Published in final edited form as:
Biochim Biophys Acta. 2014 March ; 1841(3): 362–368. doi:10.1016/j.bbalip.2013.09.016.

Fatty acid transporters in skin development, function and disease

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Abstract

Fatty acids in the epidermis can be incorporated into complex lipids or exist in a free form, and they are crucial to proper functions of the epidermis and its appendages, such as sebaceous glands. Epidermal fatty acids can be synthesized de novo by keratinocytes or taken up from extracutaneous sources in a process that likely involves protein transporters. Several proteins that are expressed in the epidermis have been proposed to facilitate the uptake of long-chain fatty acids (LCFA) in mammalian cells, including fatty acid translocase/CD36, fatty acid binding protein, and fatty acid transport protein (FATP)/very long-chain acyl-CoA synthetase. In this review, we will discuss the mechanisms by which these candidate transporters facilitate the uptake of fatty acids. We will then discuss the clinical implications of defects in these transporters and relevant animal models, including the FATP4 animal models and ichthyosis prematurity syndrome, a congenital ichthyosis caused by FATP4 deficiency. This article is part of a Special Issue entitled The Important Role of Lipids in the Epidermis and their Role in the Formation and Maintenance of the Cutaneous Barrier.

Keywords

acyl-CoA synthetase; epidermis; fatty acid; fatty acid binding protein; fatty acid translocase; fatty acid transport protein; ichthyosis prematurity syndrome

1. Introduction

For the mammalian skin to confer a permeability barrier, keratinocytes in the epidermis undergo a series of differentiation events, culminating in forming a lipid-enriched intercellular matrix [1] (for details see the chapter in this issue by Feingold, K. and Elias, P.). In addition to epidermis, lipids also contribute significantly to the functions of epidermally-derived skin appendages, such as sebaceous glands [2]. Sebaceous glands produce a lipid-enriched fluid called sebum, the lipids of which lubricate hair shafts [3], reinforce the skin barrier, exhibit antimicrobial activities [4], and in furry mammals, contribute to water repulsion and thermoregulation [5]. Fatty acids, whether incorporated into complex lipids or present in a free form, are crucial to proper functions of epidermis and

sebaceous glands. In this review we discuss the roles for fatty acids and their transporters in healthy skin and in disease.

2. Functions of fatty acids in epidermis

Fatty acids have multiple functions in the epidermis. In addition to their well-known functions in energy generation and storage as well as in membrane lipid bilayer formation, they are crucial to the epidermis in four other respects. First, fatty acids and ceramides, one of the complex lipids derived from fatty acids, are vital for the permeability barrier [6,7]. Second, fatty acids serve as building blocks for complex lipids in sebum produced by sebaceous glands [2]. Third, fatty acids play important roles in signaling keratinocytes to regulate epidermal homeostasis. For example, fatty acids can function as ligands for the peroxisome proliferator-activated receptors, promoting keratinocyte differentiation and improving the permeability barrier [8] (for details see the chapter in this issue by Schmuth, M. et al.) They can also modify signaling molecules in the skin, as recent studies have reported that palmitoylation of proteins regulates epidermal homeostasis and hair follicle differentiation [9,10]. Polyunsaturated fatty acids (PUFA) such as linoleic acid (C18:2, n6) and arachidonic acid (C20:4, n6) can be converted by epidermal enzymes to metabolites that exhibit anti-proliferative and anti-inflammatory properties [11]. Generation of hepoxilin from linoleic acid also plays a role in skin barrier function, probably through a structural or signaling role [12,13]. Fourth, fatty acids contribute to the acidification of the stratum corneum, promoting its structural integrity and barrier function [14].

Fatty acids used in the epidermis can be synthesized *de novo* by keratinocytes or taken up from the diet or extracutaneous sites of the body. Fatty acids up to 16 carbons in length can be synthesized by the enzyme complex fatty acid synthase, which is strongly expressed in the upper epidermis and sebaceous glands [15]. Fatty acids synthesized by fatty acid synthase or taken up from an extracellular source can be further elongated into very long-chain fatty acids (VLCFA) containing 18 or more carbon atoms [16]. During cornification of the epidermis, the composition of fatty acids is shifted from short-chain species to long-chain, highly saturated ones, with 22-24 carbons in length being the predominant species [17]. Linoleic acid and other essential fatty acids are unable to be synthesized by keratinocytes in the skin and must be acquired from the diet. In addition, epidermis lacks *delta 5* and *6* desaturase enzymes that are involved in converting linoleic acid to arachidonic acid [18]. Arachidonic acid thus must be synthesized elsewhere, for example in liver, and transported to the epidermis.

Several lines of evidence support the concept that fatty acids from the diet or from extracutaneous sites are transported across the plasma membrane of keratinocytes (see references in review [19]). Studies with cultured human cells reveal that the putative fatty acid transporter in keratinocytes has preference in uptake of linoleic acid over oleic acid, compared to no preference between these two types of fatty acids in either hepatocytes or dermal fibroblasts [20]. This is likely to ensure the sufficient availability of linoleic acid for barrier lipid synthesis in the epidermis. Studies with cultured human keratinocytes also show that the uptake of linoleic acid but not that of oleic acid by cells is influenced by extracellular fatty acid composition, and that supplementation of culture medium with essential fatty acids results in cells that better mimic keratinocytes *in vivo* [21].

3. Mechanisms of fatty acid transport to epidermis

Although fatty acids were initially proposed to traverse the plasma membrane of cells by simple diffusion due to their lipophilic nature, data from recent years suggest that protein-facilitated transport mediates the majority of fatty acid uptake in tissues with robust long-

chain fatty acids (LCFA) metabolism such as adipose tissue, liver, skeletal muscle, and heart (see references in [22]). It is speculated that the candidate proteins facilitate the delivery of fatty acids to the plasma membrane, flip-flop of fatty acids between the two membrane leaflets, and movement of fatty acids out of the membrane prior to downstream metabolism [23]. Several proteins have been proposed to facilitate LCFA uptake in mammalian cells, including fatty acid translocase (FAT/CD36) [24], fatty acid binding protein (FABP) [25], and members of the fatty acid transport protein/very long-chain acyl-CoA synthetase (FATP/ACSVL) family [26,27]. Whereas these candidate proteins exhibit diverse expression patterns and subcellular localizations, they are able to facilitate fatty acid uptake independently of each other. However, the exact molecular mechanism of transport across the plasma membrane is not yet clear.

FAT/CD36 is an integral transmembrane glycoprotein, expressed on different cell types. It has been hypothesized that FAT/CD36 is involved in transport of fatty acids across plasma membranes by binding to albumin-bound fatty acids, accelerating their dissociation from albumin, and generating high local concentrations of free fatty acids at close proximity to the membrane [28]. The accumulated fatty acids are then translocated across the plasma membrane by a flip-flop mechanism. Recent studies have suggested that uptake of LCFA is regulated by dynamic association of FAT/CD36 and lipid rafts [29]. In contrast to FAT/CD36, FABP is a cytosolic non-enzymatic protein of low molecular weight. It functions as a lipid chaperone capable of binding free LCFA [30], overcoming the insolubility of LCFA in aqueous phase and facilitating the delivery of LCFA to different intracellular sites.

After translocation to the cytosol, almost all fatty acids need to be converted into an acyl-coenzyme A (CoA) form before they can be directed to different metabolic pathways [31]. Acyl-CoA binding protein (ACBP) has been shown to bind long-chain acyl CoA with high affinity and is proposed to play important roles in intracellular acyl-CoA transport and pool formation. Together with FABP, ACBP also functions to buffer fluctuations in the intracellular concentration of free, long-chain acyl CoA [32] (for details see the chapter in this issue by Mandrup, S.). The activation of fatty acids to acyl-CoA species is mediated by several families of enzymes called acyl-CoA synthetases (ACS). Human and mouse genomes encode 26 ACSs, 22 of which can be grouped into five subfamilies that include short-, medium-, long-, and very long-chain activating enzymes as well as two proteins homologous to the “bubblegum” protein of *Drosophila melanogaster* [31].

The FATP/ACSVL family consists of six integral membrane proteins that are encoded by solute carrier family 27 member 1 to 6 genes (*SLC27A1* to *SLC27A6*) [26,27]. Most FATP members are detected in multiple tissues, each with its own predominant pattern of expression [22,26]. They facilitate the uptake of fatty acids of 16 to 24 carbon atoms [33,34,35,36]. All FATPs exhibit ACS activity and are proposed to facilitate uptake of fatty acids by the vectorial acylation mechanism, whereby free fatty acids are esterified into an acyl-CoA form after import, thus diminishing the intracellular pool of free fatty acids and creating a gradient across the membrane that drives further influx of free fatty acids [23]. It is not known whether FATPs carry an inherent transport activity or whether another transport protein is required to facilitate the import of fatty acids in this model (Fig. 1).

Complementation experiments in yeast have shown that mouse FATP1, FATP2, and FATP4 each carries two separate functions, transport of exogenous VLCFA across the plasma membrane and activation of VLCFA [37,38]. However, unlike the plasma membrane localization of mouse FATPs in the yeast experimental system [38], the subcellular localization of FATPs in mammalian cells varies from plasma membrane to distinct organelles, and it could be dynamic in response to hormonal stimulation (see references in review [39]). In addition, knockdown of FATP3 or FATP4 in cultured cells decreases ACS

activity but does not affect the initial rate of fatty acid uptake [40,41]. Moreover, studies on stably transfected FATP4-overexpressing cells suggest that FATP4 is an endoplasmic reticulum-localized ACS that is able to drive uptake of fatty acids dependent on its enzymatic activity [42,43]. These data suggest that at least some FATP members, such as FATP3 and FATP4, do not function as a transmembrane transporter *per se* but facilitate fatty acid uptake indirectly by the aforementioned vectorial acylation mechanism. It is also possible that in addition to activating VLCFA, organelle-localized FATPs function to transport VLCFA across organellar membranes for downstream metabolic pathways. Recent studies have identified FATP4 to be a component of a new fatty acid synthesis-transport machinery at the peroxisomal membrane where peroxisomal ABC transporters interact with proteins functioning in fatty acid synthesis and activation, facilitating fatty acid metabolism in peroxisomes [44].

Of the 26 mammalian ACSs , only a few have been reported to be expressed in the skin, including long-chain ACS 5 and several members of the FATP/ACSVL family [45,46,47]. The distribution of FATP members in the skin also varies substantially. FATP1, FATP3, FATP4, and FATP6 are all detected in the epidermis and hair follicles of adult mice [47]. In contrast, only FATP1 and FATP4 are robustly expressed in subcutaneous fat, and FATP4 is the only FATP member that is detected in sebaceous glands [47]. In comparison to adult epidermis, FATP1 expression is decreased and FATP4 is increased in late fetal epidermis. These dynamic changes in FATP expression could indicate regulation of FATPs for a fetus to prepare for terrestrial life [47]. We will discuss in the following section the clinical implications and animal models addressing the function of these candidate transporters in the skin.

4. Roles for fatty acid transporters in epidermis

4.1. FAT/CD36

4.1.1. Clinical implications of FAT/CD36—FAT/CD36 is strongly expressed in tissues with high fatty acid metabolism, including adipose tissue, heart, intestine, and muscle [48]. FAT/CD36 functions as a transmembrane protein that binds and concentrates fatty acids at the membrane, facilitating their translocation across the plasma membrane [28]. It is weakly expressed in mouse epidermis but its expression is induced upon permeability barrier disruption [47]. It is not normally expressed in human epidermis, but it is detected in skin lesions of patients with psoriasis and several other dermatological diseases [49,50]. The induction suggests a role for FAT/CD36 in epidermal homeostasis.

4.1.2. Animal model of FAT/CD36 deficiency—FAT/CD36 null mice do not show any apparent skin abnormalities, although they exhibit defective uptake and incorporation of LCFA into complex lipids in muscle and adipose tissue [51] and abnormal lipoprotein metabolism [52]. Similarly, deficiency in FAT/CD36 in humans, found more frequently in Africans, does not lead to skin phenotypes [53]. It is thus likely that other fatty acid transporters can compensate for FAT/CD36 deficiency in the skin.

4.2. FABP5

4.2.1. Clinical implications of FABP5—FABP5, also called epidermal FABP (E-FABP) or psoriasis-associated FABP (PA-FABP), is widely expressed in the body [25]. It was first identified in epidermis, and its cutaneous expression also includes sebaceous glands and hair follicles [54,55]. FABP5 functions as an intracellular lipid chaperone that binds LCFA [30]. Under certain conditions, FABP5 also binds and translocates fatty acids and retinoic acid into the nucleus to activate the nuclear peroxisome proliferator-activated receptor, leading to increased cell survival and proliferation [56,57]. FABP5 in normal skin

is detected in the granular layer where lipid synthesis is active for establishing the barrier. In contrast, FABP5 expression is enhanced and expanded in patients with psoriasis, a skin disease characterized by hyperproliferation, abnormal differentiation, and impaired lipid metabolism [30]. Elevation in FABP5 is also observed in other hyperproliferative skin diseases such as atopic dermatitis [58]. It is possible that FABP5 expression is increased in response to the increased lipid trafficking that accompanies abnormal proliferation and differentiation of keratinocytes.

4.2.2. FABP5 and the permeability barrier and wound healing—FABP5 null mice appear to have normal skin at the gross and histological levels. While the fatty acid composition of the skin is not altered, FABP5 null mice exhibit delayed recovery in transepidermal water loss upon barrier disruption [55]. FABP5 mutant mice also show impaired keratinocyte motility during wound healing, suggesting that an elevation of FABP5 is required for energy production as a lipid chaperone for active cell migration during wound repair [59]. In both *Fabp5* heterozygous and homozygous mice, heart-type FABP (*Fabp3*) mRNA is markedly induced in the skin, but whether the protein level is also increased in the skin of those mice is unknown [55]. Whereas adipocyte-type FABP (*Fabp4*) mRNA is increased about 4-fold in FABP5 null keratinocytes, its protein level is unchanged [60]. Therefore, it is not clear whether FABP5 deficiency may be compensated for by upregulation of other FABPs.

4.2.3. FABP5 and sebaceous glands—FABP5 null mice display small sebaceous glands but increased volumes of sebum manifesting an elevated proportion of cholesteryl ester and a reduced proportion of fatty alcohol [61]. The increased sebum volume is likely due to the expanded expression of retinoic acid binding protein-2, a competitor of FABP5 for retinoic acid signaling, thereby accelerating the terminal differentiation and apoptosis of sebocytes and secretion of sebum. These data suggest that FABP5 regulates sebaceous gland activity by modulating lipid signaling and/or lipid metabolism in sebocytes.

4.2.4. FABP5 and signaling in keratinocytes—Incorporation of linoleic acid is significantly reduced in FABP5 null keratinocytes. Reduction of linoleic acid leads in turn to decreased cellular 13-hydroxyoctadecadienoic acid content, which results in abnormal differentiation of keratinocytes through downregulation of NFκB activity [60]. Given this mechanism by which FABP5 exerts its function in keratinocytes, the increased expression of FABP5 in psoriasis suggests a cause-and-effect relationship between impaired fatty acid metabolism and pathogenesis of psoriasis.

4.3. FATP4/ACSVL4

4.3.1. Clinical implications of FATP4 deficiency—Mutations in human *FATP4* (a.k.a. *SLC27A4*) have been identified in patients with ichthyosis prematurity syndrome (IPS), a rare disorder of cornification classified under the heterogeneous group of autosomal-recessive congenital ichthyoses [62]. Prenatal sonographic signs of IPS are separation of the amniotic and chorionic membranes, echogenic amniotic fluid and echo-free chorionic fluid occurring between 28 and 32 weeks of gestation [63]. IPS is characterized by premature birth, often with respiratory complications, peripheral blood eosinophilia, and edematous skin with severe caseous scaling [64,65,66]. Symptoms of surviving IPS patients become mild during childhood and manifest mainly as dry and pruritic skin, though respiratory and/or food allergy are common [67]. So far, 19 mutations in *FATP4* have been identified in IPS patients worldwide (D. Khnykin et al. unpublished). Histological and ultrastructural analyses of skin biopsy samples from IPS patients show hyperkeratosis, acanthosis, dermal inflammation, and curved lamellar structures in both the granular and cornified layers [64,66,67].

4.3.2. Animal models of FATP4 deficiency—Before *FATP4* mutations were identified in IPS patients, three laboratories had reported mice with mutations in *Fatp4*, two produced by targeted disruption of *Fatp4* and one induced by spontaneous *Fatp4* mutation (*wrinkle-free*). While homozygous targeted mutation of FATP4 causes very early embryonic lethality in one case [68], it does not lead to lethality in the other targeted mutant or in the *wrinkle-free* mouse until the neonatal period [69,70]. In *wrinkle-free* mice, the putative protein translated from the retrotransposon-disrupted *Fatp4* gene contains only the amino-terminal 133 amino acids of a full-length protein of 643 amino acids. Similar to the most commonly reported mutation in IPS, this mutant FATP4 does not contain the ACS domain. A recent study has identified a new *Fatp4* mutant mouse model, called pigskin, caused by a spontaneous splice site mutation in *Fatp4*, resulting in premature translational stop and loss of the ACS domain [71]. The pigskin mutant mice show skin phenotypes similar to those previously described for the *Fatp4* knockout mice and the *wrinkle-free* mice.

The neonatal lethality of the *Fatp4* mutant mice is likely due to dehydration and restricted movements resulting from a defective skin barrier and tight, thick skin, respectively. The *Fatp4* mutant mice are also characterized by hyperkeratosis and sparse hair follicles. *Fatp4* is normally expressed in the skin and several other tissues with high fatty acid utilization [70,72]. *Fatp4* RNA is detected in suprabasal keratinocytes of the epidermis, in hair follicle progenitors, and in sebaceous gland progenitors during embryogenesis. FATP4 protein is localized in the epidermis, primarily in the granular layer, and in sebaceous gland progenitors in fetal skin and after birth, as well as in differentiated hair follicles after birth [73]. Suprabasal keratinocyte expression of a *Fatp4* transgene in *Fatp4* mutant skin rescues the neonatal lethality and ameliorates the skin phenotype. In contrast, transgenic FATP4 with its ACS activity disrupted does not have the rescuing effects, underscoring the crucial, skin-intrinsic roles for FATP4 and the importance of activation of fatty acids by FATP4 in the development and function of skin [74]. An important role for FATP4 activity in the permeability barrier has also been reported in worms, where mutations in genes homologous to mammalian *Fatp* genes lead to a defective cuticle barrier; the barrier defects can be rescued by a human *Fatp4* transgene [75].

While deficiency of total FATP4 during embryogenesis leads to dramatic skin abnormalities in mice, conditional FATP4 deficiency in the adult epidermis induces only mild skin phenotypes [76]. Those mice show hyperplastic epidermis and compromised barrier function, but the phenotypes are considerably less severe than those seen in *Fatp4* mutant newborns. This suggests that FATP4 is more critical for the development of fetal skin but less important for the maintenance of adult skin. Consistent with this, FATP1 and FATP3 are the FATPs predominantly expressed in adult epidermis of mouse and human, whereas FATP4 expression predominates in fetal epidermis [47].

4.3.3. FATP4 and the permeability barrier—FATP4 is normally detected in the granular layer of the epidermis, where barrier lipid precursors are synthesized. During epidermal differentiation, the lipid-enriched contents of lamellar bodies in the uppermost cells of the granular layer are secreted into the extracellular space and processed into ceramides, cholesterol, and fatty acids, the major lipids required for permeability barrier function of the cornified layer [6]. Epidermal lipid analyses on *Fatp4* mutant newborns by mass spectrometry reveals a significantly decreased proportion of ceramides with fatty acid moieties containing 26 carbon atoms or more, and a significantly increased proportion of those containing 24 or fewer carbon atoms [69,74]. This is consistent with the defective barrier observed in *Fatp4* mutant mice. In contrast, the disturbed fatty acid composition of epidermal ceramides is ameliorated in *Fatp4* mutants rescued by transgenic FATP4 expression in suprabasal keratinocytes [74]. Epidermal lipid analyses by thin layer chromatography also showed that *Fatp4* mutant newborns displayed an abnormal pattern of

ceramides including a significantly decreased proportion of omega-O-acylceramide (M.-H. Lin et al, unpublished). Omega-O-acylceramide is an unbound ceramide species unique to epidermis that contains a very long chain amide-linked fatty acid with a terminal ω-hydroxy group that is further esterified with some other fatty acid, mainly linoleic acid, and is thought to be most critical for barrier function [6,77]. In addition, the bound lipid fraction of *Fatp4* mutant newborn epidermis showed a significant decrease in omega-hydroxyceramide (M.-H. Lin et al, unpublished), a derivative of omega-O-acylceramide and an important ceramide species that contains a very long chain amide-linked fatty acid and is required for the corneocyte lipid envelope formation and barrier function [13,78,79]. While the corneocyte lipid envelope did not show any abnormalities in *Fatp4* mutant mice and IPS patients (D. Khnykin et al. unpublished), the abnormalities in epidermal ceramide composition of *Fatp4* mutant newborns support roles for FATP4 in metabolism of VLCFA in keratinocytes during epidermal differentiation.

4.3.4. FATP4 and sebaceous glands—In addition to defects in epidermis, FATP4 insufficiency also affects the formation of sebaceous glands and meibomian glands, the specialized sebaceous glands of the eyelids. Studies of engrafted *Fatp4* null mouse skin show dystrophic sebaceous glands enwrapped by thick layers of epithelial cells [73]. Transgene-rescued *Fatp4* mutant mice lacking FATP4 expression in sebocytes displayed ectopic ductal epithelial cells at the expense of lipid-secreting sebocytes in both sebaceous glands and meibomian glands. Further analyses reveal that sebum from sebaceous glands of transgene-rescued *Fatp4* mutant mice contains a reduced level of type II diester wax, a major mouse sebum lipid species [73]. The mutant sebum also shows a significant decrease in the abundance of diester wax species of high molecular mass with fatty acid moieties containing 26 carbon atoms or more. In addition, the altered production and composition in sebum is associated with the inability of transgene-rescued *Fatp4* mutant mice to repel water and regulate body temperature after water immersion. These results suggest that FATP4 regulates the trafficking of VLCFA necessary for proper synthesis of sebum lipids as well as barrier lipids. In contrast to crucial roles for FATP4 in the development of skin and sebaceous glands, deficiency of FATP4 in enterocytes of the intestine does not affect dietary lipid absorption in mice [80].

4.3.5. FATP4 and signaling in keratinocytes—In addition to hyperkeratosis, *Fatp4* null embryos display epidermal hyperplasia from E15.5 onwards that results from hyperproliferation of suprabasal keratinocytes [81]. By microarray analyses of skin at E15.5, *Fatp4* mutants show upregulation of three members of the epidermal growth factor family that is associated with elevated epidermal activation of the epidermal growth factor receptor (EGFR) and STAT3, a downstream effector of EGFR signaling [81]. *Fatp4* mutant skin also shows increased expression of genes encoding proteins involved in keratinocyte differentiation and cornified envelope formation, consistent with the premature barrier observed at E16.5 that never progresses into a complete barrier at later stages. Pharmacological studies in vivo with Tyrphostin AG1478, an EGFR tyrosine kinase inhibitor, and curcumin, an inhibitor of both STAT3 and EGFR, indicate that epidermal hyperplasia and hyperkeratosis and premature barrier formation in *Fatp4* mutant mice results from activation of EGFR and STAT3 signaling pathways. However, the pharmacological blockade does not remedy the tight and wrinkle-free skin, incomplete skin barrier, and sparse hair phenotypes, suggesting that other signaling pathways mediate these phenotypes. It has been hypothesized that lack of FATP4 in epidermal keratinocytes induces abnormal lipid metabolism in the epidermis that initiates the observed alterations in epidermal signaling pathways. Consistent with this, neutral lipid droplets are found in the granular and cornified layer of *Fatp4* null mouse skin [70,73] and in the cornified layer of the skin in IPS patients [64] (D. Khnykin et al. unpublished).

4.3.6. FATP4 and cellular stress—To obtain insights into the etiology of IPS, *Fatp4* mutant mice provide a useful model for identifying the lipid metabolic abnormalities caused by the lack of FATP4. With high-performance thin layer chromatography, *Fatp4* mutants showed a significant increase in total free fatty acids in the cornified layer of fetal epidermis as compared to controls (D. Khnykin et al. unpublished). Metabolomics analyses showed that *Fatp4* mutant fetal skin displayed significant increases in several fatty acids with 20 carbon atoms or longer and decreases in shorter chain fatty acids, including several essential fatty acids (D. Khnykin et al. unpublished). It remains to be determined whether the alteration in fatty acids in *Fatp4* mutants affects the acidification of the stratum corneum. Studies on cultured cells have shown that saturated LCFA like palmitic acid cause cell death through remodeling of lipids, oxidative stress, or endoplasmic reticulum stress [82,83]. In contrast, unsaturated LCFA like oleic acid can protect cells from the lipotoxicity by channeling palmitic acid into triacylglyceride pools [83]. Several recent in vitro studies report that the ACS activity of FATP4 is necessary for transporting VLCFA into cells through the mechanism of vectorial acylation [42,84]. Therefore, it is possible that the elevated level of VLCFA detected in the cornified layer of *Fatp4* mutant skin reflects the inability of mutant keratinocytes to utilize VLCFA in a CoA form, leading to accumulation of free VLCFA intracellularly; this may in turn cause lipotoxicity. Elevation of intracellular VLCFA concentrations has been revealed in yeast with disruption of *FAT1*, a homologue of mammalian *FATP1* [85].

Consistent with the hypothesis of an increased VLCFA concentration in *Fatp4* mutant keratinocytes, metabolomics analyses on *Fatp4* mutant fetal skin revealed increased levels of markers of oxidative stress, including increases in the oxidized form of glutathione, cysteine-glutathione disulfide, and metabolites from the purine degradation pathway via xanthine oxidase, as well as a decrease in the level of reduced forms of glutathione (D. Khnykin et al. unpublished). *Fatp4* mutant fetal skin also displayed a significant increase in uric acid, an inflammatory mediator of allergy that is released from dying or stressed cells [86]. Skin inflammation and eosinophilia were established in IPS patients before birth (D. Khnykin et al. unpublished). These data suggest that cellular stress caused by altered lipid metabolism in fetal FATP4-deficient epidermis can activate keratinocytes and drive atopy-like inflammation in IPS patients, independent of cutaneous penetration of environmental allergens.

4.3.7. Speculation on FATP4 pathobiology—As proposed previously [19], there are several possible mechanisms by which FATP4 deficiency may cause dramatic abnormalities in both human and mouse skin. First, FATP4 deficiency could lead to decreased activation and incorporation of VLCFA into epidermal lipids, impairing the formation of a complete skin barrier. Second, the inability of FATP4 to activate VLCFA could lead to accumulation of free VLCFA in cells, resulting in induction of oxidative stress and proinflammatory signals in the epidermis. Third, lack of FATP4 may affect the metabolism of arachidonic acid, an essential fatty acid that plays a critical role in skin barrier formation [12]. A recent report of a functional linkage between FATP4 and ichthyin, a protein suggested to be both a magnesium transporter and a receptor for metabolites produced by the 12R-LOX and eLOX-3 lipoxygenases in the hepoxilin pathway, highlights the possible involvement of FATP4 in common pathways essential for lipid processing in the epidermis [87].

4.4. FATP1/ACSVL5

4.4.1. Animal models of FATP1 deficiency—FATP1 is highly expressed in adipose tissue, skeletal muscle, and heart [22]. *Fatp1* null mice display thermogenesis defects but are protected from fat-induced insulin resistance and diet-induced obesity [88,89]. Within the mouse FATP family, FATP1 is most closely related to FATP4 in protein sequence [72].

However, these two FATPs are expressed in nearly complementary compartments in embryonic mouse skin. *Fatp4* RNA is expressed in suprabasal keratinocytes, sebaceous gland progenitors, and hair follicle progenitors [73]. In contrast, *Fatp1* RNA was detected in clusters of cells within the basal layer of the epidermis, in adipocytes of subcutaneous fat, and in hair follicle progenitors (M.-H. Lin et al, unpublished). Despite this cutaneous expression pattern, knockout of *Fatp1* in mice does not lead to skin phenotypes [88]. Given the high homology between FATP1 and FATP4, they should exhibit similar substrate specificities and may normally facilitate the transport of fatty acids into different compartments for various metabolic purposes during the differentiation of fetal skin. Preliminary studies in transgenic mice suggest that the two proteins may exhibit similar functions in vivo (M.-H. Lin et al, unpublished).

4.4.2. Speculation on FATP1 pathobiology—As in adult mouse epidermis, FATP1, -3, -4, and -6 are also normally expressed in human epidermis [47]. In contrast to weak expression of FAT/CD36 in adult mouse epidermis, FAT/CD36 is not expressed in human epidermis. Upon sustained disruption of the permeability barrier in adult mice, the epidermal expression of FATP6 and FAT/CD36 is increased, while that of FATP1, -3, and -4 is unchanged. This induction suggests potential roles for FATPs in restoring the steady state of barrier lipids [47]. It will be important to examine whether the expression of other FATP family members or other transport proteins in IPS patients is increased after birth to compensate for the absence of FATP4, perhaps partially ameliorating the skin abnormalities. Given the likely functional similarities between FATP4 and FATP1, such compensation by FATP1 would not be unexpected.

5. Concluding remarks

Studies on candidate fatty acid transporters have revealed their crucial roles in homeostasis of the epidermis and functions of sebaceous glands. Animal models of FATP4 deficiency support roles for FATP4 in VLCFA uptake into keratinocytes during fetal barrier formation. Data from these animal models also shed light on the link between altered lipid metabolism and skin abnormalities and atopy-like inflammation in IPS, and on potential therapies for IPS. Although much has been accomplished in recent years, it is still unclear exactly how fatty acids are transported into keratinocytes. It is also unknown whether various candidate transporters cooperate in transporting fatty acids into keratinocytes, and whether they participate in directing fatty acids to different metabolic fates. Further investigation is needed to elucidate the subcellular localization of FATP1, -3, -4, and -6 in keratinocytes and to identify their interacting partners in keratinocytes.

Acknowledgments

We thank Jeffrey Miner for critical reading and editing of the manuscript. MHL was supported by NIH grant R01AR049269 (to J. H. Miner).

Abbreviations

ACBP	Acyl-CoA binding protein
ACS	acyl-CoA synthetase
ACSVL	very long-chain acyl-CoA synthetase
CoA	coenzyme A
EGFR	epidermal growth factor receptor

FABP	fatty acid binding protein
FAT	fatty acid translocase
FATP	fatty acid transport protein
IPS	ichthyosis prematurity syndrome
LCFA	long-chain fatty acid
SLC27	solute carrier family 27
VLCFA	very long-chain fatty acid

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Highlights

In this review, we are discussing the mechanisms by which candidate transporters facilitate the uptake of fatty acids. Then, we are discussing the animal models and clinical implications of the candidate transporters in the skin, including the FATP4 animal models and Ichthyosis Prematurity Syndrome, a congenital ichthyosis caused by FATP4 deficiency. These recent studies provide an overview on the roles for LCFA and their candidate transporters in the homeostasis of the epidermis and sebaceous glands.

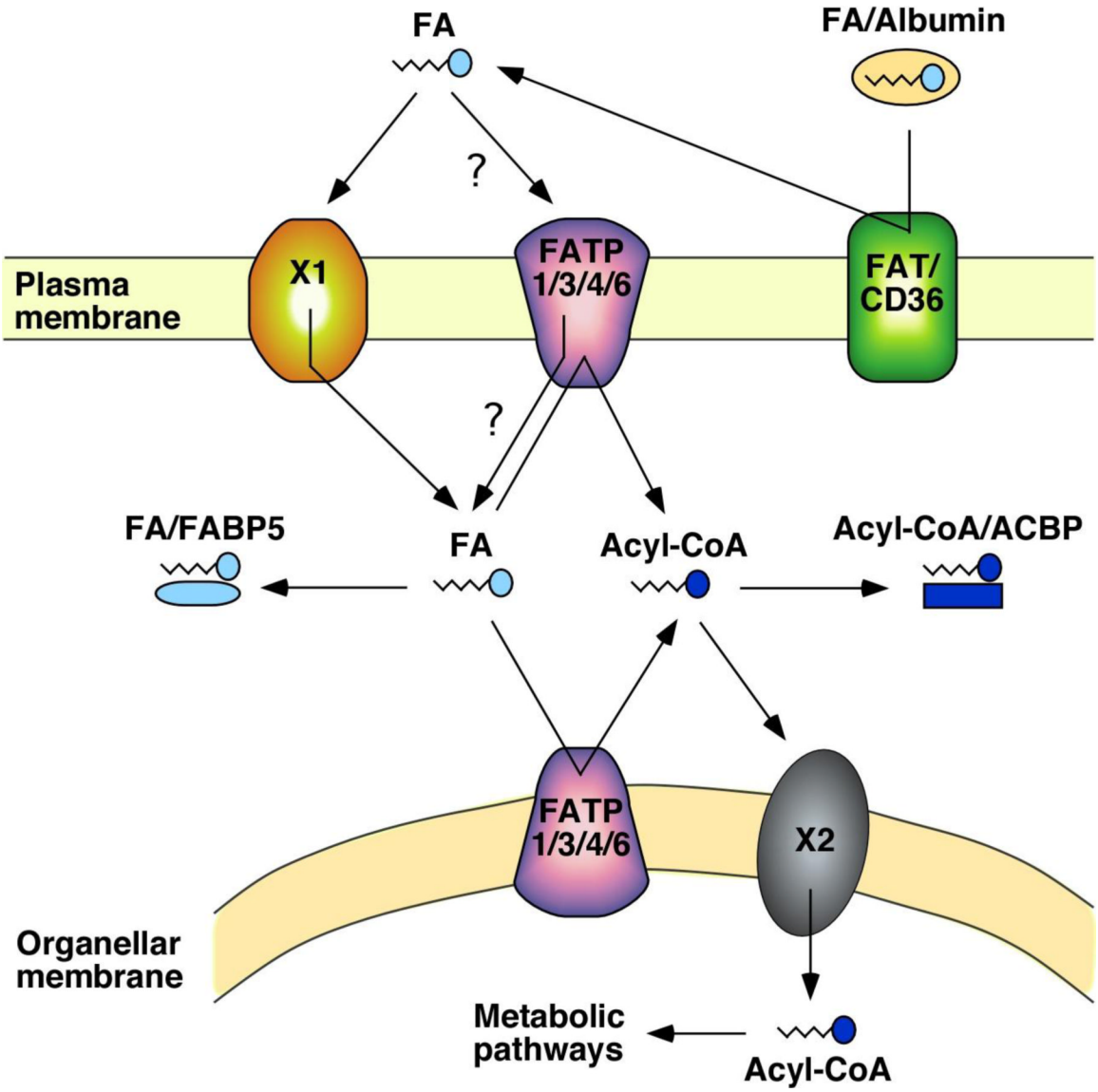

Figure 1. Model of long-chain fatty acid uptake in keratinocytes of the mammalian skin

FAT/CD36 at the plasma membrane is hypothesized to bind to albumin-bound, longchain fatty acids and accelerate dissociation of fatty acids from albumin, generating high local concentrations of free fatty acids at the membrane. Fatty acids could then be translocated across the membrane via FATP1, -3, -4, or -6 (FATP1/3/4/6) by the vectorial acylation mechanism, whereby fatty acids are converted into acyl-CoA after import by the ACSVL activity of FATPs themselves, generating a gradient of free fatty acids across the membrane that drives further influx of free fatty acids. Fatty acids could also be imported by an unknown transporter (X1) on the plasma membrane, and converted into acyl-CoA by the FATPs located on the plasma membrane or on organellar membranes. Fatty acids in the cytosol could then be imported into various organelles for downstream metabolic pathways through unknown transporters (X2) on organellar membranes. FABP5 and ACBP bind to long-chain fatty acids and long-chain acyl-CoA, respectively, facilitating the intracellular trafficking of fatty acids.