The role of stearoyl-CoA desaturase-1 in skin integrity and whole body energy balance

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Abstract
The skin is the largest single organ in humans serving as a major barrier to infection, water loss, and abrasion. The functional diversity of skin requires the synthesis of large amounts of lipids, such as triglycerides, wax esters, squalene, ceramides, free cholesterol, free fatty acids, and cholesterol- and retinyl-esters. Some of these lipids are used as cell membrane components, signaling molecules, and as a source of energy. An important class of lipid metabolism enzymes expressed in skin is the delta 9 desaturases, which catalyze the synthesis of delta-9 monounsaturated lipids, primarily oleoyl- (18:1n9) and palmitoyl-CoA (16:1n7), the major monounsaturated fatty acids of cutaneous lipids. Mice with a deletion of the delta-9 desaturase-1 isoform (SCD1) either globally (Scd1−/−) or specifically in the skin (SKO) present with marked changes in cutaneous lipids and skin integrity. Interestingly, these mice also exhibit increased whole-body energy expenditure, protection against diet-induced adiposity, hepatic steatosis, and glucose intolerance. The increased energy expenditure in SKO mice is a surprising phenotype as it links cutaneous lipid homeostasis with whole body energy balance. This review summarizes the role of skin SCD1 in regulating skin integrity and whole body energy homeostasis and offers a discussion of potential pathways that may connect these seemingly disparate phenotypes.

Stearoyl-CoA desaturase-1
Stearoyl-CoA desaturase is a delta-9 desaturase anchored in the ER membrane via four transmembrane domains (1). As the name implies, this delta-9 desaturase catalyzes the conversion of 12-18 carbon saturated fatty acids into monounsaturated fatty acids (MUFAs) through the insertion of the first cis-double bond at the delta-9 position (rev. in (2,3)). These endogenously synthesized MUFAs are important to a variety of cellular functions, including synthesis of complex lipids such as diacylglycerols, phospholipids, triglycerides (TGs), wax esters, and cholesterol esters. The degree of unsaturation of cellular lipids can also play a role in membrane fluidity and cell signaling. Therefore, SCD is highly conserved with multiple isoforms providing overlapping but distinct tissue and substrate specificity (2,3).

In the mouse, there are four known isoforms of SCD. These are all located within a 200-kb region on chromosome 19 and encode for 350–360 amino acid proteins with >80% amino acid sequence similarity. SCD1 is ubiquitously expressed, with significant expression in the adult liver, where it is dramatically induced by both dietary carbohydrate and saturated fat (4-11). In addition to liver, it is expressed in the undifferentiated cells of sebaceous glands in the skin and is critical to sebocyte development (12-14). As will be discussed for the majority of this review, skin specific expression of SCD1 appears to play a role...
not only in the maintenance of skin integrity, but also, unexpectedly, in whole body energy balance. SCD2, which shares significant sequence homology with SCD1, is also ubiquitously expressed but is especially enriched in the murine brain, particularly during myelination in the neonate (15). In the liver, SCD2 expression is reciprocally regulated with SCD1 expression, with expression levels being high during development and decreasing dramatically at weaning, corresponding with an increase in hepatic SCD1 expression. Further evidence of the importance of SCD2 during development comes from the observation that mice lacking SCD2 are born with an impaired skin barrier, resulting in death due to loss of water across the skin within hours of birth in a majority of animals (15). SCD3 is expressed in the Harderian gland and skin of the mouse, with skin expression mainly in differentiated sebocytes (16,17). SCD3 is the only isoform of SCD that exhibits a preference for palmitate over stearate as a substrate (17). SCD4 is mainly expressed in the murine heart (18).

Humans express two different isoforms of SCD, both of which are microsomal proteins. Human SCD1 (hSCD1) is highly homologous to mouse SCD1 and is expressed in adult adipose tissue, liver, lung, brain, heart, pancreas, and skeletal muscle (19-21). The second human SCD isoform is termed hScd5 and appears to be a primate specific isoform that is predominantly expressed in brain and pancreas with some limited expression in heart, kidney, lung and placenta (22-24). The regulation of human SCDs and their role in disease has been reviewed elsewhere (25).

Although the MUFA products of SCD are abundant in the diet, SCD1 is highly regulated, indicating a critical role for endogenously synthesized MUFAs. The regulation of SCD1 has been reviewed extensively, elsewhere (2,3). Briefly, the Scd1 gene is under positive regulation by a variety of dietary and cellular factors, including glucose, fructose, and saturated fatty acids, as well as insulin and transcription factors such as sterol regulatory element binding protein-1c and the nuclear receptor, liver X receptor. Negative regulation of the Scd1 gene is affected by the actions of the adipokine leptin, as well as polyunsaturated fatty acids (2,3,26). Additionally, the SCD1 protein is also subject to degradation by proteases and through the proteasomal pathway (27-30), conferring an additional layer of regulation.

Much of what we know regarding the physiological function of SCD1 comes from studies conducted in mice with a targeted deletion of the Scd1 gene. These mice are characterized by a lean, hyper metabolic phenotype, which includes resistance to diet- and genetically-induced obesity and insulin resistance, as well as marked changes in nonshivering thermogenesis (6-11,31-37). In addition to these changes in energy metabolism, SCD1-deficient mice also have a marked cutaneous phenotype. Indeed, SCD1 was first identified in mice with a naturally occurring mutation in the Scd1 gene (Table 1). These 'asebia' mice were characterized by the presence of dry, flaky skin and severe alopecia resulting from sebocyte atrophy, underscoring a critical role for SCD1 in sebocyte development (12,13,34,38,39). Subsequent studies in these naturally SCD1 deficient asebia mice, as well as mice with a targeted deletion of the Scd1 gene (Scd1-/- mice) have revealed that SCD1 is in fact expressed in the sebaceous glands of mouse skin and is regulated throughout the hair cycle (13,34).

In an effort to understand tissue-specific contributions of SCD1 to the whole body energy metabolism phenotype observed in Scd1-/- mice, a series of tissue-specific Scd1-/- mice have been generated and characterized (11,35,40). While it was clear from studies in global Scd1-/- model that SCD1 regulates skin integrity, the generation of a skin-specific Scd1-/- animal model (SKO mouse) has revealed surprising connections between skin-specific expression of SCD1, the maintenance of the integrity of the skin, and whole body energy metabolism (34,36).

**Sebaceous and epidermal lipids regulate skin permeability barrier**

As the largest organ in the body, the skin serves a variety of functions, the most important of which is to serve as a barrier against external insults. The skin is a highly structured organ and consists of various different cell types with specific
functions that help maintain the integrity of the tissue. The skin also houses a variety of specialized structures such as hair follicles, sweat glands, and sebaceous glands, that impart functional diversity to this organ (14,41-43).

One of the primary functions of the skin is to serve as the permeability barrier, preventing heat and water loss across the skin's surface (14,41,42,44,45). Therefore, maintenance of the integrity of skin is critical in preventing dehydration and in regulating core body temperature in homeotherms. The permeability barrier of the skin is comprised of various different cell types, including keratinocytes and corneocytes in the stratum corneum of the epidermis (42,43). In addition, skin cells are bathed in a rich array of lipids, including free cholesterol, triglycerides, ceramides, and free fatty acids. It is now clear that these lipids, many of which are actively synthesized in the skin, play an important role in the maintenance of the skin barrier and functionality (14,15,34,41,42,44,45).

Skin SCD1 regulates skin integrity and energy balance

While cutaneous abnormalities were initially described in mice with a global deletion of SCD1, a potential link between the favorable metabolic phenotype and the skin abnormalities of Scd1 mice was not suspected until the generation of mice lacking SCD1 in the skin (34). Skin-specific Scd1-/- mice (SKO) were generated by targeting the deletion of Scd1 using a keratin 14 promoter. Skin-specific deletion of Scd1 recapitulated the cutaneous abnormalities observed in Scd1-/- mice (34). Interestingly, in addition to severe alopecia and sebocyte hypoplasia (Table 1), SKO mice were also lean and protected from diet-induced obesity, similar to Scd1-/- mice (34). This lean phenotype was accompanied by a significant upregulation of metabolic rate, similar to Scd1-/- mice. Similar to global Scd1-/- mice, SKO mice were hyperphagic on both chow, as well as high-fat diets, but were almost completely protected from weight gain on either of these diets. While WT animals go on to become insulin resistant when fed a HFD, both Scd1-/- and SKO mice are protected from this secondary complication of obesity (34). One of the phenotypes of global SCD1 deficiency is a lack of the de novo lipogenesis response in liver to insults such as high-carbohydrate or saturated fat feeding (5,8,10). However, this hepatic lipogenesis response is not affected in SKO mice, suggesting that skin-specific deletion of SCD1 is not sufficient to impair hepatic lipogenesis (34). Indeed, it appears that liver-specific deletion of SCD1 impairs hepatic lipogenesis to a similar extent as observed in global Scd1-/- mice (11).

While hepatic lipogenesis was unaffected in SKO mice, these animals presented a co-ordinated set of metabolic changes in peripheral tissues, indicating increased lipid catabolism and activation of thermogenesis. This included an upregulation of uncoupling genes in liver, skeletal muscle, white and brown adipose tissues. In addition, genes of fatty acid oxidation were increased in liver and adipose tissues of SKO mice, indicating increased lipid catabolism in these animals (34).

One of the most striking phenotypes of global SCD1 deficiency is an extreme cold sensitivity, such that Scd1-/- mice do not survive longer than 2-4 hours when exposed to 4°C (31). Similar to Scd1-/- mice, SKO mice also displayed significant cold sensitivity (Figure 1), with most animals dying of hypoglycemia within 3 hours of cold exposure (34). This extreme cold susceptibility was brought on by an inability to maintain plasma glucose levels during cold exposure and a precipitous depletion of hepatic glycogen stores in SKO mice exposed to cold for as little as 90 minutes. Interestingly, if these animals were fed a HFD for 3 weeks prior to cold exposure, their cold sensitivity was dramatically improved, with SKO animals being able to tolerate over 24 hours of cold exposure. After 90 minutes of cold exposure, HFD-fed SKO mice were able to maintain plasma glucose levels and were spared from the near complete depletion of hepatic glycogen that was observed in chow-fed SKO mice upon 90 minutes of cold-exposure. This protection from energy depletion upon cold exposure occurred in HFD-fed SKO mice even though they did not gain any measurable amount of body weight due to 3 weeks of HFD-feeding (34). These results suggest that while body weight may not be rescued by dietary intervention in SKO mice, it is possible to rescue
at least some of their energetic deficit by feeding a hypercaloric diet.

During routine investigations, mice are housed at 25°C, which is well below thermoneutrality and has been documented to contribute to changes in energy metabolism (46-49). Given the cutaneous phenotype of the SKO mice, it was hypothesized that SKO mice may be in a constant state of increased energy expenditure to maintain body temperature, when housed at 25°C. Indeed, markers of cold exposure, including β3-AR signaling in BAT were elevated in SKO mice, suggesting increased cold perception in these mice even at room temperature (34). To follow up on this hypothesis, WT and SKO mice were housed at 33°C, and food intake and body weight gain on a HFD were measured (36). Surprisingly, SKO mice still consumed more food than WT counterparts but were resistant to weight gain during the feeding period (36). Interestingly, although SKO mice were almost completely protected from weight gain on a HFD even when maintained at 33°C for the duration of feeding, hyperphagia in SKO mice appeared to be less pronounced at 33°C compared to mice housed in conventional rooms at 25°C (34,36). When housed at 25°C, SKO mice ate over 50% more HFD by weight, as compared to WT counterparts (34). At 33°C, while SKO mice were still hyperphagic, they only ate about 30% more food than WT counterparts (36). This attenuation of hyperphagia in SKO mice at thermoneutrality indicates increased metabolic efficiency and is suggestive of cold sensing playing an important role in the hypermetabolic phenotype of SCD1 deficient animals. While these studies indicated that body weight was not rescued by maintaining animals at thermoneutrality, changes in other metabolic features such as hepatic glycogen stores and fat mass were not examined in these mice maintained at 33°C. Given the apparent attenuation of the hyperphagic response in SKO mice at 33°C, it is possible that partial rescue of alternate metabolic phenotypes may occur prior to rescue of body weight in these animals.

It is important to note that the thermoneutrality experiments reviewed above were performed in animals over 6 weeks of age and during a relatively short duration of 7-9 weeks (36). However, changes in cold sensing and metabolic adaptations could occur well before adulthood in these animals. Indeed, the cutaneous abnormalities in SKO and Scd1−/− mice are apparent before weaning. Therefore, the question of whether sustained rescue of cold sensing in SCD1-deficient mice can reverse the lean metabolic phenotype was not addressed by this study.

**SCD1-induced changes in skin lipid composition and permeability barrier**

Prevention of transepidermal water loss is one of the key barrier functions of skin, and cutaneous lipids play an important role in preserving the skin water barrier (41-43). Alterations in transepidermal water loss and barrier permeability have been reported in mice with a global deletion of SCD1 (38,44), and one set of investigations suggested that artificial occlusion of the skin in SCD1-deficient animals could potentially confer cold resistance and abolish the protection from obesity observed in Scd1−/− mice (44). In the thermoneutrality experiments described above, although ambient temperatures were maintained close to thermoneutral conditions, relative humidity was maintained at 30-40% (36). Increased water loss across the skin's surface could therefore still have accounted for the obesity resistance observed in SKO.

The cutaneous permeability barrier is significantly affected by the lipid composition of the skin. In this regard, both global SCD1 deficiency, as well as skin-specific deletion of SCD1 results in striking changes in cutaneous lipids, including a large increase in free cholesterol levels, increased ceramide levels and decreased levels of other key skin lipids, including FFAs, TGs and wax diesters (Table 1) (34,50). This set of studies and more recent investigations revealed a co-ordinated increase in expression of key cholesterol biosynthetic genes, including HMG-CoA synthase, HMG-CoA reductase, and squalene epoxidase, which may account for the increase in skin free cholesterol levels in these mice (34,36).
The increase in skin free cholesterol levels may be due to an inability to esterify cholesterol in the absence of sufficient monounsaturated fatty acids, which are important components of the skin cholesterol ester pool. The increase in skin free cholesterol content is likely to be a significant cause of the skin pathology observed in SKO mice (Figure 1). Other mouse models that display an increase in skin free cholesterol content, including mice overexpressing human apolipoprotein C1 (ApoC1) and mice deficient in the cholesterol esterification enzyme acyl-CoA:cholesterol acyltransferase-1, also display cutaneous abnormalities similar to SCD1-deficient mice (51-53). Interestingly, the ApoC1 overexpressing mouse also displays a similar lean metabolic phenotype (52), like SCD1-deficient mice, but any potential link between the cutaneous changes and metabolic alterations in this model has not been investigated.

Inflammation and wound healing in skin of SCD1-deficient mice
Among the asebia mouse strains that harbor a natural mutation in the *Scd1* gene, the asebia J1 strain has been shown to have no impairment in their skin permeability (42), despite significant sebocyte atrophy (Table 1). However, asebia 2J mice have been reported to have increased skin permeability in conjunction with altered cutaneous lipid content (38). These results suggest that ancillary factors, in addition to sebaceous lipid content of skin, may regulate the maintenance of an intact skin barrier, and thereby exert effects on whole body energy homeostasis.

It has been suggested that the extent of epidermal inflammation may help explain some of the differences in skin permeability between various strains of SCD1-deficient mice (38). SKO mice also displayed significantly increased skin inflammation, evident from increases in expression of inflammatory genes related to psoriasis, tissue damage, and the wound healing process (36). Although psoriasis is generally associated with obesity (54-56), the observation of increased markers of wound healing in the skin of SKO mice is potentially significant in explaining the increased energy metabolism in these animals. Wound healing is an extremely energy intensive process (57-59). Following injuries where skin integrity is severely compromised, including after burn injuries that result in destruction of skin structures like sebaceous glands, there is a marked increase in energy expenditure and onset of cold intolerance (59-61), similar to mice deficient in SCD1 (31,34). While elevation of ambient temperatures can apparently slow down metabolic rate in patients with extensive burn injuries, patients with more moderate burns do not show any decrease in metabolic rate when exposed to higher ambient temperatures, closer to thermoneutrality (61). These observations are quite similar to the metabolic changes observed in SKO mice (31,34,36), suggesting that an increased energetic demand due to activation of wound healing processes could at least partially account for the increase in energy expenditure observed in SCD1-deficient mice (Figure 1).

Altered retinol metabolism in skin of SCD1-deficient mice
In addition to changes in the lipid content in the skin of SKO mice, it has been recently shown that levels of vitamin A metabolites are significantly altered in the skin of these mice, relative to WT counterparts (36). Retinol, retinoic acid and retinyl esters were all significantly increased in skin of SKO mice, even when placed on a retinol deficient diet (Figure 1). This was accompanied by increased expression of genes regulated by retinoic acid activation of the retinoic acid receptor (RAR), including retinol-binding protein 1 and cellular retinoic acid-binding protein 2 (36). Additionally, the retinol esterification gene lecithin retinol acyltransferase was elevated and genes encoding proteins that oxidize retinol to retinaldehyde were decreased in skin of SKO mice (36). Changes in retinoic acid induced gene expression are evident as early as 23 days of age in SKO mice, suggesting that these changes may mediate the subsequent cutaneous abnormalities present in SKO mice.

In addition to transactivating RAR, retinoic acid has also been shown to bind to fatty acid binding protein 5 (FABP5) and transactivate peroxisome proliferator activated receptor delta (PPARδ) (62,63). Commensurate with the increased
retinoic acid levels in skin of SKO mice, FABP5 gene expression and expression of target genes of PPARδ were also found to be significantly elevated, suggesting increased PPARδ activation in skin of these mice (36). These results are potentially significant in explaining the cutaneous phenotype of SCD1 deficient mice, because PPARδ overexpressing animals also present with psoriasis and epidermal hyperplasia (64), similar to SCD1-deficient mice. PPARδ has also been shown to be important to the skin wound healing response (65-68). The increase in PPARδ signaling in SCD1-deficient mice may therefore be a compensatory response to cutaneous injury in these mice, since PPARδ has been shown to be rapidly upregulated following cutaneous insults (65-68). However, whether or not increased PPARδ signaling in skin is related to the hypermetabolic phenotype of Scd1−/− and SKO mice is yet to be determined.

Conclusion
While the exact mechanisms whereby SCD1 deficiency in the skin may mediate whole body energy expenditure are still under debate, the studies conducted thus far in mice with a global deletion of SCD1, as well as skin-specific SCD1 ablation have demonstrated an important link between sebaceous lipids and changes in diverse processes such as retinol metabolism, chronic inflammation, and cold-sensing. In order to understand the contribution of each of these pathways to the hypermetabolic phenotype of SCD1 deficient mice, future studies should be aimed at selective rescue of signaling through each of these pathways, potentially through the use of RAR or PPARδ antagonists or anti-inflammatory compounds. Additionally, experiments involving skin-specific rescue of SCD1 in the setting of global SCD1 insufficiency would provide much-needed definitive insight into the contribution of skin SCD1 to whole body energy metabolism.

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Legends

Table 1. A comparison of cutaneous and whole body phenotypes of SCD1-deficient mouse models.
Table 1 presents a comparison of various SCD1 deficient mouse models with regard to primary cutaneous phenotypes, as well as resistance to obesity. *FC, free cholesterol, HFD, high-fat diet, SC, stratum corneum, TEWL, trans-epidermal water loss, TG, triglyceride, WDE, wax diesters.*

Figure 1. Cutaneous changes in SCD1-deficient mice and relationship to whole body energy expenditure: a model. Figure 1 depicts the major cutaneous changes observed in SCD1-deficient animals. The inability to desaturate fatty acids such as palmitate and stearate results in hypoplastic sebaceous glands and a thickened stratum corneum. A concurrent increase in FC, ceramides, and retinol metabolites, along with a significant depletion of TG and WDE in skin of SCD1-deficient mice accompanies various cutaneous phenotypes, including increased inflammation and heat and water loss across the skin's surface. These cutaneous phenotypes appear to be causally linked to the favorable metabolic phenotype of SCD1-deficient mice, potentially due to an increase in energetic demand for body temperature maintenance or due to the energy intensive nature of cutaneous wound healing. *FC, free cholesterol, SC, stratum corneum, TG, triglyceride, WDE, wax diesters*
Table 1. A comparison of cutaneous and whole body phenotypes of SCD1-deficient mouse models

| Model   | Mutation                                                                 | Scd1 Expression | Skin phenotype                                                                 | Resistance to obesity                                      | Skin lipid composition                                                                 | Skin barrier function |
|---------|---------------------------------------------------------------------------|------------------|--------------------------------------------------------------------------------|------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------|
|         |                                                                           |                  |                                                                                   |                                                            |                                                                                        |                       |
| Asebia J1 | Spontaneous deletion spanning exons 1-4<sup>(13)</sup>                    | None<sup>(13)</sup> | Alopecia; sebocyte hypoplasia; slight thickening and decreased hydration of SC<sup>(42)</sup> | Resistant to leptin-deficiency induced obesity<sup>(6)</sup> | Increased FC, and decreased wax monoesters, sterol esters, WDE, and glycerol<sup>(42)</sup> | Normal<sup>(38,42)</sup> |
| Asebia 2J | Spontaneous 18 bp deletion in exon 2/intron 2 boundary<sup>(13)</sup>     | aberrantly spliced 687, 738 and 828 bp transcripts<sup>(13)</sup> | Alopecia; sebocyte hypoplasia; markedly thicker SC<sup>(38)</sup>                     | -                                                          | Reduced sterol esters, FC, and WDE<sup>(38)</sup>                                      | Increased TEWL<sup>(38)</sup> |
| Scd1<sup>-/-</sup> | Targeted germline deletion of Scd1 exons 1-6<sup>(50)</sup>               | None<sup>(50)</sup> | Alopecia; sebocyte hypoplasia<sup>(50)</sup>                                      | Resistant to HFD-induced obesity<sup>(7)</sup>                  | Increased FC, and decreased TG, WDE, cholesterol esters<sup>(50)</sup>                     | Increased TEWL<sup>(44)</sup> |
| Scd1 SKO | Targeted deletion of Scd1 exons 1-6 under keratin-14 promoter<sup>(34)</sup> | No expression in skin<sup>(34)</sup> | Alopecia, sebocyte hypoplasia<sup>(34)</sup>                                      | Resistant to HFD-induced obesity<sup>(34)</sup>                  | Increased FC and ceramides, and decreased TG and WDE<sup>(34)</sup>                      | -                     |
The role of Stearoyl-CoA desaturase-1 in skin integrity and whole body energy balance
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