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Review

Stearoyl-CoA desaturase and insulin signaling — What is the molecular switch?

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ABSTRACT

Increasing evidence suggests that stearoyl-CoA desaturase (SCD), the rate-limiting enzyme of monounsaturated fatty acid biosynthesis, is an important factor in the pathogenesis of lipid-induced insulin resistance. Mice with a targeted disruption of the SCD1 gene have improved glucose tolerance compared to wild-type mice, despite lower fasting plasma insulin levels. Increased SCD activity has been found in insulin-resistant humans and animals, whereas SCD1 deficiency attenuates both diet- and genetically-induced impairment of insulin action. Phosphorylation of serine and threonine residues on insulin receptor, insulin receptor substrates (IRS1 and IRS2), and on Akt has been shown to be the major step in insulin signaling that is altered due to the lack of SCD1. In this review we discuss perturbations in cell signaling and lipid metabolism cascades in insulin-sensitive tissues due to SCD1 deficiency. In particular, we address the role of cellular signaling molecules including free fatty acids, ceramides, fatty acyl-CoAs, AMP-activated protein kinase, protein tyrosine phosphatase 1B as well as of membrane fluidity. While the precise mechanism of SCD action on insulin signaling remains to be clarified, current findings on SCD point to a very promising novel target for the treatment of insulin resistance.

Rapid adaptation to a modernized lifestyle, characterized by reduced physical activity and increased consumption of highly palatable, energy-dense and low-cost food, has resulted in a dramatic rise in the incidence of overweight and obesity world-wide. Obesity increases the risk of numerous conditions that shorten the lifetime, including type 2 diabetes, glucose intolerance, dyslipidaemia, hypertension and cardiovascular disease, collectively known as the metabolic syndrome [1]. Insulin resistance, an impaired biological response to circulating insulin, is a disorder common to most of the obesity-related diseases and, as such, represents an important target of medical research.

Significant efforts are now being made to characterize the molecular mechanism of insulin resistance that could possibly lead to an effective treatment and prevention of this condition. The precise etiology of impaired insulin action in obese people is still unknown; however, an increasing body of evidence indicates that it may be associated with alterations in intracellular lipid metabolism [2,3]. Insulin-resistant humans and animals accumulate significant amounts of lipids not only in the adipose tissue, but also in liver, muscle and other peripheral tissues. Storage of even a modest caloric surplus in lean, insulin-sensitive tissues leads to insulin resistance [2,4]. Altered lipid metabolism as seen in the insulin-resistant states largely depends on the aberrant expression of genes encoding key metabolic enzymes. Consequently, several enzymes regulating lipid metabolism have been recently proposed as therapeutic targets (reviewed in [5]). One of these enzymes, stearoyl-CoA desaturase (SCD), appears to be of special significance, because SCD1 is the major gene target of leptin, which is the central mediator regulating energy homeostasis and a known insulin-sensitizer [6]. Herein we summarize recent findings on SCD and discuss possible mechanisms by which SCD1 may affect insulin signaling.

1. Lipids and insulin resistance

A primary role for elevated free fatty acid (FFA) availability in the development of muscle insulin resistance was first suggested by Randle et al. [7] based on the observation that a high plasma concentration of FFA is commonly associated with diabetes and other disorders of carbohydrate metabolism. Intramuscular lipid accumulation is now evident in a wide array of experimental models, including insulin resistance induced acutely by lipid infusion in both humans and rodents [8]. Animals representing genetic forms of obesity such as the Zucker rats [9] as well as dietary models of insulin resistance including chronically glucose-infused rats [4] and high-fat-fed rats also exhibit increased lipid accumulation [10]. Transgenic mice that lack the white adipose tissue are severely insulin resistant and demonstrate a twofold increase in muscle triglyceride content [11]. Moreover, in humans with various lipodystrophies, including the

Abbreviations: FFA, free fatty acid; FA-CoA, fatty acyl-CoA; PTP-1B, protein tyrosine phosphatase 1B; IR, insulin receptor; IRS, insulin receptor substrate; GLUT4, glucose transporter 4; AMPK, AMP-activated protein kinase; CPT1, carnitine palmitoyltransferase 1; PPAR, peroxisome proliferator-activated receptor; SCD, stearoyl-CoA desaturase; MUFA, monounsaturated fatty acid

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increasingly frequent HIV lipodystrophy syndrome, depletion of peripheral fat mass is associated with increased intramyocellular lipid content and insulin resistance [12].

Further support for the primary role of increased lipid content in the development of muscle insulin resistance is provided by the fact that lowering lipid availability is associated with an improvement in insulin action. For example, dietary lipid-induced muscle insulin resistance in rodents is relatively easily reversed by manipulations that lessen cytosolic lipid accumulation (e.g. diet change, exercise or fasting) [13]. Peroxisome proliferator-activated receptor (PPAR) agonists also lower muscle FA-CoA and enhance insulin sensitivity [14]. Activation of the AMP-activated protein kinase (AMPK) by AICAR leads to enhancement of muscle insulin sensitivity, though the involvement of altered lipid metabolism is less clear-cut especially in the case of glycolytic muscle [15]. In humans, reduction of plasma FFA levels by treatment of subjects with an inhibitor of lipolysis (acipimox) for 1 week improves insulin action, and this beneficial effect is lost if the reduction in plasma FFA is prevented by intralipid infusion [16]. Weight loss has been shown to improve whole body and skeletal muscle insulin action in obese patients and compliance to a low-fat diet confers sustained improvements in insulin action after 5 years [17]. A reduction in lipid availability and accumulation within the skeletal muscle is thought to be central to the insulin-sensitizing effects of the thiazolidinedione class of antidiabetic agents [18]. These drugs, which include troglitazone, pioglitazone and rosiglitazone, are potent and selective ligands of the transcription factor PPARγ. Agonists of PPARα, such as the fibrates and WY 14643, are potent hypolipidaemic agents and recent studies indicate that PPARα agonists can also improve insulin sensitivity in association with a decrease in muscle lipids [19].

Reduction in intramuscular lipids may also be the mechanism by which the adipose secreted proteins, leptin and adiponectin, improve insulin sensitivity [13]. In contrast to other 'adipokines' such as TNFα and resistin, which are proposed to have detrimental effects on insulin action, leptin and adiponectin enhance insulin action, and this effect is at least partly independent of their impact on food intake and adiposity [20]. A direct action of these hormones on peripheral tissues to stimulate fatty acid oxidation and depletion of the intracellular lipid stores is thought to contribute to their insulin-sensitizing effects. Activation of AMPK may play a role in this mechanism [21]. However, as reported for the cardiac muscle, adiponectin and leptin may act on fat oxidation also independently of AMPK, e.g. by stimulating expression of genes of β-oxidation [22].

A number of hypotheses have been put forward to explain the mechanism by which increased lipid availability induces muscle insulin resistance. One of the proposed possibilities is that excess lipids, particularly lipids that are deposited in insulin-sensitive cell types other than adipocytes, can inhibit insulin signaling. The precise identity of the lipid factor responsible is not known, although FFA, fatty acyl-CoA (FA-CoA), diacylglycerol and ceramide are likely candidates. By activating protein kinase C, the lipid molecules seem to reduce the activity of insulin receptor substrate 1 (IRS-1), a key component of the insulin signaling pathway [2,4]. Thus, regulators of tissue specific metabolic pathways that reduce fat accumulation in non-adipose sites are attractive candidates for novel therapeutic strategies in the treatment of insulin resistance, but are still mostly unexplored.

2. Role of stearoyl-CoA desaturase in lipid metabolism regulation

Stearoyl-CoA desaturase (SCD) is the rate-limiting enzyme catalyzing the synthesis of monounsaturated fatty acids, mainly oleate and palmitoleate, which are used as substrates for the synthesis of triglycerides, wax esters, cholesterol esters, and phospholipids [23]. Four isoforms of SCD have been identified in the mouse (SCD1-4) [24–27] and two (SCD1 and -5) in the human genome [28,29]. Human SCD1 shows 85% homology to murine SCD1 [28]. In an adult mouse, SCD1 isoform is expressed in lipogenic tissues including liver and adipose tissue. SCD2 is ubiquitously expressed in most tissues except liver, where it is only expressed at early stages of life (embryos and neonatals), and then, at the weaning age, is replaced by SCD1 [30]. SCD3 expression is restricted to the sebocytes in skin, harderian gland, and preputial gland [31], whereas SCD4 is expressed exclusively in the heart [27]. The physiological role of each SCD isoform and the reason for having multiple SCD gene isoforms that share considerable sequence homology and catalyze the same biochemical reaction are currently under investigation.

Studies on mouse strains that have a mutation in the SCD1 gene provided evidence that SCD1 is an important control point in lipid metabolism and body weight regulation [32–34]. Mice with a targeted disruption in the SCD1 gene have increased energy expenditure, reduced body adiposity, increased insulin sensitivity and are resistant to diet-induced obesity [23,33,35]. SCD1 was found to be specifically repressed during leptin-mediated weight loss, and leptin-deficient *ob*/*ob* mice lacking SCD1 showed markedly reduced adiposity, despite higher food intake [6]. In addition, SCD1 deficiency completely corrects the hypometabolic phenotype and hepatic steatosis of the *ob*/*ob* mice [6] and the low density lipoprotein receptor-deficient mice [36]. Lack of SCD1 function attenuates also fasting-induced liver steatosis in PPARα deficient mice [37]. Interestingly, liver-specific SCD1 knockout mice are protected from high-carbohydrate, but not from high-fat-diet-induced adiposity and liver steatosis [38]. The most recent study of skin-specific SCD1 knockout mice indicated the presence of a specific cross-talk between the skin and peripheral tissues in maintaining energy homeostasis [39]. While skin-specific SCD1 knockout mice display marked sebaceous gland hypoplasia and depletion of sebaceous lipids, they have significantly increased energy expenditure and are protected from high-fat-diet-induced obesity [39].

Much evidence indicates that the direct anti-steatotic effect of SCD1 deficiency stems from increased fatty acid oxidation, reduced lipid synthesis and increased thermogenesis [39–42]. The molecular mechanism of this effect is not completely understood. However, our study established that one likely mechanism is via increased activation of the AMPK pathway [40]. The anti-steatotic impact of SCD1 deficiency also involves transcriptional effects. We have shown that loss of SCD1 function down-regulates sterol regulatory element binding protein-1c, a lipogenic transcription factor, thereby reducing the expression of lipogenic enzymes such as fatty acid synthase, acetyl-CoA carboxylase, or glycerol-3-phosphate acyltransferase in liver [42,43]. SCD1 deficiency also up-regulates the expression of genes involved in fatty acid β-oxidation [44]. The mechanisms by which SCD1 deficiency leads to down-regulation of expression of genes of fatty acid synthesis and activation of genes of fatty acid oxidation are presently unknown.

3. Stearoyl-CoA desaturase and insulin signaling

Dysregulation of fatty acid and lipid metabolism influences insulin signaling at various levels, leading to impaired glucose tolerance, decreased fatty acid oxidation and glycogen synthesis, and finally resulting in insulin resistance. Given a significant role of SCD in the regulation of lipid metabolism and fat accumulation, we hypothesized that SCD might be an important factor in maintenance of insulin sensitivity.

Indeed, the whole-body glucose tolerance is much greater in SCD1−/− mice than in control animals [35]. Fasting insulin levels are lower in SCD1−/− mice on a chow diet compared with wild-type mice. On a high-fat diet, insulin levels are similar between the two groups. However, after a 30-min glucose load, both male and female SCD1−/− mice tend to have lower plasma glucose levels and show improved glucose tolerance compared with wild-type mice [35]. In addition, the glucose-lowering effect of insulin is greater in

the SCD1−/− than in wild-type mice as demonstrated by the insulin tolerance test. However, when the SCD1 mutation was introduced in mice with lipodystrophy or in leptin-deficient BTBR mice, the mutant mice had reduced insulin levels coupled with increased glucose levels, suggesting that there might be a β-cell failure. The reason for the reduced insulin levels and a possible β-cell failure is still being investigated. One possible explanation is accumulation of lipids and down-regulation of fatty acid oxidation in pancreatic β-cells [45,46].

Results from studies performed in liver-specific SCD1-knockout mice indicated an important role of hepatic SCD1 in carbohydrate induced adiposity and lipogenesis [38]. Liver-specific SCD1 deficiency caused a severe impairment of gluconeogenesis, resulting in hypoglycemia and depletion of lipogenic carbohydrate metabolites such as glucose-6-phosphate and xylulose-5-phosphate [38]. Guttierez-Juarez et al. [47] showed that a decrease in hepatic SCD1 activity can improve insulin action and can prevent diet-induced insulin resistance in rats and mice. A 5-day treatment with a sequence-specific antisense oligodeoxynucleotide (ASO) decreased liver SCD1 expression (by 80%) and total SCD activity (by 50%) in rats and mice, which completely reversed the severe hepatic insulin resistance caused by a high-fat diet. The treatment with ASO also decreased glucose production, gluconeogenesis, and glycogenolysis. Down-regulation of SCD1 also led to increased Akt phosphorylation and marked decreases in the expression of glucose-6-phosphatase and phosphoenolopyruvate carboxykinase. Protein tyrosine phosphatase 1B (PTP-1B) expression was modestly decreased in response to SCD1 deficiency, accounting in part for the increased phosphorylation of IRS1 [47]. Also, angiotensin II type 1 blocker ameliorates hepatic steatosis and insulin signaling in obese *fa/fa* Zucker rats due to suppression of SCD1 gene expression [48]. All these data support the hypothesis that SCD1 expression and activity are required for the onset of diet-induced hepatic insulin resistance.

A connection between SCD1 and insulin signaling was also observed in muscle of the insulin receptor (IR) knockout mice, where the lack of insulin action present in these animals resulted in down-regulation of SCD1, as well as in up-regulation of some signaling-related genes, such as Akt2, and of the fatty acid transporter CD36 [49]. Reversely, Voss et al. [50] showed that stable overexpression of SCD1 in muscle cells decreases tyrosine phosphorylation of IRS1 and serine 473 phosphorylation of Akt1/protein kinase B and is sufficient to impair glucose uptake and insulin signaling. Moreover, insulin-resistant skeletal muscle of ZDF rats is characterized by a specific gene expression profile with increased levels of SCD1 [50]. These observations support the hypothesis that elevated SCD1 expression in muscle is a possible cause of insulin resistance. In line with the above, studies on genetic polymorphism of human SCD showed that inherent variations in the SCD1 gene are associated with body fat distribution and insulin sensitivity [51]. Polymorphisms located in this gene cluster were genotyped in 1143 elderly Swedish men. Subjects homozygous for the rare alleles of rs10883463, rs7849, rs2167444, and rs508384 had decreased BMI and improved insulin sensitivity. The allele of rs7849 demonstrated the strongest effect on both insulin sensitivity and waist circumference, corresponding to 23% higher insulin sensitivity and 4 cm less waist circumference [51]. Moreover, recent studies on primary human myotubes of 39 metabolically characterized individuals showed that palmitate-induced inflammation, ER stress, and insulin resistance are positively correlated with myocellular SCD1 expression [52]. SCD1 was also shown to be a major gene affected by pioglitazone treatment in humans [53]. These clinical

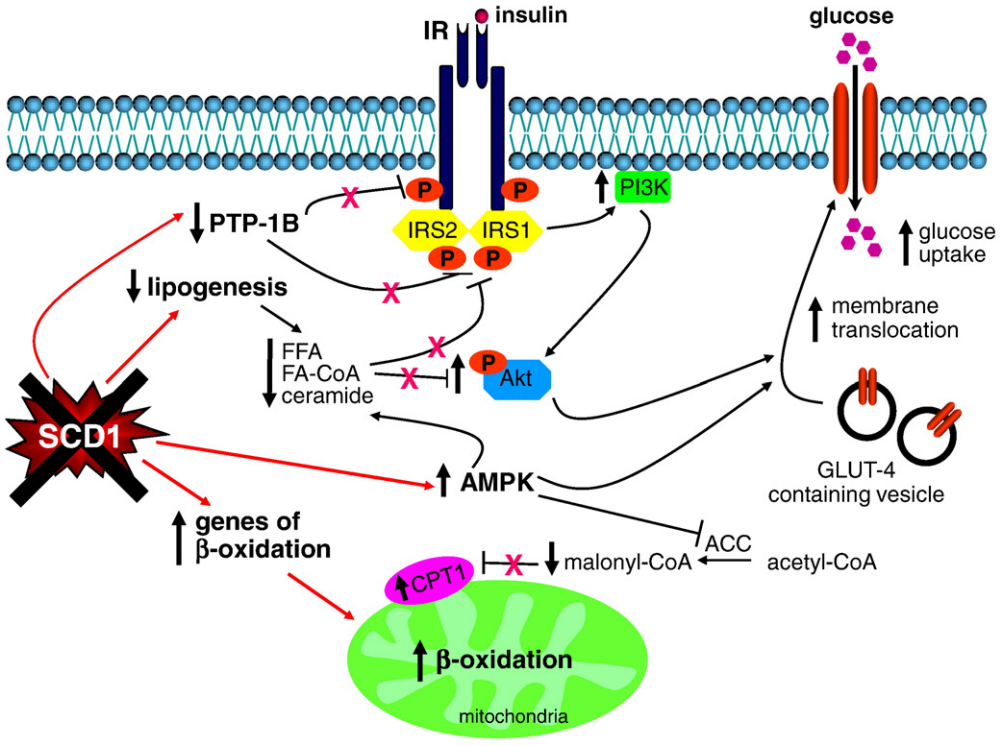

Fig. 1. The effect of SCD1 deficiency on insulin signaling — proposed mechanism. In the absence of SCD1, the expression of fatty acid oxidation genes, the activity of AMPK pathway and the rate of β-oxidation are significantly increased which, together with reduced lipogenesis, lead to a decrease in the intracellular accumulation of FFA, FA-CoA and ceramide. The reduction of the lipid content disinhibits Akt and IRSs. Also, the expression and activity of PTP-1B are decreased leading to an increase in phosphorylation of IR and IRS-1 and -2. These phenomena, together with the consequent activation of Akt kinase lead to increased GLUT4 membrane translocation and enhanced glucose transport. FFA — free fatty acids; FA-CoA — fatty acyl-CoA; PTP-1B — protein tyrosine phosphatase 1B; IR — insulin receptor; IRS — insulin receptor substrate; GLUT4 — glucose transporter 4; AMPK — AMP-activated protein kinase; ACC — acetyl-CoA carboxylase; PI3K — phosphoinositide 3-kinase; CPT1 — carnitine palmitoyltransferase 1.

trials additionally confirm the important role of SCD in regulation of insulin sensitivity.

4. How does loss of SCD1 function protect against insulin resistance?

The mechanism by which SCD1 affects insulin signaling is not completely understood. However, numerous studies established that the basal tyrosine phosphorylation of IR and of insulin receptor substrates (IRS1 and IRS2), the association of both IRS1 and IRS2 with the αp85 subunit of phosphatidyl-inositol 3-kinase, the phosphorylation of Akt and GLUT4 membrane translocation are all elevated in skeletal muscle and in the brown adipose tissue of SCD1−/− compared to wild-type mice [35,54].

There are several possible mechanisms that may account for increased insulin signaling in SCD1−/− mice despite lower level of plasma insulin. One possibility that is consistent with current results is that SCD1 deficiency leads to a decrease in the intramuscular levels of FFA, FA-CoA and ceramides (Fig. 1) [41]. Accumulation of these molecules may result in reduced IRS1 phosphorylation and Akt activity, and finally lead to impaired GLUT4 translocation to the plasma membrane, while reduction in FFA, ceramide and FA-CoA contents was shown to have an opposite effect [2,4]. Decrease in ceramide biosynthesis due to SCD1 deficiency was shown to be a consequence of 50% reduction in expression of SPT, a rate-limiting enzyme of *de novo* ceramide synthesis, in muscle of both wild-type and *ob*/*ob* mice [41]. In addition, SCD1 deficiency entails an increase in the rate of β-oxidation in skeletal muscles due to up-regulation of genes of fatty acid oxidation and through activation of the AMPK pathway [41]. AMPK inhibits acetyl-CoA carboxylase and thus reduces cellular levels of malonyl-CoA [41,55]. Malonyl-CoA is required for fatty acid biosynthesis and also inhibits the mitochondrial carnitine palmitoyltransferase 1 (CPT1) shuttle system, the rate-limiting step in the import and oxidation of fatty acids in mitochondria. A decrease in the cellular levels of malonyl-CoA in the muscle of SCD1−/− mice would thus relieve the inhibition of CPT1 and direct fatty acids into mitochondria, where they are oxidized [40] (Fig. 1). The combination of an increase in FA oxidation and a decrease in lipogenesis could account for the reduction in intracellular lipid content. It was shown that in the muscle AMPK activation attenuates insulin resistance induced by a high-fat diet [15,56]. In fat-fed rats, a single injection of 5-amino-4-imidazolecarboxamide riboside (AICAR) [15] or exercise [57], both of which increase AMPK activity, caused an increase in insulin-stimulated glucose uptake in the muscle 24 h later. AICAR has also been shown to increase insulin-stimulated glucose uptake by the muscle of control rats [15,56]. Thus, reduced contents of FFA, FA-CoA, and ceramides as well as increased AMPK phosphorylation [41] might contribute to increased insulin sensitivity in the muscle of SCD1−/− mice (Fig. 1).

SCD1 deficiency also results in down-regulation of the expression of PTP-1B, an enzyme that catalyzes rapid dephosphorylation of IR and of IRS1 and 2 [35,54]. Down-regulation of PTP-1B expression and activity is responsible for the sustained IR autophosphorylation despite reduced levels of plasma insulin in the SCD1−/− mice (Fig. 1). Insulin-mediated glucose uptake was also higher in the soleus muscle from SCD1−/− mice, suggesting that IR is more responsive to insulin in SCD1−/− than in SCD1+/+ mice [41]. Consistent with these observations PTP-1B knockout mice exhibit increased tyrosine phosphorylation of IR and IRS1 in the muscle [58]. PTP-1B−/− mice also show increased insulin sensitivity and are resistant to diet-induced obesity. Thus, the phenotypes exhibited by PTP-1B−/− mice are similar in many ways to those of SCD1−/− mice. It is not known at present whether PTP-1B is a downstream target of SCD1 expression or whether the decrease observed in its expression is a secondary consequence of altered lipid homeostasis, due to changes in intracellular lipid levels, as a result of SCD1 deficiency.

The other possible mechanism that could lead to increased insulin signaling in SCD1−/− mice is that alterations in the properties of the cell membrane, which is composed largely of lipids, activate the IR. Oleate is the major monounsaturated fatty acid (MUFA) found in membrane phospholipids, and the ratio of saturated to monounsaturated fatty acids has been implicated in alteration of membrane fluidity [31]. It is proposed that the decrease in the MUFA content of the membrane phospholipids in the SCD1−/− mice is compensated by polyunsaturated fatty acids causing an increase in membrane fluidity due to the presence of more double bonds in the fatty acyl chain. It was shown that the degree of insulin resistance in rodents and humans is inversely correlated with the amount of polyunsaturated fatty acids within the skeletal muscle phospholipids [59,60]. The increased membrane fluidity would enhance IR aggregation, thus increasing its phosphorylation upon insulin binding. More studies will, however, be required to demonstrate a direct correlation between insulin sensitivity and membrane fluidity.

Finally, one of the recent studies showed that expression of SCD1 is closely related to increased gene expression of adiponectin R2 receptor in human adipocytes [53]. It is thus possible that the metabolic effect of SCD may be partially due to increased lipogenesis in adipose tissue and potentiation of adiponectin signaling. However more work needs to be done to confirm this hypothesis.

5. Conclusion

Over the past 7 years a substantial progress has been made in identifying the physiological role of SCD. Using the knockout mouse model, we have learned that SCD1, the isoform that is most widely expressed and shows 85% homology to human SCD1, is a critical control point of lipid partitioning. While high SCD activity favors fat storage, suppression of the enzyme activates metabolic pathways that promote the burning of fat and decrease lipid synthesis. SCD1 deficiency up-regulates insulin-signaling components and affects glycogen metabolism in insulin-sensitive tissues. Phosphorylation of serine and threonine residues on IR, insulin receptor substrates (IRS1 and IRS2), and on Akt has been shown to be the major regulatory event in insulin signaling that is altered due to the lack of SCD1 function. Much evidence indicates that the insulin-sensitizing effect of SCD1 deficiency stems from increased activity of AMPK, improved β-oxidation rate, depletion of the intracellular lipid stores as well as from down-regulation of PTP-1B (Fig. 1). Increased SCD1 expression has been found in insulin-resistant humans and animals, whereas SCD1 deficiency attenuates both the high-fat-diet- and genetically-induced impairment of insulin signaling. Furthermore, exercise and several pharmacological agents and hormones, e.g. thiazolidinediones and leptin, that have been useful in treating insulin resistance, were shown to inhibit SCD1. The findings on SCD1 thus point to a potentially novel strategy for the treatment of insulin resistance. However, the potential use of an SCD inhibitor as a human therapeutic agent awaits a more complete understanding of the mechanism underlying the effects of SCD deficiency and an indication that inhibition of this enzyme is both safe and efficacious.

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