Trends in Endocrinology & Metabolism

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REVIEWS

Review

Insights into Stearoyl-CoA Desaturase-1 Regulation of Systemic Metabolism

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Stearoyl-coenzyme A desaturase 1 (SCD1) is a central regulator of fuel metabolism and may represent a therapeutic target to control obesity and the progression of related metabolic diseases including type 2 diabetes and hepatic steatosis. SCD1 catalyzes the synthesis of monounsaturated fatty acids (MUFAs), mainly oleate and palmitoleate, which are important in controlling weight gain in response to feeding high carbohydrate diets. In this review, we evaluate the role of SCD1 isoform in the regulation of lipid and glucose metabolism in metabolic tissues. These highlights of recent findings are aimed toward advancing our understanding of the role of SCD1 in the development of metabolic diseases, which may help evaluate the possible health outcomes of modulating MUFA levels through targeting SCD1 activity.

Introduction

Excess dietary carbohydrate is converted into fat mainly in the liver and adipose tissues. The surplus of glucose or fructose is metabolized into pyruvate through glycolysis and then to acetyl-coenzyme A (CoA), which serves as substrate for the carboxylation reaction catalyzed by acetyl-CoA carboxylase (ACC) [1]. Acetyl-CoA carboxylation is a tightly regulated reaction synthesizing malonyl-CoA, which suppresses fatty acid (FA) oxidation and serves as substrate for FA biosynthesis [2]. Other nutrients, including acetate and amino acids, are also used as substrate for lipogenesis. Synthesized saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) are incorporated into different lipid species, including triglycerides (TGs) and phospholipids (PLs). Lipids synthesized in the liver are packaged in very low-density lipoproteins and delivered to adipose tissue for storage [2].

The process of lipogenesis is modulated by several dietary and hormonal factors, which control the expression of lipogenic enzymes and provide substrate for FA biosynthesis. Lipogenesis is transcriptionally regulated by key transcription factors, including liver X receptor (LXR), sterol regulatory element-binding protein-1c (SREBP-1c), and carbohydrate response element-binding protein (CHREBP). LXR and SREBP-1c play an important role in regulating lipogenesis in response to insulin, whereas CHREBP mediates glucose-induced lipogenesis [3–5]. Apart from transcriptional regulation, some lipogenic enzymes and transcription factors are also modulated by covalent modifications and feed forward inhibition. For example, ACC phosphorylation by AMP-activated protein kinase (AMPK) inhibits ACC activity and leads to higher FA oxidation [6]. AMPK also phosphorylates SREBP-1c, limiting its nuclear translocation [7]. Palmitate and oleate reduce ACC activity [8]. Despite tight regulation, dysregulated lipogenesis has been reported in several chronic diseases including cancer, insulin-resistance type 2 diabetes, and other aspects of the metabolic syndrome. Therefore, there have been many attempts to identify a suitable target to control lipogenesis and ameliorate metabolic diseases.

Trends

SCD1 tissue-specific deficiency in liver and skin protects against HCD and HFD, respectively, indicating that SCD1 carries out distinct metabolic functions in different tissues.

SCD1 products, oleate and palmitoleate, have different metabolic properties. Palmitoleate reduces hepatic lipogenesis and improves insulin sensitivity, while oleate promotes ectopic fat accumulation and increases glucose intolerance.

Reduced SCD1 activity in the liver caused ER stress that was only normalized by exogenous or endogenous oleate but not palmitoleate.

Hepatic oleate, but not palmitoleate, regulates body weight.

Exercise increases SCD1 activity in skeletal muscle, indicating increased FA synthesis, and was proposed to be protective against weight gain.

SCD1 deficiency-mediated glucose uptake in skeletal muscle and BAT feeds toward glycogen synthesis.

Hepatic oleate modulates FA synthesis and oxidation in WAT.

Localized and systemic SCD1 deficiency increases glucose uptake in WAT through apparently different mechanisms involving GLUT1 and GLUT4, respectively.

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Stearoyl-Coenzyme A desaturase

Stearoyl-CoA desaturase (SCD) is a central lipogenic enzyme that represents a potential target for the control of lipogenesis. It is an integral protein anchored in the endoplasmic reticulum (ER) membrane and catalyzes the synthesis of MUFAs, primarily oleate and palmitoleate, from SFAs, palmitate and stearate, respectively. This is achieved by introducing a *cis* double bond between carbons 9 and 10 of the acyl-CoA substrate. In addition to molecular oxygen, the SCD1 reaction requires NAD(P)H, cytochrome b_5 reductase, and cytochrome b_5 through which the electrons flow to SCD and then to molecular O_2, which is reduced to H_2O. To date, four mouse SCD isoforms (1–4) and two human isoforms (1 and 5) have been identified. In the mouse, SCD1 is ubiquitously expressed and shows higher expression in metabolic tissues. Like SCD1, SCD2 is ubiquitously expressed in most tissues except adult mouse liver. Mouse SCD3 is mainly expressed in Harderian gland, preputial gland, and in mature sebocytes of skin [9], while the SCD4 isoform is expressed mainly in the heart [10]. Similar to the mouse SCD1, human SCD1 is abundantly expressed in lipogenic tissues, whereas human SCD5 is predominantly expressed in the brain and pancreas [11–13].

SCD1 is dramatically induced during 3T3L1 differentiation [14]. This intriguing finding opened the door toward further exploration of its role in adipogenesis and lipid biosynthesis. SCD1 expression is regulated by diverse hormonal and nutritional factors [15–18]. It is positively regulated by SREBP-1c, CHREBP, and LXR, which could explain the induction of SCD1 expression during fasting–refeeding cycles [2,19].

The MUFAs, which are the products of SCD1, are preferentially incorporated into major lipid species such as TG, cholesterol ester (CE), and PL [20]. Oleate is the principal product of SCD1 and comprises nearly 45% of free fatty acids (FFAs) in human adipose tissue [21]. Apart from their structural functions, MUFAs have signaling functions and can regulate systemic metabolism and modulate chronic metabolic diseases. Increased MUFA levels in obese animal models and humans indicate a prominent role of SCD1 in the development of obesity-related chronic metabolic diseases, including nonalcoholic fatty liver disease, insulin resistance, and hyperlipidemia [22–24]. The involvement of SCD1 in the pathogenesis of various diseases indicates that SCD1 has a significant role in regulating diverse cellular functions. Consistently, SCD1 has been shown to be involved in the development and progression of several types of cancer and is being avidly explored as a potential therapeutic target against the deadly disease [25]. In addition, studies in transgenic mouse models have demonstrated an essential role of SCD1 in regulating cellular processes including lipid synthesis and oxidation, thermogenesis, hormonal signaling, and inflammation [20,26]. This review will be focused on recent advances in understanding the role of the SCD1 isoform in regulating localized and systemic glucose and lipid metabolism. The findings examined here are mainly inferred from SCD1 knockout (KO) animal models. We will also evaluate the role of endogenous oleate and palmitoleate in regulating metabolic homeostasis, which has been investigated using SCD transgenic mouse models.

SCD1 in Liver Metabolism

Although SCD isoforms demonstrate relative similarities in amino acid sequences and synthesized products, they are differentially expressed in body tissues and the deletion of particular isoforms from specific tissues demonstrates distinct phenotypes. For example, liver-specific SCD1 KO (LKO) mice exhibit different phenotypes compared to skin-specific SCD1 KO (SKO) mice, suggesting that SCD1 products, MUFAs, carry out different functions in different tissues. Alternatively, MUFA deficiency in different tissues may lead to distinct compensatory mechanisms, which could help explain the phenotypes observed in these mice. We have

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previously shown that global SCD1 KO (GKO) mice are protected against **high carbohydrate diet** (**HCD;** see Glossary) and high fat diet (HFD)-induced adiposity and hepatic steatosis [27]. SCD1 deficiency also ameliorated SFA-induced adiposity and hepatic steatosis, suggesting that MUFAs are essential for lipid-promoted weight gain and that reduced MUFA levels limit liver fat accumulation. SCD1 GKO mice also displayed dramatic enhancement of glucose utilization in skeletal muscle and heart that occurred along with increased insulin signaling in these tissues [28,29]. The profound protection against weight gain was attributed mainly to the hypermetabolic phenotype observed in these mice, in addition to reduced hepatic lipogenesis and improved insulin sensitivity. The generation of tissue-specific SCD1 KO mouse models, using the Cre-Lox system, allowed further investigation of the role of SCD1 in different tissues. Using LKO mice, we demonstrated that hepatic SCD1 deficiency is protective against HCD but not HFD-induced adiposity and hepatic steatosis. LKO mice fed HCD showed a significant reduction of white adipose tissue (WAT) weights compared with control mice [30]. Hepatic SCD1 deficiency caused a significant reduction in hepatic lipogenic gene expression and reduced ***de novo* lipogenesis** associated with reduced hepatic TG secretion. To further determine whether the reduction of MUFAs or the accumulation of SFAs reduces adiposity and hepatic lipogenesis, LKO mice were fed triolein- or tristearin-supplemented HCD. Interestingly, triolein-supplemented HCD, but not tristearin, restored reduced expression of hepatic lipogenic genes and adiposity in LKO mice. Exogenous oleate also normalized hepatic TG accumulation and secretion, which remained significantly reduced in tristearin-fed LKO mice. These results indicate that hepatic MUFAs may regulate WAT mass and adiposity in mice fed low fat diet and these FAs are essential for the development of hepatic steatosis. Moreover, LKO mice are more insulin sensitive and showed reduced blood glucose levels following 4-h fasting compared to control mice [30,31]. This change in blood glucose levels is likely linked to reduced hepatic glycogen synthesis and gluconeogenesis in LKO mice, which was corrected upon feeding triolein-supplemented, but not tristearin-supplemented, HCD. The failure of hepatic SCD1 deficiency to reduce adiposity in mice fed HFD led to the assumption that protection against HFD-induced adiposity requires inactivation of SCD1 in both liver and WAT. Further credence to this line of thought came from findings that indicated that hepatic SCD1 deficiency did not result in significant changes in WAT FA composition. A subsequent study showed that combined deletion of SCD1 from both tissues failed to protect mice against HFD-induced adiposity [32]. It was surmised that reduced SCD1 activity in both tissues was not sufficient to elicit the hypermetabolism and increased energy expenditure phenotypes important for protection against HFD-induced body weight. Therefore, the resistance to HF diet-induced weight gain and hepatic steatosis requires SCD1 deficiency in an extrahepatic tissue.

Consistent with this idea, SKO mice showed protection against HFD-induced adiposity along with increased energy expenditure expected to be sufficient to counter increased calorie intake associated with feeding HFD [33]. In addition, similar to SCD1 GKO mice, SKO mice were hyperphagic and maintained lean phenotype accompanied by protection against extended HFD feeding-induced insulin resistance. SKO mice exhibited increased cold sensitivity and died within 3 h of cold exposure due to hypoglycemia. The cold sensitivity and the subsequent inability to maintain normal blood glucose levels were dramatically improved upon feeding HFD compared with chow diet. Surprisingly, SKO mice resembled SCD1 GKO mice phenotypes despite unaffected hepatic *de novo* lipogenesis, which is significantly decreased in mice with global SCD1 deficiency [20]. This indicated that reduced SCD1 activity in skin recapitulated the hypermetabolic phenotype observed in SCD1 GKO mice, despite the presence of intact SCD1 activity in the rest of the tissues. The exact mechanisms that led to the differential phenotypes observed upon SCD1 deletion from the liver and skin, such as reduced lipogenesis and increased energy expenditure, respectively, are not completely understood. However, they

Glossary

***De novo* lipogenesis (DNL):** the process of fat synthesis from nonfat resources, mainly carbohydrate.

GLS3 transgenic mice: SCD1 GKO liver-specific SCD3. This animal model allows partial restoration of endogenous palmitoleate levels in the liver through overexpression of mouse SCD3 isoform, which preferentially catalyzes palmitoleate synthesis.

GLS5 transgenic mice: SCD1 GKO liver-specific SCD5. This animal model allows partial restoration of endogenous oleate levels in the liver through overexpression of human SCD5 isoform, which preferentially catalyzes oleate synthesis.

High carbohydrate diet (HCD): a modified diet high in sucrose and has low fat content, known to potently induce DNL.

indicate that reduced MUFA synthesis in different tissues may lead to distinct metabolic phenotypes. Table 1 summarizes major changes in SCD1 animal models.

Role of Dietary and Hepatic MUFAs in the Regulation of Systemic Metabolism

To delineate the differential metabolic effects of SFAs and MUFAs, Sampath *et al*. [34] performed a study in which they fed mice either triolein- or tristearin-supplemented fat-free HCD as a source of oleate or stearate, respectively [34]. Oleate and stearate are among the most abundant FAs and have the same carbon chain length. Despite lower food intake, mice fed triolein-supplemented diet gained more weight and showed higher WAT weight compared with tristearin-supplemented diet. Triolein-supplemented diet also increased liver fat accumulation and impaired glucose tolerance relative to tristearin-supplemented diet. In addition, endogenously synthesized MUFAs were more associated with ectopic fat accumulation relative to dietary fat. Mice fed HCD exhibited increased SCD1 activity and had higher levels of MUFAs in the liver relative to HFD-fed mice [35]. These findings indicated that endogenous MUFAs have higher capacity to promote adiposity and the development of metabolic diseases.

Studies focusing on oleate and palmitoleate have yielded substantial insights into the distinct impact of these FAs on systemic metabolism. The findings that adipose tissue-derived palmitoleate downregulates hepatic lipogenesis and increases insulin sensitivity in peripheral

Table 1. Major Changes in SCD1 Animal Models[a]

SCD1 model	Mutation	Skin lipid composition	Hepatic lipid composition	Resistance to obesity	Reported phenotypes
GKO [1,2]	Global SCD1 deletion	Decreased TG, CE, and WDE; increased FC	Decreased TG and CE levels; no change in phospholipids	Resistant to HFD-and HCD-induced adiposity and hepatic steatosis	Increased energy expenditure and insulin sensitivity; hypoglycemia; decreased hepatic lipogenesis; increased FA synthesis and oxidation in adipose tissue; increased hepatic ER stress
LKO [3]	SCD1 liver-specific KO		Decreased TG and CE; increased FC levels	Resistant to HCD-induced adiposity and hepatic steatosis but not HFD	Increased insulin sensitivity and hypoglycemia; reduced hepatic lipogenesis; increased hepatic ER stress
AKO [4]	SCD1 adipose-specific KO				Increased GLUT1 in adipose tissue
LAKO [5]	SCD1 liver and adipose combined KO		Decreased TG and CE	Not resistant to HFD-induced adiposity	
SKO [6]	SCD1 skin-specific KO	Decreased TG, CE, WDE, and FFAs; increased FC and ceramides	Decreased TG and CE	Resistant to HFD-induced adiposity	Increased energy expenditure and insulin sensitivity; no change in hepatic lipogenesis
DLKO [6]	SCD1 and PGC-1α liver-specific double KO			Resistant to HCD-induced adiposity	Normal expression of ER stress markers
GLS5 [1]	Global SCD1 deletion; SCD5 liver-specific overexpression		Normalized TG and CE levels	Not resistant to HCD-induced adiposity	Decreased rate of FA synthesis and oxidation in adipose tissue
GLS3 [1]	Global SCD1 deletion; SCD3 liver-specific overexpression		Decreased TG and CE levels; no change in phospholipids	Resistant to HCD-induced adiposity	Increased rate of FA synthesis and oxidation in adipose tissue

[a]Abbreviations: FC, free cholesterol; WDEs, wax diesters.

tissues indicate that FA might work as lipokines [35]. This work has encouraged many to investigate the role of FA in mediating tissue crosstalk. Indeed, studies utilizing SCD transgenic mouse models elucidated that endogenously synthesized liver MUFAs, oleate and palmitoleate, regulate systemic metabolism and adiposity differently. Recently, Burhans *et al*. [36] demonstrated that partial restoration of hepatic oleate levels in GKO liver-specific SCD5 (GLS5) mice was sufficient to rescue adiposity despite SCD1 deficiency in other tissues of the body. However, restoring hepatic palmitoleate levels in GKO liver-specific SCD3 (GLS3) failed to maintain body weight relative to wild-type mice. Interestingly, oleate-mediated restoration of body weight was independent of hepatic lipogenesis, as hepatic expression of lipogenic genes remained decreased in GLS5. Hepatic oleate suppressed enhanced FA synthesis and FA oxidation in WAT, which negatively correlate with adiposity. Therefore, hepatic oleate is thought to enhance adiposity through reducing FA synthesis and oxidation in WAT. Collectively, these results indicate that hepatic oleate is the main regulator of body weight during feeding HCD and is sufficient to modulate FA metabolism in WAT (Figure 1). This is evident given that hepatic SCD1 deficiency protects against HCD-induced obesity and improves insulin sensitivity [30,31]. Similarly, hepatic SCD1 deficiency attenuated short-chain FA-mediated hepatic steatosis and insulin resistance in Toll-like receptor 5 KO mouse model [37].

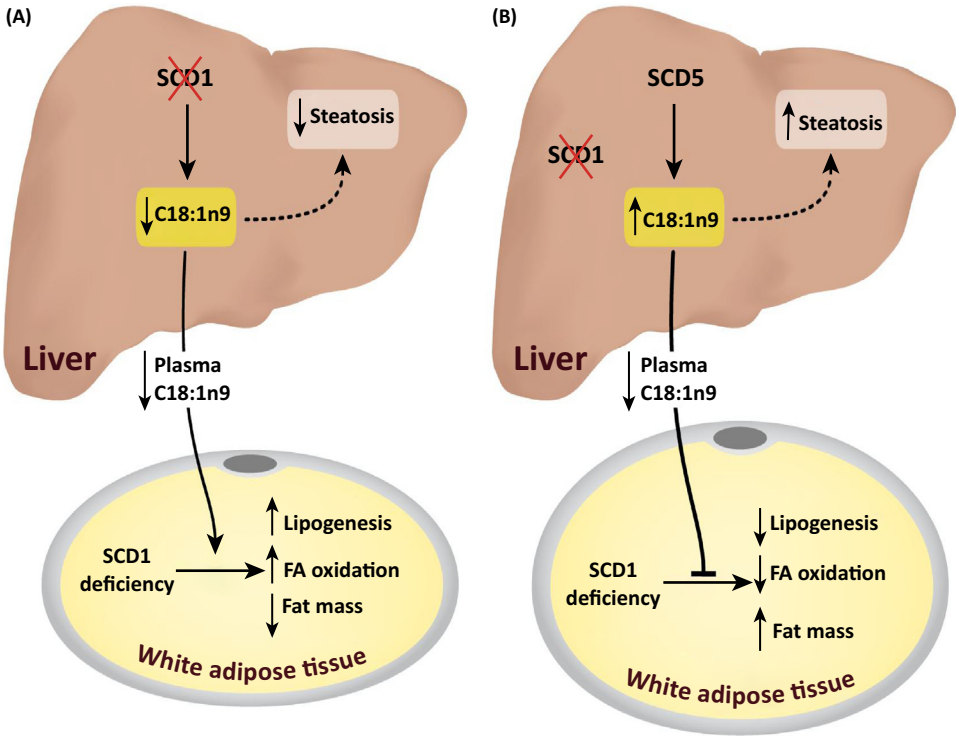

Figure 1. Hepatic Oleate Regulates FA Metabolism in Adipose Tissues. (A) In SCD1 GKO mice, reduced hepatic oleate synthesis reduces liver triglycerides accumulation and decreases plasma oleate. Reduced plasma oleate enhances lipogenesis and FA oxidation in white adipose tissue, which subsequently decrease adipose tissue fat mass. Hepatic oleate is transported to adipose tissue in very low-density lipoprotein in the form of TG and CE. (B) Global SCD1 deletion-induced changes are suppressed upon hepatic oleate restoration through human SCD5 overexpression in the liver of SCD1 GKO mice. In addition, restored hepatic oleate increased fat accumulation in the liver. Abbreviations: CE, cholesterol ester; FA, fatty acid; SCD1, stearoyl-coenzyme A desaturase 1; SCD5, stearoyl-coenzyme A desaturase 5; SCD1 GKO mice, SCD1 global knockout mice; TG, triglyceride.

It should be mentioned that the aforementioned studies have indicated unique metabolic changes in remote tissues in response to adipose tissue-derived palmitoleate or hepatic tissue-derived oleate. For instance, restoring endogenous oleate, but not palmitoleate, in the liver of SCD1 GKO mice was sufficient to modulate FA synthesis and oxidation in adipose tissue as well as restoring body weight. Moreover, feeding SCD1 GKO mice oleate-rich diet failed to restore body weight. These findings suggest that either endogenous oleate has a unique signaling property or it constitutes different cellular pools of FAs, which feed into different metabolic pathways leading to unique phenotypes. The concept of adipose tissue-derived palmitoleate working as a lipokine [38] remains controversial especially that some studies reported positive association between adipose tissue palmitoleate concentration and obesity in humans. Obesity was also positively associated with SCD1 desaturation indexes in adipose tissue [39]. Another group showed no association between insulin sensitivity and plasma palmitoleate levels [40]. Therefore, more work is needed to further investigate the metabolic functions of these FAs.

MUFAs and ER Stress

Despite preferred phenotypes of reduced adiposity and enhanced insulin sensitivity observed in SCD1-deficient mice, SCD1 deficiency causes ER stress and activates unfolded protein response (UPR; Figure 2). UPR activated in response to perturbation of homeostasis networks including oxidative stress, alteration in protein folding and maturation, and defects in post-translational modifications leads to downstream adaptive responses and/or eventually proceeds to apoptosis in case of persistent stress [31]. In addition to various pathologies such as proinflammatory conditions, neurodegenerative diseases, and cancer, UPR has been shown to be activated in response to nutrient fluctuation including glucose and amino acids. Similarly, many reports proposed that SFAs, especially palmitate, are involved in increasing ER stress and activating UPR in different cell lines. Since SCD1 deficiency increases SFA-to-MUFA ratio, increased prevalence of SFAs is expected to increase ER stress and activate UPR response. Both GKO and LKO mice fed HCD diet exhibited increased ER stress and UPR activation [31]. SCD1 deficiency induces ER stress through increasing the expression of the transcriptional coactivator peroxisome proliferator-activated receptor gamma (PPARδ) coactivator-1 alpha (PGC-1α) [31]. Mice with liver-specific SCD1 and PGC-1α double deletion demonstrated significant reduction of ER stress gene expression compared with LKO mice, suggesting that SFA increases ER stress through PGC-1α. In skeletal muscle, PGC-1α has been previously shown to mediate adaptive UPR activation through activation of transcription factor 6 (ATF6) coactivation [41]. As yet, the mechanisms through which SCD1 deficiency increases PGC-1α, which in turn upregulates ER stress genes, are not clearly understood. To add to the ambiguity, LKO mice do not exhibit a change in ATF6 expression, which has been shown to be associated with PGC-1α-induced ER stress. In an attempt to explore this further, Liu *et al*. [31] investigated the differential effects of MUFAs on ER stress, utilizing the **GLS5** and **GLS3 transgenic mouse** models. Interestingly, oleate, but not palmitoleate, caused a

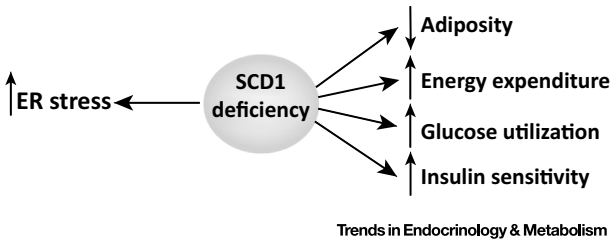

Figure 2. SCD1 Deficiency Induces ER Stress. Despite preferred phenotypes observed in SCD1-deficient mice, SCD1 deficiency is associated with ER stress, which seems independent of reduced body weight and hypoglycemia observed in these mice. Abbreviations: ER, endoplasmic reticulum; SCD1, stearoyl-coenzyme A desaturase 1.

significant reduction in PGC-1α and ER stress compared with SCD1 GKO mice [31]. In addition, triolein-supplemented HCD attenuated ER stress in the liver of LKO mice. This was further validated in *in vitro* studies where oleate treatment suppressed palmitate-induced ER stress in insulinoma cell lines [42]. Taken together, these results suggest that oleate is required to maintain homeostasis and its deficiency causes ER stress that is not suppressed by palmitoleate. In addition, SCD1 deficiency-induced phenotypes such as decreased body weight and reduced blood glucose levels seem to be independent of enhanced ER stress since DLKO mice remained protected from HCD-induced adiposity and showed low blood glucose levels similar to LKO mice [31].

SCD1 in Muscle Metabolism

SCD1 and Skeletal Muscle

SCD1 regulates fuel metabolism through modulation of FA composition, lipid esterification, lipogenesis, and β-oxidation [43]. SCD1 GKO mice exhibited an increase in basal as well as insulin-mediated glucose uptake. Downregulation of protein-tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin signaling, was found to contribute to elevated insulin receptor tyrosine phosphorylation and increases in insulin receptor substrates 1 and 2. Increased insulin signaling correlated with higher glycogen accumulation in the skeletal muscle of SCD1 KO mice [28]. Activation of AMPK in the muscles of these animals was associated with enhanced carnitine palmitoyl transferase I activity with subsequent increase in β-oxidation of FA. Downregulation of serine palmitoyl transferase subsequent to reduced palmitic acid content represses serine palmitoyl transferase activity and accounts for the decreased ceramide formation in SCD1-deficient animals [44]. Transcriptional studies in rectus abdominis muscle of nondiabetics demonstrated increased SCD1 mRNA expression in the obese versus lean individuals. This increase was associated with changes in FA composition of glycerolipids with higher content of oleate and decrease in palmitate and stearate [45]. Overexpression of SCD1 in primary myocytes acquired from lean donors simulated the obese phenotype with increased TG, suggesting that SCD1 repartitioned FA away from oxidation toward esterification [45]. Elevated SCD1 in skeletal muscle may contribute to abnormal lipid metabolism and progression of obesity through reduced FA oxidation and enhanced TG synthesis [45]. To examine if individual differences in the regulation of SCD1 influence insulin sensitivity, palmitate-induced SCD1 gene expression was scrutinized in primary myotubes obtained from metabolically characterized humans. Extensive interindividual variation in SCD1 transcript levels and inducibility by palmitate was observed [46]. This variable response may account for the increased capacity to handle excess FFA levels and TG storage by certain individuals [46].

The impact of SCD1 in partitioning excess FA and modulating glucose transport during exercise was investigated in animal models and human subjects. Surprisingly, it was shown that increasing SCD1 activity through dietary factors or exercise could be protective against excessive weight gain and type 2 diabetes [47]. It was observed previously that overexpression of SCD1 inhibited inflammation and ER stress response subsequent to palmitate exposure [47]. Dobrzyn *et al*. [48] observed that endurance training for 6 weeks resulted in increased SCD1 expression concomitant with elevated levels of FFAs, diacylglycerol, and TGs specifically in the soleus muscle of Wistar rats [48]. It was inferred that elevated SCD1 is important for TG synthesis and the adaptive response of oxidative muscle exposed to prolonged exercise [48]. Our group showed earlier that enhanced SCD1 activity improved metabolism and boosted exercise capacity in muscle-specific SCD1 overexpressing mice [47]. Elevated polyunsaturated fatty acid content in these animals was associated with increased FA oxidation and glucose transporter 1 (GLUT1) mRNA levels and depressed fasting plasma glucose levels [47]. Given

the fact that increases in PPARδ levels were observed in these studies, it is not inconceivable that increased availability of potential ligands for the receptor and its subsequent activation may be the primary mechanism for improved metabolic function in these animals.

Data obtained from animals were emulated in a human study where it was unambiguously shown that increased SCD1 levels play a key role in the adaptation of oxidative muscle to endurance training. An acute session of exercise (running on a treadmill for an hour) preceding lipid infusion was found to protect against FA-mediated insulin resistance and channeled excess FAs toward TG synthesis. Importantly, the researchers observed that the increase in intramyocellular TG was accompanied by upregulated SCD1 protein expression in human skeletal muscle [49]. Similarly, it was noted that endurance-trained male cyclists exhibit higher intramuscular TG and SCD1 levels than their sedentary counterparts [50].

SCD1 and Cardiac Muscle

In contrast to increased FA oxidation observed in skeletal muscles and liver of SCD1 GKO mice, SCD1 deficiency increases glucose transport with reduced FA uptake and oxidation in the heart [29]. The switch from FA to glucose substrate utilization was associated with upregulated insulin signaling, reduced FA transport and availability, and repressed expression of FA oxidation genes in SCD1 GKO mice [29]. Using the leptin-deficient SCD1 KO (ob/ob; SCD1KO) mouse model, it was shown that lack of SCD1 rescued cardiac function by improving systolic and diastolic dysfunction. A decrease in lipid accumulation and suppression of apoptosis were cited as primary factors involved in the observed improvement of cardiac function in these animals [51]. More recently, Bednarski *et al*. [52] showed that SCD1 deficiency was associated with reduced cardiac lipid content and activation of lipolysis independent of peroxisome proliferator-activated receptor α, an important regulator of FA oxidation in muscle.

Despite evidence suggesting that loss of SCD1 may exert a protective effect through reduction of fat accumulation, some studies indicate that SCD1 induction may be beneficial for myocardial energy metabolism [53]. The heart of obese rats maintained on a sucrose-rich diet for 3 months displayed a robust increase in SCD1 without any change in lipogenesis. *In vitro* studies revealed that SCD1 enhanced palmitate-induced lipid accumulation, but suppressed FA oxidation, ceramide synthesis, caspase 3 activation, and reactive oxygen species generation. From their findings and others, the authors proposed a model where upregulated SCD1 in response to increased SFA uptake by the obese cardiac tissue catalyzes the conversion of SFAs to MUFAs. Moreover, SCD1 suppresses FA oxidation and protects against apoptosis through repression of AMPK activity. However, in the presence of excessive nutrient stimuli and persistent oxidative stress, SCD1 is downregulated with subsequent increase in FA oxidation, induction of apoptosis, and cardiomyopathy [53]. Cumulatively, these studies indicate that SCD1 is critical in regulating fuel metabolism in heart and skeletal muscle and reducing SCD1 activity in these tissues may lead to distinct phenotypes.

SCD1 in Adipose Tissue Metabolism

Recent advances in adipocyte biology have provided a plethora of evidence that adipose tissue is not just an energy reservoir for excess energy, but also an endocrine organ that has the capacity to regulate systemic metabolic homeostasis. The adipose tissue through its communication with other organs can regulate diverse processes including appetite, energy balance, insulin sensitivity, and lipid and glucose metabolism [54]. Studies of SCD1 mouse models or 3T3-L1 preadipocytes revealed that SCD1 is a key regulator of glucose and lipid

metabolism in adipose tissue. As such, adipose tissue may contribute to the metabolic phenotypes observed in SCD1 mouse models such as reduced adiposity, improved insulin sensitivity, and reduced plasma FFA levels. Indeed, SCD1 deficiency exhibited significant changes in adipose tissue-derived hormones such as adiponectin [55]. Global SCD1 deletion increased adiponectin expression in WAT and adiponectin plasma levels [55]. In mice, adiponectin has been shown to decrease hepatic lipogenesis and ameliorate hyperlipidemia [56–58]. The fact that adiponectin receptors 1 and 2 are expressed in the liver suggests that adiponectin may contribute to the negative impact of SCD1 deficiency on hepatic lipogenesis in SCD1 GKO mice. However, further studies are required to understand the contribution of plasma adiponectin to the reduction of hepatic lipogenesis in these mice.

Consistent with a prominent role of unsaturated FA in regulating glucose metabolism, it has hitherto been described that oleate may contribute to insulin resistance through suppressing glucose transporter 4 (GLUT4) and glucose transporter 2 (GLUT2) protein expression in skeletal muscle and liver cells, respectively [59,60]. Individuals with higher SCD desaturation index, MUFA-to-SFA ratio, in adipose tissue are more likely to develop insulin resistance [23]. Our group previously showed that reduced MUFA level in response to SCD1 global deletion increases insulin sensitivity and shows enhanced glucose utilization. Similar to the phenotype observed in skeletal muscle, SCD1-deficient mice exhibited increased glucose uptake and insulin signaling in brown adipose tissue (BAT) concomitant with an increase in GLUT4 expression [61]. Enhanced glucose utilization increased glycogen accumulation in BAT of SCD1 GKO mice. In addition, increased GLUT4 expression was also reported in WAT of SCD1 GKO mice [55]. It has further been proposed that decreased MUFA levels and increased insulin signaling in peripheral tissues of GKO mice are mediated through down-regulation of PTP1B. Subsequently, activated insulin signaling leads to increased GLUT4-mediated glucose uptake in peripheral tissues. Even though these findings show the impact of SCD1 deficiency on glucose metabolism in peripheral tissues, these studies were conducted in a mouse model in which SCD1 was deleted from all tissues and the relative contribution of SCD1 from individual tissues to these phenotypes is not fully understood. In addition, whether these phenotypes were caused by SCD1 deletion in the same tissue or remote tissues remained to be elucidated.

SCD1 inhibition seems to upregulate localized glucose uptake through GLUT1. In 3T3-L1 preadipocytes, inhibiting SCD1 activity increases GLUT1 expression and glucose uptake [55]. The localized effect of reduced SCD1 activity on GLUT1 expression is further confirmed in adipose tissue of adipose-specific SCD1 KO (AKO) mice, which showed increased GLUT1, but not GLUT4, expression [55]. Treating with SCD inhibitor showed no effect on insulin signaling in 3T3-L1 cells, suggesting that inhibiting SCD1 activity induces GLUT1 expression and glucose uptake in 3T3L1 preadipocytes independent of insulin signaling. Unlike SCD1 GKO mice, which exhibited increased adiponectin expression in WAT and increased adiponectin plasma levels, AKO mice showed a significant reduction of plasma adiponectin. Similarly, SCD inhibitor-treated 3T3-L1 demonstrated decreased adiponectin expression. Adipose SCD1 deletion increases GLUT1 expression in WAT of SCD1 AKO mice; however, increased GLUT4 in WAT of SCD1 GKO mice suggests that SCD1 deficiency in remote tissues may influence the WAT in a way that overcomes localized effect of SCD1 deficiency.

In obesity mouse models, the proportion of unsaturated FA in adipose tissue correlates with larger fat mass [21]. By contrast, reduced MUFA levels in SCD1-deficient mice impaired hepatic biosynthesis of TG and CE [62]. Consistently, studies of SCD inhibitor-treated 3T3-L1

cells further supported the notion of an important role of SCD1 in regulation of fat mass. Throughout preadipocytes differentiation, total cellular lipid content is increased as well as individual lipid fractions including TG, PL, and CE [63]. However, the accumulation of cellular lipid during the differentiation process is reduced in SCD inhibitor-treated 3T3L1 preadipocytes. This reduction is mainly attributed to reduced TG content [63,64]. Inhibiting SCD1 activity in differentiating 3T3L1 preadipocytes downregulated the expression of genes involved in TG biosynthesis. In addition, SCD1 inhibition resulted in increased levels of SFAs, palmitate and stearate, in different lipids species in mature 3T3-L1 adipocytes [63,64]. SFAs have lower esterification rate compared with MUFAs [65,66]. Surprisingly, *in vivo*, the effect of SCD1 deficiency on adipose tissue seems to be different. Despite reduced adipose tissue weights, SCD1 GKO mice exhibited a dramatic induction of *de novo* lipogenesis in adipose tissue without a considerable change in the expression of lipogenic genes [36]. It could be concluded that the tissue-localized effect of SCD1 deficiency leads to decreased lipogenesis as observed in the liver of LKO mice and 3T3L1 cells [30,64]. However, induced lipogenesis in WAT of SCD1 GKO mice and its suppression by oleate, in GLS5 mice, suggest that *de novo* lipogenesis in WAT is mainly regulated by hepatic oleate [36]. This is evident in LKO mice where hepatic SCD1 deficiency reduced adipose tissue weights, despite intact SCD1 expression in adipose tissue.

Concluding Remarks and Future Perspectives

The findings reported from SCD1 global or tissue-specific KO mouse models reveal a critical role of SCD1 in lipid and glucose metabolism. However, further studies are warranted to explain the exact mechanism(s) by which SCD1 regulates systemic metabolism. SCD1 global deletion leads to decreased hepatic lipogenesis concomitant with a dramatic increase in lipogenesis in adipose tissue, indicating that SCD1 deficiency may modulate lipogenesis through different signaling pathways in metabolic tissues. Lipogenesis is linked to diverse biological processes, which might somehow be impacted by FA composition changes induced upon SCD1 deficiency. Moreover, endogenously synthesized MUFAs exert systemic metabolic effects and influence metabolic functions in tissues distinct from which they are synthesized within. One model proposes that hepatic *de novo*-synthesized oleate, but not palmitoleate, acts systemically to regulate lipogenesis rate in WAT and total adiposity [37]. By contrast, adipose tissue-derived nonesterified palmitoleate represses lipogenesis in liver and reduces hepatic lipid accumulation [38]. It is still unclear whether changes in FA in response to SCD1 deficiency modulate glucose and lipid metabolism in remote tissues through a direct effect or indirectly by regulating secreted proteins from the liver and adipose tissue. Increased glucose uptake in WAT enhances CHREBP-mediated lipogenesis [67]. Therefore, increased GLUT4 in WAT of SCD1 GKO mice may explain increased *de novo* lipogenesis in these tissues, which is suppressed by endogenous hepatic oleate [36]. This may unravel a new role of hepatic oleate in regulating glucose and lipid metabolism in WAT potentially linked to the GLUT4–CHREBP axis. The activation of this axis may also contribute to enhanced systemic insulin sensitivity in SCD1 GKO mice. In addition, the exact mechanism by which increased SFA ratio in response to SCD1 deficiency enhances ER stress and PGC-1α remains to be elucidated. The fact that SCD1 deficiency upregulates PGC-1α indicates that increased SFA levels might be associated with alterations in metabolic pathways. Elucidation of these pathways will provide more insight into the mechanism(s) by which SCD1 deficiency modulates systemic homeostasis (see Outstanding Questions).

Outstanding Questions

How does global SCD1 deficiency decrease the rate of *de novo* lipogenesis in the liver and increase it in adipose tissue?

Why increased hepatic ER stress does not promote insulin resistance in SCD1-deficient mice?

How increased glucose uptake in skeletal muscle and BAT of SCD1-deficient mice feeds toward glycogen accumulation but not lipogenesis despite increased insulin signaling?

How hepatic oleate modulates glucose uptake in WAT?

How enhanced FA synthesis and oxidation in WAT affects body weight?

Is oleate a heptokine or lipokine?

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