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Recent insights into stearoyl-CoA desaturase-1

James M. Ntambi[a,b] and Makoto Miyazaki[a]

Purpose of review

Stearoyl-Coenzyme A (CoA) desaturase is a central lipogenic enzyme catalyzing the synthesis of monounsaturated fatty acids – mainly oleate ($C_{18:1}$). Oleate is the most abundant monounsaturated fatty acid in dietary fat and is therefore readily available. Why, then, is stearoyl-CoA desaturase a highly regulated enzyme? This review summarizes the recent and timely advances concerning the important role of stearoyl-CoA desaturase in metabolism.

Recent findings

Recent findings using mice that have a naturally occurring mutation in the *SCD1* gene isoform as well as a mouse model with a targeted disruption of the stearoyl-CoA desaturase gene-1 ($SCD1^{-/-}$) have revealed the role of de-novo synthesized oleate and thus the physiological importance of *SCD1* expression. In the highlighted references, it is shown that the $SCD1^{-/-}$ mice have reduced body adiposity, increased insulin sensitivity, and are resistant to diet-induced obesity. The expression of several genes of lipid oxidation is upregulated, whereas lipid synthesis genes are downregulated. *SCD1* was also found to be a component of the novel metabolic response to the hormone leptin.

Summary

SCD1, therefore, appears to be an important metabolic control point, and inhibition of its expression could be of benefit for the treatment of obesity, diabetes and other metabolic diseases.

Keywords

stearoyl-CoA desaturase, oleate, triglyceride, obesity, leptin

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Abbreviations

ADG	1-alkyl-2,3-diacylglycerol
PPAR-α	peroxisome proliferator-activated receptor-α
SCD	stearoyl-CoA desaturase
SREBP-1	sterol regulatory element binding protein-1

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Introduction

Stearoyl-CoA desaturase (SCD) catalyzes the critical committed step in the biosynthesis of monounsaturated fatty acids from saturated fatty acids and the regulation of this process. This reaction involves the introduction of the *cis*- double bond in the Δ9 position (between carbons 9 and 10) in a spectrum of methylene-interrupted fatty acyl-CoAs. The preferred substrates are palmitoyl-CoA and stearoyl-CoA, which are converted into palmitoleoyl-CoA and oleoyl-CoA, respectively [1–4]. The roles of monounsaturated fatty acids are diverse and crucial in living organisms. Oleic acid is found to be the major monounsaturated fatty acid of membrane phospholipids, triglycerides, cholesterol esters, wax esters and alkyl-1,2-diacylglycerol. A proper ratio of saturated to monounsaturated fatty acids contributes to membrane fluidity, while changes in cholesterol esters and triglycerides affect lipoprotein metabolism [5–9]. Several SCD gene isoforms (*SCD1*, *SCD2*, *SCD3*) exist in the mouse, and one SCD isoform that is highly homologous to the mouse *SCD1* is well characterized in humans. The three mouse genes exhibit tissue-specific expression (Table 1), providing a unique model for the study of tissue-specific gene expression. Mouse *SCD1* mRNA expression differs markedly from that of *SCD2*, being constitutive in adipose tissue and markedly induced in liver in response to feeding with a high carbohydrate diet [10,11]. *SCD2* is mainly expressed in the brain [12], while *SCD3* is abundantly expressed in the Harderian gland [13–15]. The reason for having three SCD isoforms is not known but could be related to the substrate specificities of the isomers and their regulation through tissue-specific expression.

The *SCD1* isoform is regulated by numerous factors (Table 2, [2, 11,16–46]) and its expression is very sensitive to dietary components, including glucose [11, 16], fructose [17], polyunsaturated fatty acids [11], cholesterol [18–20], vitamin A [18,21–23], iron [40,41], alcohol [46, 47] and phenolic compounds [2]. Apart from being the components of lipids, monounsaturated fatty acids have also been implicated to serve as mediators in signal transduction and cellular differentiation, including neuronal differentiation [2]. Monounsaturated fatty acids have also been shown to regulate food intake in the brain [48]. Therefore, because of this diverse regulation, SCD is of considerable physiological importance and has the potential to affect a variety of key physiological variables, which include insulin sensitivity, metabolic rate and adiposity. This review focuses on current

Table 1. Tissue distribution of mouse SCD isoforms

Isoform	Liver	Brain	Heart	Lung	Spleen	Kidney	Testis	Preputial gland	Harderian gland	White fat	Brown fat	Skin	Skeletal muscle
SCD1 [10–15]	+++	+	+	++	+	++	+	++++	++++	++++	++++	++	+
SCD2 [12–15]	+	+++	+	++	+	+	++	++	+++	++	++	+	+
SCD3 [13–15]	–	–	–	–	–	–	–	+	++++	–	–	++	–

Table 2. Regulation of stearoyl-CoA desaturase

Dietary factor	Hormone	Other
↑Phenolic componds [2]	↑Insulin [17,24]	↑Developmental processes [34,35]
↑Glucose [11,16]	↑Growth hormone [24,25]	↑Temperature [36,37]
↓Polyunsaturated fatty acids [11]	↓Thyroid [26]	↓Thiazolidinediones [38,39]
↑Fructose [17]	↑Androgen [27,28]	↓Cadmium [42]
↑Vitamin A [18,21–23]	↓Leptin [29]	↑Peroxisome proliferators [43,44]
↑Cholesterol [18–20]	↓Glucagon [30]	↑Liver X receptor agonist [45]
↑Iron [40,41]	↑Estrogen [31]	
↑↓Alcohol [46,47]	↑↓Dehydroepiandrosterone [32,33]	

understanding of the physiological role of the *SCD1* isoform in lipid synthesis and regulation of metabolism.

Role of *SCD1* in lipid biosynthesis

Oleate, the main product of SCD, is one of the most abundant monounsaturated fatty acids in dietary fat and is therefore readily available. Why, then, is *SCD1* a highly regulated enzyme? Using the asebia mouse strains (ab^{j} and ab^{2j}) that have a naturally occurring mutation in *SCD1* [49], as well as a mouse model with a targeted disruption ($SCD1^{-/-}$) [50], our laboratory has recently shown that $SCD1^{-/-}$ mice are deficient in triglycerides, cholesterol esters, wax esters and alkyldiacylglycerols [50–52]. The levels of palmitoleate (16:1) and oleate (18:1) are reduced in the plasma and tissue lipid fractions of $SCD1^{-/-}$ mice, while palmitate and stearate are increased. These changes are correlated with a decrease in desaturation index (18:1/18:0 or 16:1/16:0 ratio) and low tissue SCD activity [50,51].

Normally, a high-carbohydrate diet fed to mice or rats induces the expression of the hepatic *SCD1* gene and other lipogenic genes through the sterol regulatory element binding protein-1 (SREBP-1)-dependent mechanism, resulting in an increase in monounsaturated fatty acids and hepatic triglycerides [53–55]. One of our recent observations [52] is that $SCD1^{-/-}$ mice on a lipogenic diet fail to accumulate hepatic triglycerides and cholesterol esters. Supplementation of the lipogenic diet with high levels of triolein or tripalmitolein can normalize cholesterol ester levels, but the triglyceride levels cannot be returned to the levels found in the wild-type mouse [52]. In addition, the $SCD1^{-/-}$ mice have very low levels of triglycerides in the very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) fractions compared with their wild-type counterparts. Furthermore, the rate of VLDL-triglyceride secretion, as measured by inhibition of VLDL clearance using Triton-WR1339 (Sigma, St Louis, MO), was dramatically reduced in the $SCD1^{-/-}$ mice [29]. Transient transfections of an *SCD1* expression vector into Chinese hamster ovary cells result in increased *SCD1* activity and esterification of cholesterol to cholesterol esters [51]. These observations reveal that monounsaturated fatty acids endogenously synthesized by SCD probably serve as the main substrates for the synthesis of hepatic triglycerides and cholesterol esters. The enzymes involved in the de-novo synthesis of triglycerides and cholesterol esters, including SCD, acyl-CoA:cholesterol acyltransferase, diacylglycerol acyltransferase and microsomal glycerol phosphate acyltransferase are located in the endoplasmic reticulum membrane. A possible physiological explanation for the requirement of SCD expression in the synthesis of the triglycerides and cholesterol esters is the production of more easily accessible monounsaturated fatty acids in the vicinity of acyl-CoA:cholesterol acyltransferase, diacylglycerol acyltransferase and microsomal glycerol phosphate acyltransferase. Another possibility is that the monounsaturated fatty acids are incorporated into the triglycerides but are immediately hydrolyzed and the fatty acids oxidized.

The $SCD1^{-/-}$ mice, as well as the asebia mutant mice, show cutaneous abnormalities with atrophic sebaceous glands and narrow eye fissure with atrophic meibomian glands, suggesting an important role for monounsaturated fatty acids in skin homeostasis [49,50,56]. It is known that the major function of the sebaceous gland and the meibomian gland is to secrete lipid-complex

lubricants, termed sebum and mebum [49,50,56]. They contain wax esters, triglycerides, and cholesterol esters. These fluids prevent the evaporation of moisture from the skin and the eyeball. The skin and the eyelid of *SCD1*$^{-/-}$ mice are deficient in triglycerides, cholesterol esters and wax esters. The level of free cholesterol, however, is increased [50]. Thus, under conditions of high cellular cholesterol, *SCD1* gene expression would indirectly protect the cell from the harmful effects of free cholesterol by providing monounsaturated fatty acids for the conversion into cholesterol ester by acyl-CoA:cholesterol acyltransferase for storage. In addition, the presence of normal levels of monounsaturated fatty acids would maintain a more appropriate ratio of cholesterol to other lipids, and maintain cell-membrane integrity [5,45]. Because excess free cholesterol has been known to lead to cell death [57–60], it is tempting to speculate that the atrophy of the sebaceous and meibomian glands observed in the *SCD1*$^{-/-}$ mouse may be due to an increase in the amount of cellular free cholesterol in these glands rather than to the reduced levels of sebum and meibum.

The studies of SCD gene expression in the mouse Harderian gland revealed the role of SCD in the biosynthesis of another class of lipids, i.e. alky-2,3-diacylglycerol [61,62]. The Harderian gland, first described by Johann J. Harder towards the end of the 17th century, is located in the orbit of the eye and in most species is the largest tissue. The major products of the gland vary across different species of mammals. In rodents, the gland synthesizes lipids, indoles, and porphyrins, which are secreted by an exocytotic mechanism [63]. The major lipid synthesized by the mouse Harderian gland is 1-alkyl-2,3-diacylglycerol (ADG) [64]. ADG is a lubricant of the eyeball and, along with meibum from the meibomian gland, is crucial in facilitating movement of the eyelid. In our recent study, *SCD1*$^{-/-}$ mice exhibited a deficiency in ADG and n-9 eicosenate (20:1n-9), which is the main monounsaturated fatty acid of ADG. We found that 20:1n-9 is an elongation product of 18:1n-9. Feeding with diets containing high levels of oleate or eicosenate did not result in an increase in 20:1n-9, and failed to resolve the ADG deficiency [13]. Therefore, endogenous synthesis of oleate by *SCD1* is essential for the biosynthesis of ADG and eicosenate in the mouse Harderian gland. The reasons for incorporating specific very-long-chain monounsaturated fatty acids in the ADG of the mouse Harderian gland are not clear, but it is possible that these fatty acids are required to maintain the correct physical properties of the fluids for normal eye function. We found very low levels of n-3 and n-6 polyunsaturated fatty acids in the Harderian gland, indicating that the lipids of this gland are mainly composed of saturated fatty acids and monounsaturated fatty acids of the n-9 series. $C_{18:1}$ is a major component of the Harderian gland membranes, and a decrease in the level of $C_{18:1}$ would reduce the membrane fluidity of this gland. Consistent with this observation, we noted that the Harderian gland isolated from the *SCD1*$^{-/-}$ mice was very rigid, perhaps because of reduced membrane fluidity. The Harderian gland could therefore be a useful model for the study of the metabolism of monounsaturated fatty acids of the n-9 series and their roles in physiological processes. Humans do not have a Harderian gland, but because this structure is part of the retinal axis it is likely that this tissue has evolved into the retina in humans. Consistent with this idea, high SCD expression has been reported in human retinal pigment epithelial cells [21,65] and its expression may play an important role in the pathophysiology of these cells.

Role of *SCD1* in regulation of lipogenesis and fatty acid oxidation

We found it interesting to determine whether the impairment of acyl-CoA desaturation in the *SCD1*$^{-/-}$ mice would alter the whole-animal energy homeostasis, or whether dietary monounsaturated fatty acids would ameliorate the deficiency. Although the growth curves of male *SCD1*$^{-/-}$ mice were similar to those of the wild-type siblings on a chow diet, a high-fat diet revealed large differences in weight gain in both males and females. On average, the *SCD1*$^{-/-}$ mice consumed 25% more food than wild-type mice, although they were leaner and accumulated less fat in their adipose tissue. The epididymal fat pad mass was markedly reduced in male *SCD1*$^{-/-}$ mice relative to wild-type mice on a chow diet and a high-fat diet. The livers of the wild-type and *SCD1*$^{-/-}$ mice were normal in external appearance and of similar mass on a chow diet. However, on a high-fat diet, the livers of the wild type mice were lighter in color than those of knockout mice, suggesting steatosis. Masses of white fat in *SCD1*$^{-/-}$ mice were universally decreased compared with wild-type mice, regardless of diet. Thus, *SCD1*$^{-/-}$ mice were resistant to diet-induced weight gain and fat accumulation, despite increased food intake [66].

What, then, is the fate of the excess dietary fat? We carried out indirect calorimetry to investigate whether the resistance to weight gain was due to increased energy expenditure. The *SCD1*$^{-/-}$ mice exhibited consistently higher rates of oxygen consumption (higher metabolic rates) than their wild-type littermates day and night. It was hypothesized that the increased energy expenditure in the *SCD1*$^{-/-}$ mice was due to increased lipid catabolism. Although ketone bodies were undetectable in plasma from either strain during post-prandial conditions, β-hydroxybutyrate levels were consistently much higher in knockout mice following a 4-h fast, indicating a higher rate of β-oxidation in *SCD1*$^{-/-}$ mice.

DNA micro arrays were employed to identify genes whose expression was altered in the liver of *SCD1*$^{-/-}$ mice. Two hundred mRNAs that were significantly different between the livers of *SCD1*$^{-/-}$ mice and wild-type mice were identified. The most striking pattern was that for genes involved in lipogenesis and fatty acid β-oxidation. Lipid-oxidation genes such as acyl-CoA oxidase, very-long-chain acyl-CoA dehydrogenase, carnitine palmitoyltransferase-1 and fasting-induced adipocyte factor were upregulated, whereas lipid-synthesis genes such as *SREBP-1*, fatty acid synthase (FAS) and mitochondrial glycerol phosphate acyl-CoA transferase were downregulated in the *SCD1*$^{-/-}$ mice [66]. *SREBP-1c* is the main *SREBP-1* isoform expressed in the liver, and regulates the expression of lipogenic genes [67,68]. Insulin levels, dietary carbohydrate, fatty acids and cholesterol regulate *SREBP-1* gene expression and protein maturation [69,70]. Thus, the downregulation of *SREBP-1* gene expression in the *SCD1*$^{-/-}$ mice could have numerous effects on various metabolic pathways regulated by *SREBP-1*. For instance, the induction of *SREBP-1* by insulin and cholesterol greatly enhances the synthesis and secretion of triglycerides by the liver [18,69,70]. However, in the *SCD1*$^{-/-}$ mice, carbohydrate feeding fails to induce *SREBP-1* and lipogenic gene expression to the same level as that found in the wild-type mice [52]. In *SCD1*$^{-/-}$ mice, the signals generated that lead to reduced lipogenesis are currently being studied.

Carnitine palmitoyltransferase, acyl-CoA oxidase, very-long-chain acyl-CoA dehydrogenase and fasting-induced adipocyte factor are known targets of peroxisome proliferator-activated receptor-α (PPAR-α) [71] and contain PPAR-α response regions in their promoters [72]. Since the PPAR-α mRNA level is unchanged (M. Miyazaki and J. M. Ntambi, unpublished observation), the upregulation of enzymes of fatty acid β-oxidation in the *SCD1*$^{-/-}$ mice must be downstream of PPAR-α transcription. Thus, the characteristics exhibited by the *SCD1*$^{-/-}$ mice are consistent with the presence of a PPAR-α activator with reduced activity in wild-type mice. The *SCD1*$^{-/-}$ mice exhibit increases in saturated fatty acids ($C_{16:0}$ and $C_{18:0}$) content, while the n-6 and n-3 polyunsaturated fatty acid content is unchanged. One possible mechanism is that the saturated fatty acids induce the signal in the *SCD1*$^{-/-}$ mice that activates the PPAR-α, but this remains to be determined. In the alternative mechanism depicted in Fig. 1, it is hypothesized that the absence of *SCD1* leads to increases in the intracellular pool of saturated fatty acids. Saturated fatty acyl-CoAs, but not monounsaturated fatty acyl-CoAs, are known to inhibit acetyl-CoA carboxylase allosterically, thus reducing cellular levels of malonyl CoA [73–75]. Malonyl-CoA is required for fatty acid biosynthesis and also inhibits the mitochondrial carnityl palmitoyltransferase shuttle system, the rate-limiting step in the import and oxidation of fatty acids in mitochondria [76]. Thus, reduced levels of *SCD1* would lead to a decrease in the cellular levels of malonyl-CoA and derepress fatty acid oxidation. These findings are similar to those observed in mice lacking acetyl-CoA carboxylase-2, which also have increased fatty acid oxidation in skeletal muscle and possess a lean phenotype [77].

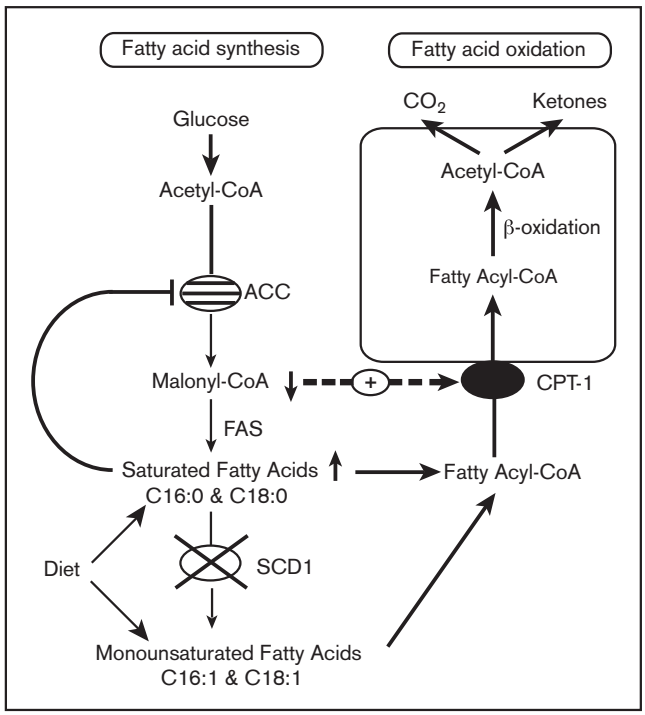
SCD1 deficiency and increased insulin sensitivity

Reduced adipose tissue mass could elicit either insulin resistance or insulin sensitivity, as demonstrated in several animal models [78,79]. Insulin levels are lower in male *SCD1*$^{-/-}$ mice on a chow diet compared with the wild-type mice. On a high-fat diet, insulin levels are similar in the two groups. Fasting glucose levels were similar in the *SCD1*$^{-/-}$ and wild-type mice. However, after a 30-min glucose load, both male and female *SCD1*$^{-/-}$ mice tend to have lower fasting plasma glucose levels and show improved glucose tolerance compared with wild-type mice. In addition, the glucose-lowering effect of insulin is greater in *SCD1*$^{-/-}$ mice than in wild-type mice. These data indicate that *SCD1*$^{-/-}$ mice have increased insulin sensitivity despite their apparent lipodystrophy. Plasma leptin was measured to determine whether changes in levels of plasma leptin could account for the protection from weight gain, increased energy expenditure and insulin sensitivity in the *SCD1*$^{-/-}$ mice. Plasma leptin was significantly reduced in the *SCD1*$^{-/-}$ mice relative to the wild-type controls. Thus, the protection from adiposity is present despite lower leptin levels in the *SCD1*$^{-/-}$ mice [66].

SCD1 is a component of leptin signaling

The protection from adiposity despite the low levels of leptin suggested that *SCD1* acts downstream of leptin, and led to the prediction that loss of SCD function would ameliorate the severe obesity observed in leptin-deficient *ob/ob* mice. To explore the effects of *SCD1* deficiency on the *ob/ob* phenotype, heterozygous asebia (*ab*$^{J/+}$) mice were intercrossed with *ob*$^{/+}$ mice [29]. Double mutant *ab*^{J}/*ab*^{J};*ob/ob* mice were born at the expected frequency and were noticeably thinner than *ob/ob* controls. The *ab*^{J}/*ab*^{J};*ob/ob* mice showed a dramatic reduction in body weight at all ages compared to littermate *ob/ob* controls, and mice of both sexes showed a significant increase in lean mass (%) relative to *ob/ob* littermates. The increase in lean mass indicated that the double mutants with the reduced body weights were not suffering from a defect in growth and development. When energy balance was analyzed by measuring food intake and energy expenditure in *ob/ob* and lean littermates with and without homozygous *SCD1* mutation, it was found that the *ab*^{J}/*ab*^{J};*ob/ob* mice had increased oxygen consumption and consumed more food

Figure 1. Proposed mechanism of the involvement of *SCD1* in the regulation of fatty acid synthesis and fatty acid oxidation



ACC, acetyl-CoA carboxylase; CPT-1, carnitine palmitoyltransferase-1; *SCD1*, stearoyl-CoA desaturase-1; FAS, fatty acid synthase

than *ob/ob* littermates, suggesting that *SCD1* deficiency may modulate central nervous system pathways that regulate food intake perhaps secondary to the increased oxygen consumption. The *ob/ob* mice have massively enlarged livers that are engorged with lipid. Gross inspection revealed that both the hepatomegaly and steatosis of *ob/ob* mice was normalized in ab^J/ab^J;*ob/ob* mice. Consistent with this histological appearance, the levels of liver triglyceride in the ab^J/ab^J;*ob/ob* mice were reduced to levels comparable to those of the lean controls. In addition, the *SCD1* deficiency attenuates triglyceride synthesis and VLDL secretion in the *ob/ob* mice, implying that *SCD1* represents a crucial 'bottleneck' in triglyceride synthesis and is responsible for the development of the obese phenotype of *ob/ob* mice. The observations further suggested that a significant proportion of the metabolic effects of leptin might result from inhibition of this enzyme. The metabolic effects of leptin on *SCD1* in liver, however, are likely to be the result of central action, as mice lacking the leptin receptor in the brain display enlarged, fatty livers, whereas livers from mice with a liver-specific knockout of the leptin receptor appear normal [80]. Leptin also reduces hepatic *SCD1* activity when administered intracerebroventricularly. However, the nature of the central nervous system signals that modulate liver metabolism in response to leptin is still unknown and is currently under study.

Conclusion

The recent studies using knockout mouse models have revealed the phenotypes generated as a result of *SCD1* gene deficiency. We have learned here, and from recent reviews on SCD [81], that this enzyme is critical in the biosynthesis of neutral lipids triglycerides, cholesterol esters, wax esters and 1-alkyl-2,3-diacylglycerol. We have also learned that *SCD1* deficiency either directly or indirectly induces a signal that partitions fatty acids towards oxidation rather than synthesis. *SCD1* deficiency leads to leanness, increased metabolic rate and insulin sensitivity [66]. *SCD1* is a component of the novel metabolic response of leptin signaling [29] and therefore appears to be an important metabolic control point; it is emerging as a promising therapeutic target that could be used in the treatment of obesity, diabetes and other metabolic diseases.

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