Published in final edited form as:
Curr Opin Lipidol. 2010 June ; 21(3): 192–197. doi:10.1097/MOL.0b013e32833854ac.

Stearoyl-coenzyme A desaturase 1 inhibition and the metabolic syndrome: considerations for future drug discovery

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Abstract

Purpose of review—The metabolic syndrome has become a leading health concern in developed countries. In the search for strategies to combat this growing problem, stearoyl-CoA desaturase 1 (SCD1) inhibition has been proposed as an attractive therapeutic strategy. However, recent studies warn of potentially harmful consequences of SCD1 inhibition. The purpose of this review is to discuss recent insights into the potential for SCD1 inhibitors as viable metabolic syndrome therapeutics.

Recent findings—SCD1 converts saturated fatty acids (SFAs) to monounsaturated fatty acids (MUFAs). Although SCD1 inhibition protects against diet-induced obesity, hepatic steatosis, and insulin resistance, recent studies have demonstrated that the accumulation of SCD1 substrates (SFA) can promote inflammation, atherosclerosis, steatohepatitis, and pancreatic beta cell dysfunction in preclinical rodent models. This suggests SCD1 may play a critical role in suppressing inflammatory diseases by shuttling proinflammatory SFAs into less biologically active MUFA-enriched neutral lipids. Given this, SCD1 inhibitors given in conjunction with anti-inflammatory agents may provide a useful strategy to prevent the metabolic syndrome without deleterious side-effects seen with SCD1 inhibition alone.

Summary—SCD1 inhibitors continue to hold promise as metabolic syndrome therapeutics; yet consideration must be taken to avoid the proinflammatory side-effects secondary to accumulation SCD1 substrates (SFAs).

Keywords

inflammation; metabolic syndrome; saturated fatty acids; stearoyl-CoA desaturase

Introduction

Developed countries throughout the world are now facing increased prevalence of the metabolic syndrome [1], which represents a collection of symptoms including abdominal obesity, insulin resistance, hypertriglyceridemia, hypertension, and low high-density lipoprotein cholesterol (HDL-C) levels [1–3]. Although each of these individual symptoms likely arises from distinct origins, there has been a concerted effort to identify drug targets that may comprehensively ameloriate all symptoms of the metabolic syndrome simultaneously. SCD1 inhibitors have shown promise to do just this, given that genetic deletion or pharmacologic inhibition of SCD1 improves most of the aspects of the metabolic

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syndrome in preclinical rodent models [4–6]. Simply by catalyzing the conversion of saturated fatty acid (SFA) to monounsaturated fatty acid (MUFA), SCD1 plays a gatekeeper role in partitioning endogenous and dietary fatty acids into metabolically active or inactive pools. As a result, inhibition of SCD1 results in striking protection against most aspects of the metabolic syndrome, yet promotes some inflammatory diseases. Given the fact that SCD1 inhibition has been reported to have both beneficial and detrimental effects, the purpose of this review is to discuss how SCD1 integrates aspects of the metabolic syndrome and inflammation, and to critically discuss the potential for SCD1 inhibition to become a viable and well tolerated therapeutic strategy in humans.

SCD1 and metabolic disease: the good news for SCD1 inhibitors

Since being originally identified in the late 1980s [7], SCD1 has been the focus of over 300 studies examining its critical role in lipid metabolism. Mice harboring a natural mutation in the SCD1 gene have impaired biosynthesis of hepatic triglycerides and cholesteryl esters, initially linking SCD1 function to both hepatic steatosis and hyperlipidemia [8]. Several subsequent studies have confirmed that SCD1 promotes both steatosis [9–12, 13••,14••] and hypertriglyceridemia [13••,14••,15,16]. Additionally, mice with targeted deletion of SCD1 are protected against both diet-induced and leptin deficiency-induced obesity [17,18]. In fact, down-regulation of SCD1 expression may be a critical component of leptin's potent antiobesity and antisteatotic actions [18]. SCD1 deficiency also improves glucose tolerance [17–21], which may be explained by enhanced insulin sensitivity in the liver [19], adipose tissue [22], and skeletal muscle [23]. Proof of concept that SCD1 inhibitors may be useful to combat the metabolic syndrome have come from recent studies utilizing antisense oligonucleotide (ASO)-mediated inhibition of SCD1 [13••,14••,19,24]. Collectively, these studies demonstrated that targeted inhibition of SCD1 is extremely effective in preventing diet-induced obesity, hepatic steatosis, and insulin resistance [13••,14••,19,24].

Although the protective effects of SCD1 inhibition on obesity, hepatic steatosis, and insulin resistance are quite striking, effects on plasma lipid levels in rodents have not been as remarkable. Indeed, SCD1 activity is positively correlated with plasma triglyceride levels in mice and in humans [15], yet SCD1 inhibition or deletion does not always result in lower plasma triglyceride [12,21,25]. The most striking plasma triglyceride lowering effects of SCD1 deficiency are seen in chow-fed asebia mice (the naturally occurring SCD1 mutant) [8,15], and in hyperlipidemic mice lacking the low-density lipoprotein receptor ($LDLr^{-/-}$) [13••,14••,20]. However, chow-fed mice with targeted deletion of SCD1 only have a modest reduction in plasma triglyceride when maintained on a SV129 background [10,11, 15,16], and no difference in plasma triglyceride when maintained on a C57BL/6 [12,25] or BTBR [21] background. Hence, the background strain of experimental mice and diet must be taken into consideration when examining the effects of SCD1 inhibition of plasma triglyceride. SCD1 inhibition or deficiency also has inconsistent effects on plasma cholesterol levels in circulating low and high-density lipoproteins (LDL-C and HDL-C). As for HDL-C, chow-fed asebia mice have a substantial increase in HDL-C levels [8]; yet mice with targeted deficiency of SCD1 have either normal or diminished HDL-C levels [16,21,25]. We have likewise seen that ASO-mediated inhibition of SCD1 lowers HDL-C levels in $LDLr^{-/-}$, $apoB^{100/100}$ mice [13••,14••]. However, a recent study suggests that SCD1-deficient mice treated with the liver x receptor (LXR) agonist T0901317 have significantly more HDL-C than T0901317-treated wild-type controls [16]. For LDL-C, SCD1 inhibition either has no effect [13••, 14••,20] or slightly increases LDL-C levels [12,21,25, 26]. Collectively, these mixed results demonstrate that additional work is needed to determine whether SCD1 has a role in modulating the dyslipidemia associated with the metabolic syndrome.

Although the metabolic syndrome has been the target of most SCD1 inhibitor programs, recent evidence suggests that SCD1 inhibitors may also hold promise as anticancer agents [27–35,36••,37]. In support of this, SCD1 expression and activity is increased in several human cancers, chemically induced tumors, and transformed cell lines [27–32]. It is generally agreed that SCD1 expression in these hyperproliferative models is critical for driving the terminal steps of de-novo lipogenesis to provide for increased energy needs. Using an unbiased RNAi screen, SCD1 was identified as a potent regulator of human cancer cell survival [33]. Also, specific inhibition of SCD1 impairs cancer cell proliferation, in-vitro invasiveness, and tumor formation [34,35,36••,37]. In a series of elegant studies, work from the laboratory of Ariel Igal has demonstrated that SCD1 may be required for neoplastic cells to survive lipotoxic stress, given that SCD1 inhibition augments basal apoptosis and sensitizes cancer cells to the cytotoxic effects of SFA [34]. Recent mechanistic insight has shown that cancer cells require SCD1 to complete glucose-driven lipogenesis, and SCD1 inhibition results in the activation of AMP-activated protein kinase (AMPK), thereby inactivating acetyl-CoA carboxylase to functionally impair uncontrolled proliferation [35]. Collectively, these studies suggest that SCD1 inhibitors continue to hold promise as anticancer therapeutics.

SCD1 and inflammatory disease: the warning signs against SCD1 inhibition

Although SCD1 inhibition has profoundly positive effects on many aspects of the metabolic syndrome and cancer, several recent studies have uncovered some unexpected warning signs that suggest the accumulation of SCD1 substrates (SFA) may be problematic. One major concern originates from a striking skin phenotype seen in mice lacking SCD1 [37–39]. It has been well documented that gene-targeted SCD1-deficient mice [37] and asebia 2J mice [38] have an epidermal lipid barrier dysfunction that results in accelerated transepidermal water loss. In line with this, SCD1-deficient mice have impaired cold tolerance and maladapted thermoregulation [40,41]. Recently, it has been demonstrated that a portion of the metabolic abnormalities seen in SCD1-deficient mice may arise directly from alterations in skin barrier dysfunction [41,42••]. In an important study, Sampath and colleagues [42••] demonstrated that mice lacking SCD1 specifically in the skin have increased energy expenditure and are resistant to high-fat diet-induced obesity and glucose intolerance. These results illustrate an underappreciated cross-talk between skin SCD1 and peripheral tissue in maintenance of energy homeostasis.

In addition to side-effects of SCD1 inhibition seen in the skin, we have recently uncovered an unexpected problem in the artery wall [13••,14••]. The rationale for studying effects of SCD1 on atherosclerosis originated from the fact that hepatic cholesterol esterification driven by acyl-CoA : cholesterol acyltransferase 2 (ACAT2) is intimately involved in promoting the secretion of atherogenic MUFA-rich apoB-containing lipoproteins [43–45]. Since mice lacking SCD1 have severely impaired hepatic MUFA-rich cholesteryl ester biosynthesis [8], we hypothesized that SCD1 inhibition would diminish the cholesteryl ester-driven atherogenicity of LDL-C, and therefore protect against atherosclerosis. To test this idea we utilized ASO-mediated knockdown of SCD1 in a well characterized mouse model of hyperlipidemia and atherosclerosis. In agreement with previous studies [8–12,13••, 14••,15–24], inhibition of SCD1 strongly protected against diet-induced obesity, hepatic steatosis, and insulin resistance. However, to our surprise, SCD1 inhibition dramatically augmented aortic atherosclerosis and macrophage inflammatory response [13••]. Similarly, mice with a genetic deletion of SCD1 also had increased systemic inflammation and atherosclerosis, despite being largely protected against symptoms of the metabolic syndrome [46•]. Collectively, three studies have warned strongly that inhibition SCD1 results in accelerated atherosclerosis in appropriate hyperlipidemic mouse models [13••,14••,46•]. Interestingly, there is one study that suggests SCD1 inhibition reduces atherosclerosis in

cholesterol-fed C57BL/6J mice exposed to chronic intermittent hypoxia (CIH) [47]. However, it is important to consider that this model represents a condition when plasma cholesterol levels only reached an average of 228 mg/dl, giving rise to very modest atherosclerotic lesions in the mice [47]. Hence, it is difficult to know whether these results should be applied to the typical cholesterol-driven progression of atherosclerotic lesion formation, which is primarily associated with chronic elevation of LDL-C in rodents and humans.

In addition to problems with skin barrier dysfunction and atherosclerosis, recent evidence suggests that SCD1 inhibitors may also promote pancreatic β cell death. In fact, pancreatic β cells are exquisitely sensitive to SFA-induced lipotoxicity [47–53,54•]. There is now overwhelming evidence that SFAs compromise secretory function and promote apoptosis in multiple β cell models [47–53,54•]. In an important study, Busch and colleagues [53] identified subpopulations of β cells that were resistant to SFA-induced apoptosis, and found that these SFA-resistance subpopulations gained resistance by up-regulating SCD1. Furthermore, SCD1 inhibition rendered the previously SFA-resistant cells to once again become sensitive to SFA-induced apoptosis [53]. A recent mechanistic insight suggests SCD1 may shuttle proapoptotic SFAs into less biologically active MUFA-enriched neutral lipids, thereby protecting against β cell apoptosis [54•]. Although many cell-based studies have warned that the accumulation of SCD1 substrates (SFA) may promote pancreatic β cell apoptosis, most of these warnings have not been taken seriously since mice lacking SCD1 have overall improved insulin sensitivity and glucose tolerance [13••,14••,17–23]. However, it was recently demonstrated that the warnings seen in cultured β cell models occur *in vivo*. In this study by Flowers and colleagues [21], it was shown that mice lacking SCD1 in the diabetes prone BTBR *leptin*$^{ob/ob}$ background had diminished glucose-stimulated insulin secretion and signs of SFA-induced lipotoxicity in β cells *in vivo*. Collectively, these studies demonstrate that SCD1 plays an essential role in maintaining normal pancreatic β cell function, warning against SCD1 inhibition in these critical cells.

As we move forward, it will also be important to consider other recent studies of side-effects of SCD1 inhibition seen in the liver and colon. Recently, Chen and colleagues [55] demonstrated that mice lacking SCD1 had accelerated dextran sulfate sodium (DSS) and bacterial colitis. However, a subsequent study questioned these results challenging that SCD1-deficient mice have increased fluid intake [56], which may have confounded the original study since DSS was administered via a water vehicle. Additional studies are needed to clarify whether SCD1 inhibitors affect inflammatory colitis. In the liver, it has long been thought that SCD1 inhibition would be beneficial since SCD1-deficient mice are protected against steatosis and hepatic insulin resistance [9–12, 13••,14••]. However, two recent studies demonstrate that SCD1 inhibition in the context of a very-low-fat (VLF) or methionine-choline-deficient (MCD) diet is not without consequences. When SCD1-deficient mice were fed a VLF, high-sucrose diet, a progressive phenotype of hypercholesterolemia and cholestasis was uncovered [25]. Interestingly, the hypercholesterolemia and cholestasis seen with SCD1 deficiency was corrected by supplementation with dietary unsaturated fat, but not saturated fat [25]. Results from this important study suggest that SCD1 may be conditionally essential for normal hepatocyte function when dietary unsaturated fat is limited. In another interesting study, SCD1-deficient mice were fed a MCD diet in order to study effects on steatohepatitis progression [57••]. Results from this study showed that SCD1-deficient mice fed a MCD diet had markedly increased hepatocellular apoptosis, and SCD1 inhibition sensitized hepatocytes to SFA-induced apoptotic cell death [57••]. Results from this study are strikingly similar to those discussed earlier in pancreatic β cells [47–53,54•].

Is there a unifying mechanism underlying the side-effects of SCD1 inhibition?

It is reasonable to assume that many of the side-effects seen with SCD1 inhibition may stem from the abnormal accumulation of SCD1 substrates (SFA) in multiple tissues. In fact, there is a large body of evidence that SFAs are potent proinflammatory molecules, linking these SCD1 substrates to the promotion of a number of inflammatory diseases including atherosclerosis [58], β cell dysfunction [47–53,54•], steatohepatitis [59,60], and colitis [61]. In fact, recent evidence suggests that SFAs can activate multiple toll-like receptors (TLRs), which play a key role in innate immunity [62–67]. Therefore, one of the key roles of SCD1 may be to suppress inflammation by preventing excessive accumulation of SFA-derived TLR4 ligands. Interestingly, long-chain ω-3 polyunsaturated fatty acids (ω-3 PUFA) have been shown to counteract SFA-induced TLR4 activation in cultured macrophage cell systems [63,65–67]. Therefore, we reasoned that dietary supplementation with fish oil-derived ω-3 PUFAs may prevent the SFA-driven TLR4 hypersensitivity and accelerated atherosclerosis previously seen with SCD1 inhibition in mice-fed SFA or MUFA-enriched diets [13••]. Indeed, the accelerated atherosclerosis seen with SCD1 inhibition can be completely prevented by moderate dietary fish oil supplementation [14••]. Importantly, the proinflammatory effects of SCD1 ASO treatment can be overcome by dietary ω-3 PUFA supplementation, and the dual therapy of SCD1 ASO and dietary ω-3 PUFA provides dramatic protection against atherogenesis [14••]. Therefore, this synergistic dual therapy of SCD1 inhibition in the presence of dietary fish oil may provide a novel therapeutic approach for the metabolic syndrome and atherosclerosis. Given this outcome, it is tempting to speculate that SCD1 inhibitors given in conjunction with other anti-inflammatory agents could provide useful strategies to prevent the metabolic syndrome, while avoiding deleterious side-effects stemming from the accumulation of SCD1 substrates (SFA). Additional work to formally test this possibility is required (Fig. 1).

Conclusion

The metabolic syndromehas become a major global health concern, and SCD1 inhibition shows promise as an attractive strategy to treat this complex syndrome. However, recent evidence suggests that the accumulation of SCD1 substrates (SFA), namely the saturated fatty acid products of endogenous lipogenesis, is not without side-effects. Recent evidence suggests SCD1 may play a critical role in suppressing multiple inflammatory diseases by shuttling proinflammatory SFAs into less biologically active MUFA-enriched neutral lipids. Hence, SCD1 inhibitors given in conjunction with anti-inflammatory agents such as fish oil may provide a useful strategy to prevent the metabolic syndrome while avoiding the deleterious side-effects stemming from the accumulation of SCD1 substrates (SFA). SCD1 inhibitors continue to hold promise as metabolic syndrome therapeutics, yet additional work is needed to ensure these compounds are well tolerated in the context of inflammatory disease.

Acknowledgments

The authors are supported by grants from the National Institutes of Health (NIH-1K99HL096166–01 to J.M.B. and NIH-P01-HL49373 to L.L.R), and the National Center for Complimentary and Alternative Medicine (NCCAM-P50AT002782 to L.L.R.).

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 266–267).

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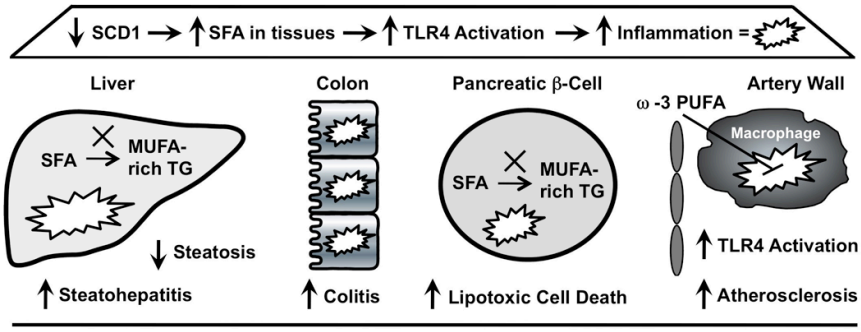

Figure 1. Proposed mechanism underlying the side-effects seen with SCD1 inhibition

Under normal conditions, SCD1 catalyzes the conversion of saturated fatty acids (SFAs) to monounsaturated fatty acids (MUFAs), which are preferred substrates for esterification into cellular triglyceride (TG). It is reasonable to assume that many of the side-effects seen with SCD1 inhibition may stem from the abnormal accumulation of SCD1 substrates (SFA) in multiple tissues. SFAs are known to promote the activation of toll-like receptor 4 (TLR4) and drive inflammation. In the liver the accumulation of SFA promotes steatohepatitis in response to a methionine-choline-deficient diet. In the colon, the accumulation of SFA promotes DSS and bacterial-driven inflammatory colitis. In the pancreatic β-cell, the accumulation of SFA results in lipotoxicity and cell death. In the artery wall, the accumulation of SFA promotes TLR4 activation in macrophages and augments atherosclerosis. Importantly, dietary ω-3 polyunsaturated fatty acid (ω-3 PUFA) supplementation can prevent the accelerated atherosclerosis seen with SCD1 inhibition in part by dampening inflammatory signaling in macrophages.