REVIEW ARTICLE

The Role of Stearoyl-coenzyme A Desaturase 1 in Liver Development, Function, and Pathogenesis

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Abstract

Stearoyl-coenzyme A desaturase 1 (SCD1) is a microsomal enzyme that controls fatty acid metabolism and is highly expressed in hepatocytes. SCD1 may play a key role in liver development and hepatic lipid homeostasis through promoting monounsaturated protein acylation and converting lipotoxic saturated fatty acids into monounsaturated fatty acids. Imbalanced activity of SCD1 has been implicated in fatty liver induction, inflammation and stress. In this review, the role of SCD1 in hepatic development, function and pathogenesis is discussed. Additionally, emerging novel therapeutic agents targeting SCD1 for the treatment of liver disorders are presented.

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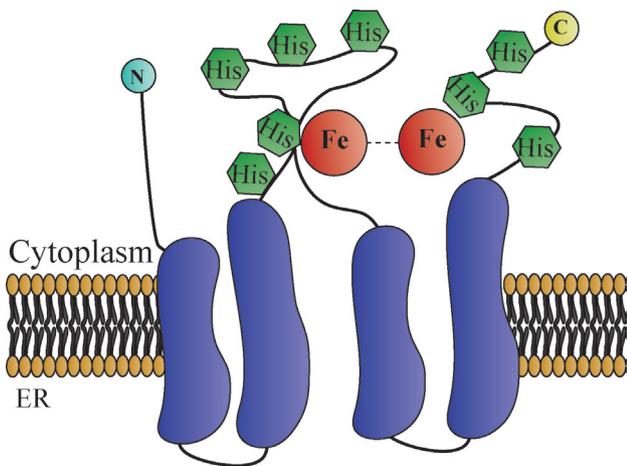
Introduction

Stearoyl-coenzyme A desaturase 1 (SCD1) was discovered in 1988 when Ntambi and colleagues identified an mRNA transcript whose expression was highly induced during adipogenic differentiation (1). SCD1 is an iron-containing lipid-regulating enzyme that is highly expressed in the liver and is the main enzyme responsible for *de novo* synthesis of monounsaturated fatty acids (MUFAs). Palmitoyl-CoA and stearoyl-CoA are the main substrates of this enzyme, converting them into palmitoleoyl-CoA and oleoyl-CoA, respectively (2).

SCD1 is coded by its gene on the long arm of chromosome 24, in the sub-band 3 of region 24 (3). Promoter activity region is located within the initial 609 bp upstream of transcription initiation site which constitutes a CCAAT-box identified as

a *cis*-element binding site. Sterol regulatory element-binding transcription factor 1 (SREBP-1c), liver X receptor (LXR), peroxisome proliferator-activated receptor alpha (PPAR-α) and CCAAT/enhancer-binding protein alpha (C/EBP-α) are among the most important transcription factors that bind to SCD1 promoter and control its gene expression (4). The pseudogene of SCD1, containing two premature stop codons downstream of the original start codon, is located on the short arm of chromosome 24 in the sub-band 32 of region 11 (5).

SCD1 protein is a microsomal enzyme containing four transmembrane domains in which both the N-terminus and C-terminus are located in the cytoplasm (Figure 1). Eight histidine residues on the single cytoplasmic loop and C-terminus are conserved and important for desaturase catalytic activity (6). Purified SCD1 protein migrates as a 37 kDa band by SDS gel electrophoresis (7, 8). As fatty acids are important components of phospholipids, triglycerides and esterified cholesterol, changes in SCD1 expression and activity can affect membrane stability, lipid metabolism and the amount of adipose tissue; consequent changes may be associated with obesity, fatty liver, cancers, diabetes and atherosclerosis (9). This review provides an overview of the role of SCD1 on various aspects of liver pathophysiology such as development, hepatic lipogenesis and inflammation. It also summarizes the role of novel small molecules targeting SCD1 as potential agents for the treatment of various liver disorders.

SCD1 Activity Contributes to Liver Development through Protein Acylation

The Wnt family of proteins are signaling molecules that orchestrate numerous homeostatic events from embryonic development to adult tissue function (10). Their malfunction causes various hepatic abnormalities. The products of SCD1 can regulate Wnt trafficking and function through MUFA acylation or lipidation (Figure 2). Monounsaturated fatty acyl moieties render Wnts hydrophobic and insoluble in aqueous environment (11). During the embryonic stage, the inner layer, endoderm, is partitioned into three regions termed as foregut, midgut, and hindgut, with the foregut containing liver precursors. The liver and biliary tracts develop from the foregut at the 4th week of gestation (12). The intermediate germ layer, mesoderm, produces Wnt which contributes to the development of hindgut in the posterior endoderm. In the anterior endoderm, however, suppression of Wnt signaling retains foregut fate and allows subsequent development of the liver (13, 14). Overall, Wnt signaling is tightly regulated during embryo development, which is particularly important at the initial stages of liver development. Absence of Wnt signaling activity will result in impaired hepatic development. This is supported by the elevated expression of Wnt downstream core transcription factors during the terminal differentiation of hepatocytes (15).

SCD1 shows a determinant role in the *in vitro* differentiation process of human-induced pluripotent stem cells toward hepatic lineage. Inhibition of SCD1 by a selective inhibitor in early stages of *in vitro* induced differentiation has resulted
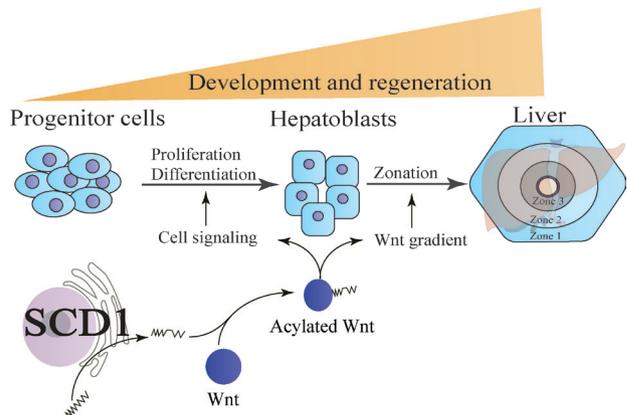

Figure 1. Stearoyl-coenzyme A desaturase 1 (SCD1) is an iron-containing transmembrane enzyme. SCD1 protein is exclusively localized on the ER membrane with both the N- and C-terminal domains stretched into the cytosol. It has four transmembrane helices (purple cylindrical shapes). The eight histidines (hexagonal shapes) on the single cytoplasmic loop and C-terminus are highly conserved, particularly regions surrounding the di-iron center. The cytosolic domain provides a structural frame for the regioselectivity and stereospecificity of the desaturation reaction (6).

Figure 2. Stearoyl-coenzyme A desaturase 1 (SCD1) contributes to liver development and regeneration by modulating Wnt activity. Microsomal SCD1 produces monounsaturated fatty acids that can be attached to Wnts. This process, termed acylation, enables Wnt secretion and activation. Wnt acylation is also a prerequisite for the formation of concentration and activity gradients of Wnts. The Wnt gradients mediate zonal development of liver and regeneration.

in decreased hepatic markers. In the rescue experiments with the combination of the SCD1 inhibitor and its main product oleate, the effect of inhibitor was strongly reversed (16). Our ongoing *in vivo* work is to identify the role of SCD1 in the early stages of liver organogenesis and development, especially its role in the formation of a complete liver before birth.

Apart from hepatocyte differentiation, Wnt signaling pathway plays a central role in liver zonation (17). Hepatocytes adjacent to portal vein are named periportal hepatocytes (zone 1) and involved in glyconeogenesis and β-oxidation, whereas those near the central vein are called pericentral hepatocytes (zone 3) and play a distinct role in drug metabolism and glycolysis. Hepatocytes in zone 2 exhibit an intermediary role having both periportal and pericentral functions. In a recent study, a high β-catenin-dependent Wnt signaling activity was observed in zone 3 (17–19). These findings collectively highlight the importance of the SCD1-produced MUFAs in mediating liver development through Wnt regulation.

Recent studies using animal models of partial hepatectomy have also implicated the direct involvement of Wnt signaling pathway in liver regeneration. The expression and nuclear translocation of β-catenin significantly increase within minutes of hepatectomy and promote hepatocyte proliferation rate (20). In acetaminophen-induced liver injury, Wnt/β-catenin not only induces the expression of enzymes involved in drug metabolism such as cytochrome P450 2E1 and cytochrome P450 1A2 but also helps liver regeneration (21, 22). In line with this finding, *SCD1* gene expression was increased 3.5-fold in regenerating liver following major liver resection (23). After tissue damage, the residual cells start the repair process (24), and the proliferating cells accumulate several categories of lipids including triglycerides, fatty acids (both saturated and unsaturated), and cholesterol esters (25). These lipids are thought to undergo oxidation and provide the required energy for cell proliferation. In addition, they are the main components of newly synthetized membranes. Besides, these lipids can contribute to various signal transduction cascades related to cell proliferation and differentiation such as Wnt and hedgehog signaling pathways (26). It is hypothesized that MUFAs produced by SCD1 not only provide metabolic energy source and structural components, but also promote protein acylation–mediated signaling, which are essential for liver regeneration.

SCD1 Prevents Lipotoxicity and Controls Hepatic Lipogenesis

Palmitic acid and stearic acid are the major *de novo* synthesized lipotoxic saturated fatty acids (SFAs) in the liver. SCD1 mediates the addition of a double bond to the saturated carbon chain. On one hand, SCD1 activity attenuates SFAs lipotoxic effects through their conversion into the MUFAs palmitoleic acid and oleic acid (27). On the other hand, SCD1 generates unsaturated fatty acids serving as rate-limiting

substrates for lipogenesis (28). Thus, an improper increase in its activity may cause hepatic lipid accumulation.

Despite oleate being the major dietary MUFA, SCD1 expression is highly regulated in response to developmental, dietary, environmental, and hormonal factors. *De novo* synthesized MUFAs are the preferred substrates for neutral hepatic lipid synthesis including triglycerides and cholesterol ester. SCD1 inhibition protects against high-fat high-carbohydrate diet, leptin-deficiency-induced obesity, and hepatic steatosis (29). Leptin-deficient mice exhibit SCD1 overexpression causing palmitoleate and oleate accumulation in liver as fat droplets. Recent studies on high-carbohydrate-fed rats have revealed that deficiency in SCD1 decreased lipid synthesis, elevated fatty acid oxidation and thermogenesis, and insulin susceptibility in different tissues, especially in the liver (30).

Sampath et al. (31) showed that stearate-rich diet causes SCD1 induction and hepatic lipid accumulation in wild-type mice but not in scd1$^{-/-}$ mice. However, in scd1$^{-/-}$ mice, stearate does not induce genes involved in lipogenesis. Additionally, sterol regulatory element-binding protein-1c (SREBP-1c) and peroxisome proliferator-activated receptor coactivator-1 (PGC-1) transcription factors, which are necessary mediators for pro-lipogenic activities of saturated fatty acids (SFAs), were downregulated in scd1$^{-/-}$ mice. Instead, fatty acid oxidation genes such as carnitine palmitoyltransferase-1 (CPT-1) were induced, resulting in hepatic glycogen depletion. Lui et al. (32), in a study on zinc finger transcription factor knockout mouse model, showed a significant decrease in SCD1 expression and triglyceride accumulation compared to controls. Binding of this transcription factor to SCD1 promoter in hepatocytes was also reported in this study, indicating its critical role in the activation of SCD1 expression.

The role of SCD1 in gut microbiota-dependent hepatic lipogenesis has been studied by Singh et al. (28). They reported that mice with deficient Toll-like receptor-5, which is expressed in gut epithelial cells and plays an important role in microbiota homeostasis, exhibit a microbiota-dependent metabolic syndrome with elevated hepatic lipogenesis, SCD1 expression and activity, and hepatic neutral lipids accumulation with a high oleate and palmitoleate content.

Furthermore, the expression level of SCD1 and fatty acid synthase along with endoplasmic reticulum (ER) stress markers was downregulated in response to the inhibition of poly ADP-ribose polymerase (PARP), which is overexpressed in long-term high-fat high-sucrose diet in mice, indicating the PARP-SCD1 interaction as a major mechanism in the induction of non-alcoholic fatty liver disease (33). The role of SCD1 in an alcoholic fatty liver disease model was studied by Louinis et al. (34). In that study, mice fed with a low-MUFA diet containing 5% ethanol for 10 days and a single ethanol gavage (5 g/kg) developed severe hepatic injury. Liver-specific Scd1-knock-out (SCD1-LKO) mice were resistant to such hepatic injury.

In a recent cross-sectional clinical study, it has been shown that the serum SCD1 activity index is significantly related to the risk of non-alcoholic fatty liver disease in patients with primary dyslipidemia (35). Of course, while interpreting these data, it should be noted that the index of serum SCD1 activity is not solely determined by the liver. In this field, the Ntambi laboratory has recently shown that hepatic triglyceride accumulation in mice may be induced by increased hepatic trafficking of MUFAs originating from non-liver tissues (36). The latter finding further supports the hypothesis that fine-tuning of hepatic SCD1 activity is critical in variable metabolic states.

SCD1 Modulates Hepatic Inflammation and Oxidative Stress

Current evidence indicates the regulatory role of fatty acids in cellular inflammation. SCD1 plays an important role in maintaining the balance between SFAs and MUFAs. Toxic accumulation of SFAs that are reflected as MUFAs/SFAs imbalance leads to activation of oxidative stress imbalance in hepatocytes (37, 38). SFAs mediate cellular inflammatory response through binding to Toll-like receptor-4, CD14, and myeloid differentiation protein-2, causing increased production of bacterial lipopolysaccharides, oxidized phospholipids, and oxidized low-density lipoproteins through intestinal microbiota modification (39). These findings support the hypothesis that SCD1 activity may be protective against SFA-induced oxidative stress and hepatic inflammation. Lu et al. (40) reported that IKK2 (an activator of NFκB) activation can induce hepatic SCD1 overexpression and triglyceride accumulation in mouse. However, such activation decreased the expression of oxidative stress and prevented hepatic inflammation and fibrosis. Paradoxically, there is evidence that increased SCD1 activity may contribute to inflammation and oxidative stress. In the high-carbohydrate or high-sucrose, very-low-fat diet, oleate supplementation leads to decreased hepatic injury and oxidative stress in mice with liver-specific SCD1-LKO (41). A high-fructose diet in female C57BL/6J mice also induced oxidative stress characterized by hepatic SCD1 overexpression and elevation of inducible nitric oxide synthase levels (42). Ochi et al. (43) also showed the association of SCD1 with the development of non-alcoholic steatohepatitis (NASH) under induced stress condition. Indeed, a knockout C57BL/6 mice model with a low expression and activity of SCD1 showed lower hepatic lipid accumulation and steatosis following tunicamycin-induced ER stress than the wild-type mice with ER stress.

Overall, as illustrated in Figure 3, balanced activity of SCD1 is important for stabilizing the ratio of unsaturated to saturated fatty acids. An increase in this ratio can lead to lipid accumulation and a decrease in this ratio is associated with lipotoxicity. A rise in both lipid accumulation and lipotoxicity may lead to hepatic inflammation and oxidative stress.
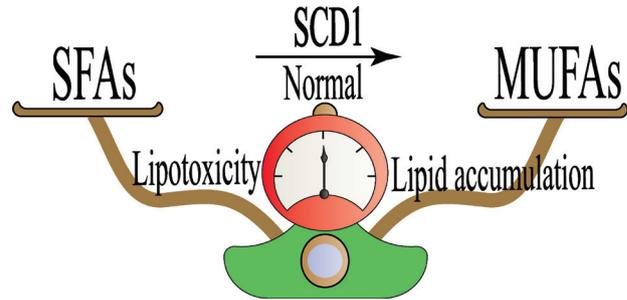
Figure 3. Stearoyl-coenzyme A desaturase 1 (SCD1) activity is associated with normal liver function. The schematic balance represents that the equilibrium between saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) is important in the physiological state. The loss of this equilibrium is due to overactivity and underactivity of SCD1 in hepatic lipid accumulation and lipotoxicity, respectively.

SCD-1 as a Potential Therapeutic Target

The aforementioned studies highlight the significant role of SCD1 activity in hepatic pathophysiology. Therapeutic strategies targeting SCD1 may have applications in managing liver disorders. Several studies have examined small molecule inhibitors in this regard. The following sections review recent advances in small molecule SCD1 inhibitors and their potential therapeutic application in hepatic disorders (Table 1).

MK-8245

SCD1 enzyme is expressed in many cell types of the body. Therefore, potential SCD1 inhibitors for the treatment of liver diseases will have a lot of side effects although they might be highly selective toward SCD1. For example, SCD1-knockout rodent models and SCD1 inhibitor–treated rats develop severe skin and eye abnormalities (44, 45). Therefore, liver-specific targeting of SCD1 may be an effective strategy for the treatment of liver-related disorders. One such inhibitor is MK-8245 (46). It has a transporting element that specifically interacts with heptocytes via the liver-specific organic anion transporting polypeptides. Administration of MK-8245 to mice fed with a high-fat diet did not reduce food intake. Despite this, a reduction in liver steatosis and a decrease in liver triglyceride levels were observed. MK-8245 also exhibited anti-diabetic and anti-dyslipidemic properties. Administration of MK-8245 to individuals with type 2 diabetes mellitus in a phase II clinical trial showed no serious adverse events (47). MK-8245 may also be an option for anti-hepatitis C virus (HCV) therapy as evaluated using recombinant HCV culture systems (48). The potential therapeutic effects of this compound on liver diseases are yet to be clinically examined.

Table 1. Stearoyl-coenzyme A desaturase 1 small molecule inhibitors with potential applications for hepatic diseases.

Compound	Liver-selective	Therapeutic application	Current evidence	Reference
MK-8245	+	Diabetes, dyslipidemia, HCV	Preclinical/animal/ phase II clinical trial	(46, 48)
Hydroxy pyridone	+	Dyslipidemia-	*In vivo*	(49)
N-(2-hydroxy-2-phenylethyl)-6-[4-(2-methylbenzoyl)piperidin-1-yl] pyridazine-3-carboxamide	-	Reduction in triglyceride accumulation in NASH	*In vivo*	(50, 51)
Thiazole analogs	-	HCV infection	*In vitro*	(54)
Thiazol-4-acetic acid derivatives	+	Diabetes, hepatic steatosis and obesity	*In vivo*	(55)

HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; OATP, organic-anion-transporting polypeptide.

Hydroxy pyridone

Another compound that was used for targeted liver SCD1 inhibition is 4-hydroxy pyridine (49). According to the pharmacokinetic analysis, this SCD1 inhibitor had a significantly higher concentration in liver than in plasma and eyelid. It showed a good potency in reducing the mouse liver ratio of palmitoleate to palmitate as a biomarker for SCD1 activity (49).

Pyridazine derivative

A piperazine-based SCD-1 inhibitor, N-(2-hydroxy-2-phenylethyl)-6-[4-(2 methylbenzoyl)piperidin-1-yl]pyridazine-3-carboxamide, has been shown to produce beneficial effects in experimental modes of NASH (50, 51). When administered orally for 8 weeks, once daily, triglyceride accumulation in the liver was reduced by 80% from the fourth week. It also attenuated the increase of aspartate aminotransferase and alanine transaminase by 86% and 78%, respectively. Hepatic steatosis, hepatocellular degeneration, and inflammatory cell infiltration were also ameliorated after the treatment (50).

Thiazole analogs

Current evidence shows that host cell lipid homeostasis plays a critical role in the pathogenesis of HCV by facilitating the formation of viral membrane-associated replication complex. Since inhibiting lipogenesis has a negative effect on virus proliferation, inhibiting the lipid synthesis enzyme SCD1 is a potential strategy for HCV treatment (52, 53). Lyn et al. (54) showed that the thiazole compound MF-152 can repress HCV infection in human hepatoma cells by modifying membrane functions which are required for HCV replication. Cell imaging studies showed that the inability of viral RNAs to interact with modified membranes exposes them to degradation by endogenous nucleases. This process ultimately prevents the formation of HCV viral complexes and arrests HCV replication.

Thiazole-4-acetic acid derivative

Another potent liver-selective SCD1 inhibitor, compound 48 (a thiazole-4-acetic acid derivative), has recently been discovered through high-throughput screening efforts following an *ex vivo* assay approach on mice liver and eyelids (55). Administration of compound 48 to mice fed a high-fat diet for 43 days improved glucose tolerance and decreased body weight without adverse effects on skin or eyes. Furthermore, compound 48 significantly attenuated hepatic triglyceride accumulation in rats fed a high-sucrose, very-low-fat diet (55). These findings suggest that compound 48 may have clinical benefits in the treatment of diabetes, hepatic steatosis, and obesity through targeting SCD1 activity in liver.

Conclusion

SCD1, one of the predominantly expressed enzymes in the liver, is a major factor in fatty acid metabolism. It plays a regulatory role in posttranslational protein modifications via protein acylation. Wnts play an important role in hepatic differentiation, zonation, and regeneration. The Wnts pathway, at least in part, is regulated by SCD1-mediated palmitoleoylation and oleoylation. In addition, SCD1 is crucial for SFA detoxification and MUFA production. SFAs overproduction induces hepatic inflammation and oxidative stress, and SCD1 attenuates these effects via monounsaturation of SFAs. Meanwhile, *de novo* produced MUFAs promote and participate in cellular lipogenesis and their overproduction can lead to hepatic lipid accumulation. Targeting SCD1 as a novel therapeutic approach may be beneficial in liver disorders. In this regard, several studies have tested small molecule inhibitors of SCD1

in vitro and *in vivo*, which opens a promising point of view in the treatment of liver metabolic diseases.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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