

Chapter 9

Stearoyl-CoA Desaturase-1 Activity in Skeletal Muscle: Is It Good or Bad?

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Introduction

Skeletal muscle is known to be an important site for metabolic processes such as glucose disposal and fatty acid oxidation, and, as such, dysregulation of these processes in muscle is associated with and may play a causative role in many disease states and comorbidities including obesity, hypertension, insulin resistance, and hypertriglyceridemia (Lee et al. 2003; McGarry 2002; Petersen and Shulman 2002; Scheuermann-Freestone et al. 2003). Specifically, these disease/co-morbid states are associated with dysregulated glucose and fatty acid metabolism and excess lipid accumulation in skeletal muscle (Flowers and Ntambi 2009; Kahn and Flier 2000). Studies in humans show that SCD1 is associated with insulin resistance, increased intramuscular triacylglycerol (IMTG) content, and reduced fatty acid oxidation (Dubé et al. 2011; Hulver et al. 2005). Studies in rodents clearly show that genetic deletion of SCD1 prevents high-fat diet-induced weight gain and insulin resistance (Ntambi et al. 2002). Conversely, others have suggested that heightened SCD1 activity in skeletal muscle may be protective (Dobrzyn et al. 2010; Schenk and Horowitz 2007). To date, the role of SCD1 in dysregulated metabolism, specifically in skeletal muscle, is not definitively known, as there are conflicting reports. The purpose of this chapter is to highlight the available evidence for both the deleterious and protective roles of SCD1 in the context of metabolic deranged states such as insulin resistance and obesity. The role of SCD1 in the context of inflammatory signaling and adaptation to exercise will also be touched upon.

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A Causative Role for SCD1 in Dysregulated Metabolism

Data from experiments using mouse models with whole-body deletion, a naturally occurring mutation in the gene, or through limited cell culture models with a gain or loss of SCD1 function have all provided insight into this topic; however, there is still much to be learned. Tissue specific deletion of SCD1 has contributed a great deal to the current understanding of the role of SCD1 in the modulation of whole-body metabolism (Liu et al. 2011). Currently, no data from skeletal muscle specific knockout of SCD1 has been published. Cell culture models, where studies in which SCD1 function has been interrupted in myotubes have shown a direct effect on fatty acid metabolism (Hulver et al. 2005; Kim et al. 2011; Peter et al. 2009), suggest a causative role for SCD1 in dysregulated substrate metabolism.

The Role of SCD1 in the Modulation of Substrate Metabolism and Insulin Sensitivity

Obesity is associated with ectopic lipid accumulation and insulin resistance, both of which are risk factors for the development of the metabolic syndrome and type 2 diabetes (Virtue and Vidal-Puig 2010). A majority of research has shown a causative role for SCD1 in the development of obesity, inflammation, and insulin resistance (Kim et al. 2011; Miyazaki et al. 2002; Ntambi et al. 2002; Pinnamaneni et al. 2006; Rahman et al. 2003). However, this causality as it relates to skeletal muscle has been difficult to discern. SCD1 expression is relatively low in skeletal muscle compared to other tissues such as the liver and sebaceous glands of the skin (Paton and Ntambi 2009). However, under high-fat fed conditions, rodent models of SCD1 deletion are protected from insulin resistance and possess reduced levels of intramyocellular lipid intermediates, which are known to disrupt insulin-stimulated glucose uptake (Rahman et al. 2003). Skeletal muscle is an important tissue for postprandial glucose homeostasis; 80 % of insulin-stimulated glucose uptake is accounted for by muscle tissue (Baron et al. 1988). The importance of skeletal muscle in glucose clearance taken along with current research showing a role for SCD1 in contributing to defects in insulin-signaling and glucose uptake suggest a causative role for SCD1 in mediating the alterations in metabolic function. Interestingly, mouse models with liver and/or adipose tissue specific deletion of SCD1 are not protected from the diet-induced obesity observed with the whole-body deletion of SCD1 (Flowers et al. 2012). Because the liver and adipose tissue are paramount to normal whole-body metabolic regulation and substrate homeostasis and the protective effects of high-fat feeding of SCD1 deletion at these sites are not observed, this points to SCD1 function in some other metabolically-important tissue (e.g., skeletal muscle) as the culprit for whole-body metabolic dysregulation.

SCD1 mRNA levels in skeletal muscle are elevated in the obese state and associated with dysregulated lipid metabolism (Hulver et al. 2005). Specifically, a hallmark

feature of obesity is blunted fatty acid oxidation and elevated triacylglycerol accumulation in skeletal muscle, both of which are associated with increased levels of monounsaturated fatty acids (Aguilera et al. 2008). Hulver et al. showed higher SCD1 expression in skeletal muscle of obese humans, relative to non-obese controls, which was associated with decreased AMP-activated kinase (AMPK) phosphorylation and increases in acetyl-CoA carboxylase (ACC) beta levels, both of which occurred in the context of decreased FA oxidation. Consequences of whole-body SCD1 deficiency include increased rates of fatty acid oxidation as well as a reduction in triglyceride synthesis and storage in various tissues including liver, BAT, and skeletal muscle (Flowers et al. 2008; Ntambi et al. 2002; Sampath and Ntambi 2011). SCD1 deficiency appears to increase the rates of FA oxidation in a muscle-fiber type-dependent manner as rates of FA oxidation were increased with SCD1 deficiency in soleus and gastrocnemius, oxidative and oxidative/glycolytic fiber types, respectively (Dobrzyn et al. 2005). Conversely, rates of fatty acid oxidation were not observed in white gastrocnemius or extensor digitorum longus, which are primarily glycolytic fiber types (Dobrzyn and Dobrzyn 2006).

The mechanism by which SCD1 deletion increases FA oxidation is thought to be dependent on AMPK signaling (Dobrzyn et al. 2004a; Kim et al. 2011). It was shown by Dobrzyn et al. that increased AMPK signaling caused a decrease in ACC activity with subsequent reductions in cytosolic malonyl-CoA levels. Malonyl CoA inhibits carnitine palmitoyl transferase 1 (CPT1), which has a primary function of shuttling FA into the mitochondria for oxidation (Hardie and Pan 2002). These findings in SCD1 KO mice are similar to other models in which AMPK signaling is up-regulated (Tomas et al. 2002; Yoon et al. 2006). A similar study in which C2C12 myotubes were treated with the SCD1 inhibitor, 4-(2-chlorophenoxy)-*N*-(3-(methylcarbamoyl)-phenyl) piperidine-1-carboxamide, showed a decrease in ACC and fatty acid synthase (FAS) expression and increase in expression of (CPT1), alternative oxidase (AOX), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1- α) (Kim et al. 2011).

Altered levels of SCD1 expression in skeletal muscle can also have effects on the synthesis sphingolipids molecule, ceramide. Ceramide synthesis occurs through either a de-novo process involving esterification of palmitoyl-CoA and serine by serine palmitoyl transferase (SPT) or through the hydrolysis of sphingomyelin (Menaldino et al. 2003; Perry 2002). Ceramide is known to play a role in apoptosis and insulin resistance through the modulation of intracellular signaling processes (Blázquez et al. 2001; Shimabukuro et al. 1998). In particular, increases in substrates for ceramide synthesis such as FFAs have been shown to contribute to β -cell apoptosis (Shimabukuro et al. 1998). SCD1 KO mice show a 42 % and (Hayashi et al. 1998) 48 % decrease in ceramide content in soleus and gastrocnemius. In addition, sphingomyelin content was significantly reduced (~30 %) in the soleus and gastrocnemius muscles of SCD1 KO compared to their WT counterparts, with no changes in the mRNA levels of the sphingomyelinases. This suggests a limited role for SCD1 specifically in sphingomyelin hydrolysis (Dobrzyn and Dobrzyn 2006). Expression of SPT and ceramide are regulated by many factors including intracellular FA content. As such, SCD1 activity may be very important in the modulation

of ceramide-mediated effects on apoptotic processes and the inhibition of signaling events that contribute to insulin resistance.

One factor shown to down-regulate ceramide synthesis is AMPK signaling. This was shown through the use of the ribonucleoside AICAR that stimulates AMPK activity (Hayashi et al. 1998). As stated previously, AMPK signaling has been shown to be responsible for the up-regulation of FA oxidation shown with SCD1 KO mice. Treatment with AICAR resulted in significant decreases in palmitate-induced ceramide synthesis (Blázquez et al. 2001). Another FA and product of SCD1, oleate, has been shown to down-regulate ceramide levels, and this appears to occur through prevention of the generation and/or the scavenging of ceramide molecules (Listenberger et al. 2003). These data suggest that deletion of SCD1 has beneficial effects on cellular signaling processes through increases in AMPK activity and decreases in transcriptional events regulating lipogenic processes.

A consequence of abnormalities in lipid metabolism such as intramyocellular fat accumulation and increased FFA flux in skeletal muscle is insulin resistance (Kahn and Flier 2000; Kelley and Goodpaster 2001; Liu et al. 2007; Roden 2004). Dysregulated lipid metabolism disrupts insulin-signaling and the normal process of glucose transporter 4 (Glut4) translocation to the cellular membrane, and thus, reduces insulin-stimulated glucose uptake (Savage et al. 2007). Lipid metabolites such as ceramide and diacylglycerol can lead to endoplasmic reticulum stress that can cause serine/threonine phosphorylation of the insulin receptor as well as activation of inflammatory pathways (Könner and Brüning 2011; Peter et al. 2009). Decreases in expression of protein tyrosine phosphatase 1-beta (PTP-1b) expression can cause dephosphorylation of the insulin receptor. It can also lead to an inability of the insulin receptor to bind substrates, and through changes in membrane fluidity, it can affect aggregation of the insulin receptor. These effects have been shown to contribute to insulin insensitivity (Dobrzyn and Dobrzyn 2006). Increased SCD1 expression has been shown to induce the changes in FA composition that can affect insulin sensitivity particularly through an increase in the lipid products of SCD1 activity (Attie et al. 2002; Houdali et al. 2003; Warensjö et al. 2009). These lipid products are able to exert deleterious effects on the insulin-signaling machinery that can cause decreases in insulin sensitivity.

As previously stated, models with a disruption in whole-body or skin SCD1 gene expression show improvements in whole-body glucose and insulin tolerance when compared to WT counterparts on the same high-fat diet (Brown and Goldstein 1998; Flowers et al. 2008; Miyazaki et al. 2009; Ntambi et al. 2002). Specifically, KO mice in these studies show improvements in their fasting insulin levels and when put on a high-fat diet, KO mice have an increased ability to clear glucose compared to their WT littermates (Ntambi and Miyazaki 2004). These mice are also resistant high-fat diet induced obesity, which is related to increases in FA oxidation. Increases in FA oxidation lead to decreases in lipid metabolites such as ceramide and fatty acyl CoAs, metabolites that are known to activate protein kinase C (PKC), which has negative effects on the insulin-signaling machinery such as decreased AKT and IRS1 phosphorylation (Geraldes and King 2010; Turban and Hajduch 2011). Along the same line of thought, insulin-resistant, ob/ob mice given the SCD1 inhibitor sterculic acid,

showed improvements in glucose tolerance, which was associated with decreases in both 16:0/16:1 and 18:0/18:1 desaturase indices (Ortinau et al. 2013).

The mechanism by which SCD1 is able to exert these effects on glucose tolerance appears to be through changes in the cell's normal response to glucose. This appears to include, in addition to the above-mentioned mechanisms, a negative influence on the intracellular Glut4 machinery responsible for glucose uptake, particularly under insulin-stimulated conditions (Rahman et al. 2003; Voss et al. 2005). When subjected to over-expression of SCD1, rat myoblasts show a 1.75-fold decrease in total Glut4 levels. These decreases track with suppressed basal and insulin-stimulated glucose uptake measured by 2-deoxyglucose uptake experiments (Voss et al. 2005). Additionally, mice with a deletion of SCD1 show increases in Glut4 levels that occur along with increases in glucose uptake compared to WT mice (Rahman et al. 2003). Whereas SCD1 can negatively influence the insulin receptor and its ability to bind substrate, it can also affect important downstream molecules such as Glut4. Most likely these negative influences on the downstream molecules such as Glut4 are occurring through a mechanism by which upstream molecules such as AKT are inhibited (Dobrzyn et al. 2005).

Another molecule thought to be modulated by SCD1 activity in skeletal muscle is the PTP-1b. This molecule is responsible for the rapid dephosphorylation and subsequent down-regulation of insulin receptor function as well as that of the insulin receptor substrates 1 and 2 (Rahman et al. 2003, 2005). This has been shown through the use of PTP-1b KO mice that have an increase in IR tyrosine phosphorylation in muscle (Elchebly et al. 1999). PTP-1b is down-regulated with SCD1 deletion, and this leads to the autophosphorylation and sustained activity of the insulin receptor. This was associated with increases in insulin-stimulated glucose uptake, and these changes were shown to be independent of circulating insulin levels (Rahman et al. 2003). As of yet, it isn't understood whether the changes in PTP-1b are a direct consequence of decreases in SCD1 activity or a consequence of the alterations in lipid metabolism caused by a lack of SCD1.

There are data showing up-regulation of SCD1 in the presence of certain dietary factors other than fatty acids. Diseases such as type 2 diabetes have been shown to be caused by diets high in carbohydrates (Flowers and Ntambi 2009). High levels of dietary carbohydrates including glucose, sucrose, and fructose significantly up-regulate the expression and activity of SCD1 (Hasty et al. 2000; Matsuzaka et al. 2004; Miyazaki et al. 2004). In the case of a 6-month diet consisting of high sucrose levels, there is a significant increase in levels of oleic acid, the product for SCD1 (Brenner 2003). Excess carbohydrates are metabolized and acetyl-CoA levels rise beyond that needed for ATP production. This results in increased de novo lipid synthesis, which is transcriptionally controlled by lipogenic transcription factors such as SREBP1c and positive modulation SCD1 expression (Hasty et al. 2000; Paton and Ntambi 2009). Rats fed a diet high in glucose show an up-regulation of SCD1 levels (Houdali et al. 2003), and muscle cells treated with high levels of glucose show a very similar effect (Voss et al. 2005).

Another mechanism by which altered SCD1 activity can lead to changes in insulin sensitivity is through its regulation of membrane fluidity; this occurs through the

alteration of the FA composition of the cell membrane (Agatha et al. 2001; Ntambi 1999; Storlien et al. 1996). The ratio of saturated to monounsaturated fatty acids is the major determining factor of membrane fluidity and has been shown to influence insulin signaling. This is related to the amount of polyunsaturated FAs present (Ntambi and Miyazaki 2004). In SCD1 KO models, a decrease in monounsaturated FA content of membranes is met with an increase in polyunsaturated FAs in order to maintain membrane integrity (Ntambi and Miyazaki 2004). This causes increased membrane fluidity, which can lead to aggregation of the IR and subsequent hyperphosphorylation of the IR in response to insulin (Frangioudakis et al. 2010; Lamping et al. 2013) Therefore, data has shown a direct correlation between increases in PUFA content of membranes and the degree of insulin resistance in these same tissues (Dobrzyn and Dobrzyn 2006).

SCD1 and Inflammation

SCD1 has also been shown to play a role in the pro and anti-inflammatory processes that are associated with metabolic disease. Free fatty acids are known to activate pro-inflammatory pathways (Boden et al. 2005; Shi et al. 2006). The substrates as well as the products of SCD1 have been shown to both stimulate and inhibit an inflammatory response (Fessler et al. 2009; Kim and Sears 2010). Specifically, the fatty acid product of SCD1, palmitoleic acid, has been shown to bind to and activate inflammatory signaling pathways (Staiger et al. 2006; Weigert et al. 2004). Palmitoleic acid initiates an inflammatory response through binding of the toll-like receptor 4 and the subsequent activation of the nuclear factor kappa beta (NF κ B) transcription factor and stimulation of the machinery involved in initiating inflammatory pathways (Schäffler et al. 2006). NF κ B causes the production and activation of inflammatory cytokines, chemokines, and other various inflammatory molecules that can function to inhibit insulin-signaling processes (Hotamisligil 2006; Shoelson et al. 2006; Wellen and Hotamisligil 2005). Free fatty acids such as palmitoleate can also bind to various G-protein coupled receptors that can cause an inflammatory response and down-regulation of the insulin-signaling machinery (Talukdar et al. 2011). In humans, increases in SCD1 activity measured by increases in plasma stearic to oleic acid ratios have been positively correlated with elevated whole-body C-reactive protein, a marker for inflammation (Black et al. 2004; Stryjecki et al. 2012). Research pertaining to an anti-inflammatory role for these substrates and products of SCD1 centers around studies showing that treatment with these molecules can have protective roles against an inflammatory response (Grimble and Tappia 1998; Vassiliou et al. 2009). Similarly, the substrates for SCD1 such as palmitate show a pro-inflammatory role that also appears to function through a TLR4-dependent mechanism (Kim et al. 2007). Mice given diets high in saturated fats such as palmitate show increases in various inflammatory markers including NF κ B (Kim et al. 2007; Suganami et al. 2007).

The increases in plasma fatty acids shown with obesity have been shown to cause defects in insulin signaling (Roden et al. 1996). Excess FFAs are able to affect

insulin signaling through their ability to elicit an inflammatory response (Eizirik et al. 2008). Both stearate and palmitate are strong inducers of an inflammatory response and are tightly controlled by SCD1 as they are its primary substrates (Miyazaki and Ntambi 2003). There appears to be an interesting phenomena relating to the role of SCD1 in modulating inflammation. Evidence exists that SCD1 activity can control the activation of inflammatory pathways that can be causative of problems, especially insulin resistance. The question remains whether this controlling force is by activation or deactivation of these pathways. Mice treated with antisense oligonucleotides (ASO) to inhibit SCD1 show marked increases in saturated fatty acid accumulation in plasma and tissues when fed a westernized high-fat diet. These increases are also demonstrated in macrophages, and these show concomitant increases in TLR4 inflammatory gene expression (Brown et al. 2008). Another model in which mice are deficient in both SCD1 and the low-density lipoprotein receptor shows improvements over control littermates in their metabolic characteristics when given a westernized diet; however, these mice also show a similar increase in inflammation to the Brown et al. study (MacDonald et al. 2009). Saturated FAs have been shown to induce macrophage inflammation through a TLR4-dependent mechanism and ASO treated macrophages show a marked hypersensitivity to TLR4 agonist (Brown et al. 2008; Shi et al. 2006; Suganami et al. 2007). It has been demonstrated previously that macrophage infiltration into adipose and skeletal muscle, and subsequent activation by FFAs can mediate the inflammatory response that can be causative of skeletal muscle insulin resistance (Hevener et al. 2007; Odegaard et al. 2007). This would support a protective role for increases in SCD1 activity. Evidence also exists showing a role for DAG and ceramide in mediating an inflammatory response (Bilan et al. 2009; Holland et al. 2011). Along with this, research using exercise and models with over-expression of SCD1 in skeletal muscle has suggested a role for SCD1 in protecting the body against many of the negative effects of lipid intermediates and alterations in lipid metabolism as they relate to inflammatory pathway activation (Dobrzyn et al. 2010; Schenk and Horowitz 2007). This includes research showing improvements in metabolic outcomes that track with increases in SCD1 levels and activity (Dubé et al. 2008; Peter et al. 2009).

Interestingly, these findings have not been universal as certain models of SCD1 deficiency have shown improvements in inflammatory and stress responses (Liu et al. 2011). Those models that show deleterious effects SCD1 include studies of mice fed a high saturated diet where SCD1 expression and activity correlate with decreased insulin responsiveness (Lee et al. 2006). However, this was shown without studying activation of inflammatory markers. When SCD1 expression was knocked out in two mouse models of obesity, there were marked reductions in adipose tissue-derived inflammatory markers when compared to control mice. This was associated with improvements in basal insulin signaling (Liu et al. 2011). This suggests a possible mechanism by which SCD1 is influencing circulating FA composition and thus contributing to the chronic low-grade inflammation that is characteristic in the obese insulin-resistant state.

With all of this taken into consideration, it is possible that the involvement of SCD1 in these inflammatory processes is cell and model dependent. In models

where the substrates for SCD1 are causing pro-inflammatory responses, SCD1 could have a protective effect by removing these substrates. In the cases where 16:1 or 18:1 fatty acids are causing a similar response, it is possible that SCD1 is contributing to the defect.

A Protective Role for SCD1

While there is considerable evidence for a causative role of SCD1 in the metabolic syndrome and its related comorbidities, there appears to be a collection of research showing SCD1 as a much needed and protective molecule. Both over-expression and exercise models have demonstrated a protective capacity for SCD1 (Dubé et al. 2011; Listenberger et al. 2003; Pinnamaneni et al. 2006). Research in this area has shown, both in rodent and human models, that there are improvements in FA partitioning and oxidation that are dependent on increases in SCD1, and that these lead to positive changes in glucose clearance (Amati et al. 2011; Dobrzyn et al. 2010; Dubé et al. 2008). This leads to the belief that SCD1 may be a double-edged sword capable of both protective and harmful effects. As with the causative mechanisms shown for SCD1 in skeletal muscle, the protective mechanisms seem to differ depending on the specific comorbidity.

Dysregulated Lipid Metabolism and Insulin Resistance

Obese individuals present with increased expression and activity of SCD1 in skeletal muscle that relates to higher rates of IMTG synthesis. Acute and chronic bouts of endurance exercise show a similar phenotype to this in regards to levels of SCD1 (Amati et al. 2011; Dobrzyn et al. 2010; Dubé et al. 2008; Schenk and Horowitz 2007). These alterations appear to be dependent on the muscle-fiber type as these changes have been observed in oxidative, but not glycolytic muscles (Dobrzyn et al. 2010). This follows suit with data showing that when SCD1 is overexpressed in a CHO cell line there is a significant increase in TG synthesis (Listenberger et al. 2003). Over-expression of SCD1 in the L6 muscle cell line exhibits beneficial metabolic effects as they relate to glucose clearance. When treated with palmitate, the cells over-expressing SCD1 showed improvements in triacylglycerol synthesis, which attenuated ceramide and diacylglycerol synthesis that protected against insulin resistance (Pinnamaneni et al. 2006). These opposing data suggest that changes in SCD1 expression can have an important role in glucose clearance, but then it must also be tightly regulated to avoid metabolic consequences. There have also been mouse models supporting this hypothesis (Dobrzyn et al. 2005, 2010). In terms of causation, it is known that SREBP-1 may be central to the up-regulation of SCD1 under exercised conditions (Hodson and Fielding 2013; Sekiya et al. 2003). Data exists showing increases in this transcription factor under exercise conditions with

both mice and humans that is associated with increases in SCD1 and IMTG production (Bergman et al. 2010; Ikeda et al. 2002). Thus it is likely that SREBP1c is functioning in both the deleterious and protective roles for SCD1. There is also data suggesting that FAS may have roles in regulating SCD1 under these conditions. FAS synthesizes palmitic acid de novo, a substrate for SCD1 (Conraads et al. 2002; Mooren et al. 2004). It has been shown that increases in the substrate for SCD1 leads to up-regulation of SCD1 protein levels (Thorn et al. 2010).

In terms of a protective mechanism(s), data suggests a role for SCD1 in alleviating the stressful conditions caused by the overabundance of FA. Exercise studies have shown a role for SCD1 in enhancing the partitioning of FA into IMTG, as well as an increase in the movement of FA into the mitochondria for beta-oxidation (Dobrzyn et al. 2010). Dobrzyn et al. showed a significant increase in the expression of proteins involved in the movement of FA in to the mitochondria in mice in response to an endurance exercise protocol. Work by Schenk and Horowitz has demonstrated that an acute bout of exercise (1 h running on a treadmill) prior to being challenged with a lipid infusion was sufficient to increase TAG synthesis. These changes were characterized by increased SCD1 expression and concomitantly reduced DAG and ceramide production (Bergman et al. 2010; Bruce et al. 2006; Dubé et al. 2008). Certain studies have shown increases in DAG with exercise protocols whilst others have shown decreases (Dobrzyn et al. 2010). Schenk et al. was able to show significant increases in DAG content of soleus muscles after a 12-week treadmill running program in mice. Bioactive sphingolipids, such as ceramides, are affected by exercise regimens. Decreases in ceramide content in skeletal muscle have been shown, both in mice and in humans (Amati et al. 2011; Bruce et al. 2006; Dobrzyn et al. 2004b). These changes in lipid intermediates relate to changes seen in the local environment of skeletal muscle under exercised conditions. Adaptation to exercise by skeletal muscle entails both increasing lipogenic activity and oxidative capacity. The increased lipogenic activity serves the purpose of providing ample IMTG to provide a local fuel source of fatty acids to be oxidized in the mitochondria during exercise as well as during the postexercise recovery period. The increased oxidative capacity allows the muscle tissue to predominantly rely on fatty acids as an energy source, as this is the most efficient fuel for ATP production. It has been discussed previously that SCD1 KO mice show increases in AMPK phosphorylation, leading to increases in beta-oxidation. Along these same lines, there are increases in the ability and capacity for oxidizing fatty acids during and after endurance exercise; this appears to be through an AMPK-dependent mechanism (Bruce et al. 2006; Dobrzyn et al. 2010; Russell et al. 2003). Various exercise models using both animals and humans have shown increases in AMPK activity that correlate with increases in FA oxidation (Dobrzyn et al. 2010; Dubé et al. 2008; Schenk and Horowitz 2007). These increases in FA oxidation are shown along with increases in the activity of SCD1. Being that SCD1 is playing a prominent role in the shuttling of monounsaturated FA into TG synthesis (Paton and Ntambi 2009), and these TG are being hydrolyzed to allow influx of FA into the mitochondria, it is possible that SCD1 is playing a role in controlling FA oxidation, particularly the increases seen with endurance exercise.

This data also appears to be supported in humans. Multiple studies in human subjects have shown increases in IMTG that track with increases in SCD1 (Amati et al. 2011; Bergman et al. 2010). Bergman et al. showed that endurance-trained male cyclists have greater skeletal muscle IMTG and SCD1 mRNA expression and protein content than controls. This would suggest that high muscle SCD1 activity is an advantage for these individuals. In addition, Amati et al. showed increases in SCD1 content that was related to increases in IMTG in endurance-trained athletes. These individuals exhibited decreases in both ceramide and diacylglycerol content compared to sedentary counterparts. These data suggest a protective mechanism for SCD1 and a role for SCD1 in mediating the beneficial metabolic changes seen with exercise regimens.

The changes in FA partitioning towards oxidation and away from storage shown with the above models have also shown improvements in glucose tolerance (Amati et al. 2011; Bergman et al. 2010). Whereas increases in IMTG are correlated with insulin resistance in diseased states, in exercised states it has been shown that increases in IMTG are related to improvements in many metabolic characteristics including insulin sensitivity. This implies a certain paradox in which increases in IMTG can either be beneficial or harmful. Supporting this is research that shows individuals who are endurance trained have increased IMTG and increased mitochondria as well as increased insulin sensitivity compared to sedentary individuals. Initially, it was suspected that these changes in insulin sensitivity due to IMTG increases with endurance exercise were related to the removal of harmful lipid intermediates. However, more recent research has shown this may not be true as sedentary and exercised individuals show similar DAG content as well as reduced ceramide content in skeletal muscle (Amati et al. 2011). It is thought that neutral lipid synthesis, instead of concentration of lipid intermediate, may be causing the improvements in insulin sensitivity; that is enhanced clearance of intermediates into synthetic pathways. Research in this area has also shown a role for increases in FA partitioning into IMTG in reducing the inflammatory response seen in insulin-resistant situations (Schenk and Horowitz 2007). This is due to both the removal of pro-inflammatory FFA as they are partitioned into IMTG as well as the removal of lipid intermediates that can lead to activation of inflammatory responses (Schenk and Horowitz 2007).

Conclusions/Future Directions

At this time, knowledge regarding the exact role for SCD1 in mediating metabolic disease in skeletal muscle is lacking. It has been shown that decreases in the expression and activity of SCD1 track with improvements in various metabolic characteristics, including obesity/lipid partitioning as well as insulin resistance and inflammation. While obese and diabetic states both show increases in IMTG and concomitant increases in SCD1, the skeletal muscle of trained individuals also show similar effects. This begs the question, can SCD1 activity be both helpful and harmful.

In skeletal muscle, there appears to be a role for SCD1 in controlling the phosphorylation state of AMPK and subsequently for regulating FA oxidation. However, there are similar effects on AMPK when SCD1 is increased in exercising individuals. Either way, SCD1 appears to have direct effects on the insulin-signaling machinery through its effect on AMPK and the exact mechanism warrants further investigation. There also appears to be a role for SCD1 in controlling the expression of PTP-1b and its role in down-regulation of the insulin receptor and its substrates. PTP-1b appears to decrease with suppression of SCD1 activity and could be causative of the improvements shown in these models. This also warrants further investigation. Thirdly, a mechanism for SCD1 in either causing or suppressing an inflammatory response has been shown. This will become an important area of research as inflammatory processes are involved in many of the chronic diseases related to skeletal muscle metabolism.

Data demonstrates that there is a role for SCD1 in the modulation of skeletal muscle metabolism. However, there is disagreement whether this role is as a protective molecule preventing many of the aberrations caused by dysfunctional lipid metabolism, or whether SCD1 is a contributing factor whose malfunctioning activity is causing disease. It appears as though SCD1 may function on both sides of the argument, and this may be related to the particular metabolic environment by which SCD1 is being regulated. Research using skeletal muscle specific KO would allow for a better understanding of the molecule and its influences on the development and progression of metabolic disease. Of particular interest would be how these mice would adapt to endurance exercise. It is possible that these animals would have a decreased oxidative capacity and therefore a decreased ability to perform aerobic exercise. However, it is also possible that these animals would exhibit compensatory mechanisms that allow them to maintain correct handling and oxidation of FAs. Another research question involving a skeletal muscle SCD1 KO would be how these animals would adapt to a HF diet. It is possible that these animals would exhibit a phenotype similar to SCD1 KO in other tissues such as skin and liver in regards to insulin sensitivity given skeletal muscle's importance in whole-body glucose clearance and thermogenesis.

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