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The role of stearoyl-CoA desaturase in obesity, insulin resistance, and inflammation

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Stearoyl-CoA desaturase 1 (SCD1) is an essential lipogenic enzyme that has been shown to play an intrinsic role in the development of obesity and related conditions, such as insulin resistance. Through the generation of various mouse models of SCD1 deficiency, we have come to understand that SCD1 plays a role, directly or indirectly, in diverse metabolic processes, including lipogenesis, fatty acid oxidation, insulin signaling, thermogenesis, and inflammation. This review will address recent advances in our understanding of this key regulator of cellular metabolic processes, including the role of SCD1 in maintaining skin barrier integrity and the role of skin SCD1 in the metabolic phenotype elicited by global SCD1 deficiency.

Keywords: lipogenesis; fatty acid oxidation; skin barrier; thermogenesis; leptin resistance

Introduction

Stearoyl-CoA desaturase (SCD) is a membrane-bound delta-9 desaturase that catalyzes the insertion of the first cis-double bond at the delta-9 position of 12–19 carbon saturated fatty acids, thereby converting them to monounsaturated fatty acids (MUFAs). The degree of unsaturation of cellular lipids plays a role in cell signaling and membrane fluidity. In addition, the monounsaturated products of SCD are the major substrates for synthesis of complex lipids such as diacylglycerols, phospholipids, triglycerides (TGs), wax esters, and cholesterol esters. Therefore, SCD is a highly regulated and conserved enzyme with multiple isoforms having overlapping but distinct tissue distribution and substrate specificity.[1,2] Like other desaturases, SCD is a nonheme iron-containing enzyme and requires molecular oxygen, NADH, as well as cytochrome b5 and cytochrome b5 reductase, or an alternate electron transport system for catalytic activity. The SCD protein is anchored in the ER membrane via four transmembrane domains with both N- and C-termini facing the cytosol, and three conserved and catalytically important his-box motifs.[3,4]

There are four known isoforms of SCD (SCD1–4) in the mouse,[5–10] all located within a 200-kb region on chromosome 19 and encoding 350–360 amino acid proteins with >80% amino acid sequence identity. Differences in the 5'-flanking region confer some divergence in tissue-specificity among the isoforms. *Scd2* shares significant sequence homology with *Scd1* and is ubiquitously expressed but is especially high in the murine brain, particularly during the neonatal myelination period.[6,7] In the mouse, SCD2 appears to play an important role during development and is required for the formation of an intact skin barrier in the neonate.[7] SCD3 is expressed in the Harderian gland and skin of the mouse, albeit at significantly lower levels than SCD1, and shows a preference for palmitoyl-CoA over stearoyl-CoA.[5,9,11] SCD4 is mainly expressed in the heart and is greatly induced in the heart of $Scd1^{-/-}$ mice.[8,12]

The remainder of this review will focus on SCD1, the best-characterized isoform of SCD, and its role in obesity and related pathologies. The majority of what we know regarding the role of SCD1 in obesity and related conditions comes from studies conducted in mice with either a naturally occurring

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mutation of the *Scd1* gene (asebia mice) or mice with a targeted deletion of the enzyme. Tissue-specific roles of SCD1 are also being delineated, largely because of the creation of conditional knockout mouse models and transient knockdown models using antisense oligonucleotides (ASO). There is also significant interest in understanding the potential role of SCD1 in human disease; this topic has been recently reviewed elsewhere.[13]

SCD1: expression and regulation

The mouse SCD1 isoform has been very well characterized for both its systemic roles as well as tissue-specific contributions. It is expressed ubiquitously and is significantly induced in liver in response to high-carbohydrate feeding and saturated fat feeding.[14–17] In addition, it is expressed in the undifferentiated cells of the sebaceous gland in the skin, where it plays a critical role in maintenance of sebocyte development and skin lipid composition.[10,18,19] It prefers palmitate and stearate as substrates, converting them to palmitoleate and oleate, respectively. Despite the relative abundance of these MUFA products in both our diets and tissues, SCD1 is a highly regulated enzyme, suggesting that the endogenous synthesis of MUFAs may play a distinct role in cell signaling as compared to MUFAs derived from the diet.

The *Scd1* gene is induced by glucose, fructose, saturated fatty acids, and insulin, as well as by the actions of the lipogenic transcription factor sterol regulatory element binding protein-1c (SREBP-1c) and the nuclear receptor, LXR.[2,20] Conversely, the adipokine leptin, as well as polyunsaturated fatty acids, are known repressors of *Scd1* gene expression.[2,20] The SCD1 protein is also regulated post-translationally. SCD1 is rapidly degraded in microsomal fractions with a half-life of three to four hours at 37 °C via a microsomal protease that has been identified as a plasminogen-like protease.[21–23] In addition, SCD1 is also known to be degraded via the proteasomal pathway, which requires a 66-residue N-terminal segment of the protein containing PEST sequences.[24] Mainly through studies using various rodent models of SCD1 deficiency, SCD1 has been shown to play a critical role in the development of metabolic diseases, including diet and leptin-deficiency or leptin-resistance induced obesity, hepatic steatosis, insulin resistance, and atherosclerosis, as well as diverse metabolic processes including maintenance of skin barrier integrity and nonshivering thermogenesis.[10,12,14–18,25–36]

Role of SCD1 in hepatic lipogenesis and atherosclerosis

The SCD1 enzyme plays a central role in the *de novo* lipogenic pathway, by catalyzing the further processing of fats synthesized by fatty acid synthase into products that are primed for incorporation into storage lipids, such as TGs. Furthermore, given its upregulation by prolipogenic hormones and transcription factors such as insulin and SREBP-1c, it has become clear that SCD1 plays a vital role in *de novo* lipogenesis. Indeed, mice deficient in SCD1 because of a targeted whole-body deletion of the enzyme are extremely resistant to a high-carbohydrate diet-induced obesity and hepatic steatosis.[14–16] A large part of this protection from glucose- and fructose-induced pathologies appears to be due to reductions in hepatic lipogenesis, since liver-specific deletion of SCD1 in a conditional knockout confers the same protection from carbohydrate-induced obesity and hepatic steatosis as whole body deletion of SCD1.[15]

Interestingly, not only are $Scd1^{-/-}$ mice protected from carbohydrate-induced obesity, but also from many of the deleterious effects of saturated fats, including increased hepatic lipogenesis, hypertriglyceridemia, weight gain, and insulin resistance.[15,17,32] Both whole-body and liver-specific SCD1 knockouts are resistant to saturated fat induced increases in *de novo* lipogenesis.[15,17] Furthermore, concurrent transient knockdown of SCD1 in liver, adipose, and macrophages via ASO confers a similar protection from saturated fat–induced hepatic steatosis and obesity.[32]

Interestingly, transient knockdown of hepatic and adipose SCD1 by ASO does not seem to confer protection against atherosclerosis, despite reductions in hepatic lipogenesis and circulating lipids.[32] In fact, SCD1-knockdown mice developed greater atherosclerotic lesions, especially in the abdominal aorta, compared to control mice, with a significant enrichment of circulating lipoproteins and macrophages with saturated fatty acids.[32] This study also reported a hypersensitivity to toll-like receptor-4 agonists in macrophages derived from SCD1-knockdown animals, suggesting that increased inflammatory cytokine release from SCD1-knockdown macrophages may mediate the increased incidence of atherosclerosis in these mice.[32]

Although these phenotypes were not reversed by supplementing the diet of SCD1-knockdown animals with MUFAs, feeding n-3 PUFAs derived from fish oil in a subsequent report appeared to abolish the atherosclerosis associated with SCD1-knockdown.[37] Another study using the naturally occurring global SCD1-deletion strain ab^{J} in the hypercholesterolemic LDL-receptor deficient background reported similar increases in atherosclerosis, despite reductions in hepatic steatosis and circulating lipids in SCD1-deficient mice.[31] However, this study did not find an altered macrophage inflammatory response in macrophages derived from SCD1-deficient mice nor indeed any effect of SCD1 deficiency on macrophage function.[31] Therefore, the role of SCD1 in macrophages and associated inflammation is as yet unclear. To further complicate the story, another study[38] reported that chronic intermittent hypoxia (CIH), which is associated with atherosclerosis, was accompanied, in human subjects, with increased hepatic SCD1 levels. Conversely, ASO inhibition of SCD1 in a murine model of CIH resulted in significantly reduced rates of both dyslipidemia and atherosclerosis.[38] Therefore, further studies are certainly warranted in establishing either a pro- or antiatherosclerotic role for SCD1 and examining adjuvant therapies to combat any undesirable proatherosclerotic side effects of pharmacological inhibition of SCD1.

Role of SCD1 in fatty acid oxidation and thermogenesis

Although the essential role of SCD1 in lipogenesis elucidated via these animal studies is not entirely surprising, a unique feature of the SCD1-deficient mouse model is the observed increase in lipid oxidation. This increase in fat oxidation greatly contributes to their protection from diet-induced obesity, especially in the face of diets containing high amounts of MUFAs.[10,17,35,36,39,40] After a four-hour fast, levels of β-hydroxybutyrate were significantly higher in *Scd1*$^{-/-}$ mice, relative to WT controls, indicating increased fatty acid oxidation in these mice.[10] It has since been shown that indeed, fatty acid oxidation is significantly increased in liver, brown adipose tissue (BAT), and skeletal muscle of mice with a global SCD1 deficiency.[35,39,40] This increase in fatty acid oxidation is mediated, at least partly, by induction of the AMP-activated protein kinase (AMPK), resulting in phosphorylation and inactivation of acetyl-CoA carboxylase (ACC), and a consequent derepression of the carnitine palmitoyl transferase-1 (CPT-1) enzyme responsible for transport of fatty acids into the mitochondria for β-oxidation.[40] In addition, as the product of ACC, malonyl-CoA can act as a repressor of CPT-1, the reduction in gene expression of *Acc* in *Scd1*$^{-/-}$ mice[14–17] likely plays a role in the robust upregulation in fatty acid oxidation observed in these mice. In addition, genes of fatty acid oxidation, including *Cpt-1*, acyl CoA oxidase, and very long-chain acyl-CoA dehydrogenase are also upregulated in *Scd1*$^{-/-}$ mice.[10] Although the nuclear receptor peroxisome proliferator activated receptor-alpha (PPARα) is a major player in transcriptional regulation of fatty acid oxidation,[20] it does not appear to be required for the induction of oxidative genes because of SCD1 deficiency, because deletion of SCD1 in a PPARα-null mouse model does not abolish the effects of SCD1 deletion of fatty acid oxidation.[41] In addition to fatty acid oxidation, whole body thermogenesis is also significantly upregulated in *Scd1*$^{-/-}$ mice. Increased signaling through the β3-adrenergic receptor pathway in BAT of *Scd1*$^{-/-}$ mice results in activation of the peroxisome proliferator-activated receptor-gamma coactivator-1alpha and increased uncoupling via uncoupling protein-1, thereby increasing the rate of basal thermogenesis and consequently, whole body energy expenditure, in *Scd1*$^{-/-}$ mice.[35]

Although global deletion of SCD1 upregulates systemic fatty acid oxidation and protects animals from high-fat diet induced weight gain, liver-specific deletion of SCD1 does not confer the same protection from high-fat diet (HFD)-induced obesity, or upregulate fatty acid oxidation, or thermogenesis.[15] In addition to the metabolic role of SCD1, one of the first observations in mice lacking SCD1 was the development of severe alopecia and sebocyte hypoplasia, leading to dry skin with altered lipid composition. Given these cutaneous abnormalities in SCD1-deficient mice, a skin-specific model of SCD1-ablation was developed.[18] Interestingly, deletion of SCD1 in the skin not only recapitulated all the cutaneous phenotypes observed in *Scd1*$^{-/-}$ mice, but also induced genes of fatty acid oxidation and thermogenesis, and increased whole body energy expenditure in animals, thereby protecting them from

HFD-induced weight gain.[18] Interestingly, however, maintaining skin-specific *Scd1*$^{-/-}$ mice in a thermoneutral environment did not abolish their protection from diet-induced obesity.[42] Skin-specific deletion of SCD1, unlike global SCD1 deletion, did not protect mice from fasting–refeeding induced hepatic lipogenesis.[18] Therefore, although some of the favorable metabolic features of global SCD1 deletion may be explained by increased energy demands because of heat loss in the *Scd1*$^{-/-}$ mouse, the insights gained from liver and skin-specific SCD1 deletion have helped to uncouple the effects of SCD1 deletion on hepatic lipogenesis, specifically, from those on whole body energy expenditure, thermogenesis, and lipid oxidation. Furthermore, these studies in the skin-specific *Scd1*$^{-/-}$ mice underscore the need for similar studies in mouse models such as the *Dgat1*$^{-/-}$ mouse, which also displays protection from diet-induced obesity and cutaneous abnormalities.[43–45] For a more detailed review on the consideration of nonshivering thermogenesis in metabolic studies, the reader is directed to recent review on the topic.[46]

The role of SCD1 in insulin sensitivity

In addition to resistance to obesity and hepatic steatosis, *Scd1*$^{-/-}$ mice are also protected from the pathological decline in insulin sensitivity that often accompanies obesity and fatty liver.[28–30] Despite having lower fasting plasma insulin levels, *Scd1*$^{-/-}$ mice have increased insulin signaling through increased insulin receptor tyrosine phosphorylation and reduced Ser/Thr phosphorylation of IRS-1 in multiple tissues, including skeletal muscle, liver, adipose tissue, and heart.[12,27–30,35] In addition, levels of protein tyrosine phosphatase-1B, which has been shown to attenuate insulin signaling,[47,48] are reduced in skeletal muscle and BAT of *Scd1*$^{-/-}$ mice.[29,30] Furthermore, as mentioned above, AMPK activation and fatty acid oxidation are significantly increased in liver, muscle, and BAT, and ceramide synthesis and content is significantly reduced in muscle of *Scd1*$^{-/-}$ mice.[35,39,40] Because ceramides are thought to mediate lipid-induced aberrations in insulin signaling,[49–51] the reductions in ceramide synthesis and increased fat oxidation in *Scd1*$^{-/-}$ mice may also contribute to their increased insulin sensitivity.

SCD1 deficiency has been shown to significantly improve insulin signaling in both a high-fat-diet–induced model of obesity, as well as in the leptin-resistant agouti obese mouse.[28] Transient knockdown of hepatic and adipose SCD1 by ASO treatment has also been shown to attenuate diet-induced obesity and improve hepatic insulin signaling,[52,53] although similar effects were not observed in liver-specific *Scd1*$^{-/-}$ mice.[15] It has been recently reported that skin-specific deletion of SCD1 also completely protects mice against diet-induced insulin resistance, likely because of a protection from diet-induced obesity and hepatic steatosis.[18] A recent study also showed that inhibition of SCD1 in 3T3-L1 adipocytes stimulated basal glucose uptake via an upregulation of GLUT-1, without any changes in GLUT-4 levels.[54] However, adipose-specific deletion of SCD1, although resulting in increased GLUT-1 levels, did not confer increased insulin sensitivity in mice.[54]

Although SCD1 deficiency attenuates obesity to a significant extent in several mouse models of obesity, including the leptin-resistant *ob/ob* mouse, insulin signaling parameters are not improved by SCD1 deficiency in this background.[27,28] In fact, in the context of a diabetes-prone BtBr mouse strain, SCD1 deficiency appears to exacerbate the diabetic phenotype of leptin-deficient *ob*/*ob* mice, by impairing islet function.[27] In the more widely studied C57Bl/6 strain, however, SCD1 deficiency does not cause reduced insulin levels in *ob*/*ob* mice, arguing against an islet defect in this background.[28] However, regardless of the underlying mechanism, it appears that the increased insulin signaling observed upon global SCD1 inhibition requires the presence of leptin.[28]

SCD1 in inflammation and cancer

Obesity is generally accompanied by chronic inflammation, which plays a role in many of the secondary pathologies associated with obesity. Therefore, SCD1 inhibition, which is associated with reduced obesity, but may result in increased saturated fat accumulation, is of particular interest in studying the link between obesity and inflammation. The tissue-specific roles of SCD1 in inflammation have been recently reviewed in detail elsewhere.[55] In brief, the few studies to date examining the role of SCD1 in various types of inflammation have not yielded consistent support for either a pro- or anti-inflammatory role for SCD1. For instance, as discussed above, studies on the

role of SCD1 in atherosclerosis and insulin signaling have suggested a potential macrophage inflammation phenotype and β cell dysfunction, as well as increased systemic inflammation associated with SCD1 deletion.[27,31,32] However, other studies have also suggested that macrophage inflammation is unaffected by SCD1 inhibition.[31,56] Similarly, although SCD1 inhibition has been shown to reduce adipose inflammation,[56] adipose-specific inhibition of SCD1 results in slightly increased expression of the proinflammatory cytokine tumor necrosis factor α and reduced levels of circulating adiponectin.[54] In addition to these organ systems, SCD1 also appears to play a role in ulcerative colitis,[57,58] cutaneous inflammation,[42,59,60] and myocyte[61] and endothelial dysfunction.[62,63] Although the role of SCD1 on inflammation appears to vary somewhat by tissue-type, it is interesting to note that in so many instances, inhibition of SCD1 causes increased inflammation, despite amelioration of metabolic disease, which is generally associated with an improvement of inflammation. Given this dichotomy, it becomes particularly interesting to examine the role of SCD1 in the development of cancer, which has been associated with both obesity and lipid accumulation, as well as inflammation.[64–66] Since the hyperproliferative nature of cancer cells places a greater demand for synthesis of lipids for cellular constituents and energy demands, it follows that increased SCD1 activity may be required to meet this demand. Indeed, as has been reviewed extensively elsewhere, SCD1 has been reported to be induced in many cancers, including esophageal and colonic carcinomas and hepatic adenomas.[67] Furthermore, SCD1 inhibition appears to have an antiproliferative effect on many neoplastic cell types including lung, prostate, colon, and breast cancer cells,[68–73] leading to suggestions that SCD1 may be a druggable target in the fight against cancer.[73,74] In contrast, a study has reported a consistent reduction in SCD1 activity in prostate carcinomas,[75] suggesting that the role of SCD1 in tumorigenesis may not be generalized across cancer types. Furthermore, given that particular cancers, such as hepatocellular carcinomas (HCCs), are known to be affected by both severity of hepatic steatosis as well as by downstream inflammation,[64] it will be interesting to see if the divergence of metabolic symptoms and inflammatory markers in the *Scd1*$^{-/-}$ mouse model can be exploited to understand the mechanisms leading to the development of cancers such as HCCs.

SCD1: a double-edged sword

Initially identified from a model of alopecia and sebocyte atrophy, a compelling role for SCD1 in the development of obesity, hepatic steatosis, and obesity-associated insulin and leptin resistance has been established. Emerging evidence suggests that unqualified inhibition of SCD1, whether systemic or restricted to specific organ systems, may not be desirable as it may result in an increased propensity to cellular inflammation. Furthermore, any consideration of SCD1 as a pharmaceutical target will have to differentiate between metabolic phenotypes elicited by local SCD1 inhibition in tissues such as liver versus indirect effects of SCD1 inhibition in peripheral tissues such as skin. Nevertheless, the multiple rodent models that have been developed, as well as several pharmacological inhibitors that are currently available, will likely increase our understanding of this enzyme that appears to have a dual role in mediating the progression of obesity and related pathologies.

Conflicts of interest

The authors declare no conflicts of interest.

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