which indicates that deficient synthesis of (*R*)-HXA3 or its metabolite is responsible for the cutaneous disease [61]. Metabolism of (*R*)-HXA3 opens up the epoxide ring forming an eicosanoid, (*R*)-trioxilin A3 [abbreviated (*R*)-TXA3, with 3 internal hydroxyl groups. Like LTB4, (*R*)-TXA3 is metabolized by ω -hydroxylation to 20-OH-(*R*)-TXA3 [62,63] and subsequently oxidized to 20-COOH-(*R*)-TXA3. This latter step is potentially catalyzed by FAO (and FALDH), although aldehyde dehydrogenase-4 [64] is also a candidate enzyme for this reaction. Other recently identified forms of ichthyosis are caused by mutations in a putative receptor gene (*ichthyin*) for a (*R*)-TXA3-like lipid [65] and a putative ω -hydroxylase gene [66]. These findings have prompted speculation that the ichthyosis in SLS results from impaired synthesis of 20-COOH-(*R*)-TXA3 (or its further metabolite) due to deficient FAO and FALDH [66] (Figure 3). Although awaiting biochemical proof that 20-OH-(*R*)-TXA3 is oxidized by FAO, these intriguing results underscore the key role of the 12*R*-lipoxygenase pathway for normal epidermal differentiation and may be central to the pathogenesis of the ichthyosis in SLS.

The pruritus in SLS is probably caused by accumulation of LTB4 and 20-OH-LTB4 in the skin of patients [67]. Intradermal injection of LTB4 induces pruritus in animals [68] and pharmacologic inhibition of LTB4 synthesis by the drug zileuton alleviates the itchiness in some SLS patients [67].

Neurologic Pathogenesis

In contrast to the skin, a detailed neuropathologic examination of an enzymatically-confirmed patient with SLS has not been published. In the few autopsy cases reported prior to discovery of the enzyme defect, the most consistent neuropathologic feature in the brain was a decrease in myelin [69-71]. Subsequent brain MRI studies suggest that the white matter disease represents a process of dysmyelination rather than active demyelination [15]. Like the stratum corneum, myelin is also composed of a highly organized membrane framework to insulate axons and enhance neurotransmission. MR spectroscopy of the abnormal white matter of SLS patients reveals one or two unusual lipid peaks with a spectrum that resembles fatty alcohol or other aliphatic lipids [15,72]. It is possible that turnover of plasmalogen lipids, which are particularly abundant in myelin, generates fatty aldehydes that are poorly oxidized in SLS [47] and diverted into fatty alcohols or form adducts with phosphatidyl ethanolamine and myelin proteins.

DIAGNOSIS AND THERAPEUTIC APPROACHES

SLS is diagnosed by measuring FALDH or FAO activity in cultured fibroblasts or leukocytes using fluorometric [5,32] or gas chromatography-mass spectrometry [73] assays. Histochemical staining for FAO activity in a fresh skin biopsy is an alternate method [74]. DNA-based diagnosis by screening for common mutations in select populations or

sequencing the entire gene is possible. Prenatal diagnosis of SLS using enzymatic [75] or DNA methods [76] can be performed on amniocytes or chorionic villus cells.

Therapy for SLS consists of non-specific approaches to treat the ichthyosis, such as topical application of keratolytic agents or use of systemic retinoids. Seizures usually respond to anti-convulsant medications and spasticity is alleviated with surgical procedures. Diets supplemented with medium-chain fatty acids have been reported to improve the skin, but results are inconsistent [6].

A more rational approach is to target therapy toward the known metabolic abnormalities in SLS. Inhibition of LTB₄ synthesis by zileuton, which improves the disturbing pruritus in some patients [67], is one example. Stimulation of *ALDH3A2* transcription by bezafibrate, a PPAR agonist, increases residual enzyme activity in fibroblasts from SLS patients with certain missense mutations [77]. As more is learned about the biochemical consequences of FALDH deficiency and the key lipid abnormalities that are responsible for the symptoms, additional therapeutic interventions will undoubtedly emerge.

A more global treatment would be to replace the defective gene with its normal counterpart. Viral-mediated transfection of the wild-type FALDH cDNA into cultured SLS keratinocytes confers resistance to fatty aldehyde-induced toxicity [52]. Although the skin is readily accessible for gene transfer, technical barriers still exist for widespread therapy of the ichthyosis. Gene therapy of the nervous system in SLS may ultimately benefit from ongoing studies to treat other, more life-threatening, neurologic diseases.

CONCLUSIONS

In the decades since SLS was first recognized as a distinct genetic disease, considerable progress has been made in defining its clinical phenotype, elucidating its genetic basis and developing reliable diagnostic tests. Future studies aimed at establishing the physiologic role of FALDH in lipid metabolism will be important for gaining insight into the biochemical pathogenesis of SLS. This will require an increasing emphasis on clinical investigations of patients and the availability of an animal model. The recent generation of a gene knockout mouse that is deficient in FALDH should provide a valuable tool to complement human studies on disease pathogenesis and explore new therapeutic strategies [Rizzo, Carney, Bridger, Spieker, Bunnell, Spaulding, Stribley, Salbaum, unpublished data].

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Figure 1. Clinical features of SLS illustrating the hyperkeratosis and thickened skin folds on the neck (A), axilla (B) and flexure of the arm (C). Retinal glistening white dots are present around the fovea (D). Retinal photo courtesy of Dr. Jack A. Cohen, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL.

Figure 2.

Diagram of the *ALDH3A2* gene locus on chromosome 17p11.2. The *ALDH3A2* gene is located about 60 kb from the *ALDH3A1* gene, which is thought to have arisen from a duplication of *ALDH3A2*. In the expanded diagram of *ALDH3A2*, numbered exons are not drawn to scale. Note that the coding regions of exons 1 and 10 are filled in black, whereas the non-coding sequence is unfilled. The boxed diagram illustrates the two alternatively spliced transcripts and the differing carboxy-termini of their FALDH protein products.

Figure 3.

Role of FALDH in lipid metabolism and the biochemical defects in SLS. The shaded bar indicates FALDH-catalyzed reactions. Dotted arrows and question marks are putative FALDH- or FAO-dependent reactions that have not yet been confirmed. Lipids in bold typeface are putative substrates for FALDH/FAO. Abbreviations used: HpETE, hydro(pero)xyeicosatetraenoic acid; LTB4, leukotriene B4; 5-LOX, 5-lipoxygenase; eLOX3, epidermal lipoxygenase-type 3; 12R-LOX, 12R-lipoxygenase; (R)-HXA3, (R)-hepoxilin A3; (R)-TXA3, (R)-trioxilin A3; 20-OH-, 20-CHO- and 20-COOH-refer to lipids with hydroxyl-, keto- and carboxyl-groups, respectively, at the 20-carbon (ω) positions of LTB4 and (R)-TXA3.