The role of stearoyl-CoA desaturase in the regulation of cardiac metabolism

Sabina Tabaczar

Marcin Wołosiewicz

Anna Filip

Adam Olichwier

Paweł Dobrzyń✉

Laboratory of Molecular Medical Biochemistry, Nencki Institute of Experimental Biology, Warsaw, Poland

✉Laboratory of Molecular Medical Biochemistry, Nencki Institute of Experimental Biology of Polish Academy of Sciences, Warsaw, Poland, 3 Pasteura St., 02-093 Warsaw, Poland; phone: +48 (22) 589 24 59, e-mail: p.dobrzyn@nencki.gov.pl

Received: July 25, 2018

Accepted: August 13, 2018

Key words: fatty acids, glucose utilization, heart failure, hypertrophy, ceramide

Abbreviations: ACC – acetyl-CoA carboxylase; AMPK – adenosine monophosphate-activated protein kinase; ATGL – adipose triglyceride lipase; CPT1 – carnitine palmitoyltransferase; FA – fatty acid; FAS – fatty acid synthase; HSL - hormone-sensitive lipase; PPAR – peroxisome proliferator-activated receptor; SCD – stearoyl-CoA desaturase; SREBP – sterol regulatory element binding protein

Acknowledgments: This work was supported by grants from the National Science Center, Poland (UMO-2014/13/B/NZ4/00199 [PD], UMO-2016/22/E/NZ4/00650 [PD], UMO-2017/26/D/NZ4/00696 [AF], and UMO-2017/27/N/NZ4/01995 [AO]) and by the European Union's Horizon 2020 research and innovation program under Marie Sklodowska-Curie grant agreement no. 665735 (Bio4Med) and by funding from the Polish Ministry of Science and Higher Education as part of 2016-2020 funds for the implementation of international projects (agreement no. 3548/H2020/COFUND/2016/2).

ABSTRACT

The uptake and utilization of energetic substrates in the myocardium are under strict control, any disturbances of which may lead to myocardial dysfunction, such as in the case of ischemia and heart failure. Stearoyl-CoA desaturase (SCD) is an enzyme that converts saturated fatty acids to monounsaturated fatty acids. It is an important player in the regulation of heart metabolism. Our previous studies showed that SCD1 affects substrate utilization by the heart, with a preference for glucose. Large cohort studies established a positive correlation between the plasma fatty acid desaturation index and cardiovascular disease mortality. Therefore, SCD1 might serve as a potential target for future therapies. We review recent findings on the role of SCD1 in the heart, with a focus on cardiac metabolism reprogramming and its involvement in heart dysfunction.

INTRODUCTION

Cardiovascular disease (CVD) is responsible for 3.9 million deaths in Europe [1] and approximately 800,000 deaths in the United States [2] annually. It remains the leading cause of death and long-term disability on both continents. Changes in lifestyle and diet (i.e., an increase in the consumption of processed food products) as a consequence of progressive industrialization coincide with a higher risk of developing CVD [3]. Although still debated, one of the dietary recommendations that seeks to lower the incidence of coronary heart disease is the replacement of saturated fatty acids (SFAs) with monounsaturated fatty acids (MUFAs) or polyunsaturated fatty acids (PUFAs) [4]. The fatty acid (FA) profile of an individual is influenced by dietary fat intake and the action of endogenous enzymes that participate in FA metabolism, especially those that are involved in the desaturating reaction (e.g., stearoyl-CoA desaturase; SCD) [5,6]. The desaturase index reflects the substrate-to-product ratio. It has been used as an indirect measure of the action of SCD and is a useful tool for assessing the risk of cardiovascular mortality [7]. A correlation was found between an elevated plasma palmitoleate (16:1n-7)-to-palmitate (16:0) ratio (i.e., an indirect indicator of SCD activity) and a higher occurrence of heart failure [8]. Another study found an association between the plasma desaturation index and heart rate, linking the action of this enzyme with arrhythmia and cardiovascular mortality [9]. A recent study of the Chinese population that included 2447 participants linked high 16:0 and 16:1n-7 levels with hypertension [10]. High SCD activity is associated with metabolic syndrome, a set of metabolic abnormalities that correlate with a higher risk of CVD, in both adults [6] and children [11]. Data that suggest that the FA ratio is an indicator of SCD activity have not been validated against any specific measure of enzyme activity. Therefore, any link between these two should be considered with caution [12]. Nonetheless, the FA ratio and SCD activity are postulated to be valuable for the assessment of CVD risk, suggesting an important role for SCD in the regulation of heart metabolism. Research that seeks to decipher the actions of SCD may have clinical importance. The present review discusses recent findings on SCD in terms of cardiac metabolic reprogramming.

STEAROYL-COA DESATURASE STRUCTURE AND FUNCTION

Stearoyl-CoA desaturase is a transmembrane protein that is localized in the endoplasmic reticulum. It catalyzes the biosynthesis of MUFAs via the desaturation of SFAs, which are synthesized *de novo* or supplied in the diet. Stearoyl-CoA desaturase catalyzes the reaction of introducing a single double bond during *cis*-formation between the 9th and 10th carbon atoms of long-chain fatty acyl-CoA (Fig. 1). Thus, SCD is also referred to as Δ9-desaturase. Palmitoyl-CoA (16:0) and stearoyl-CoA (18:0) are the most often utilized reaction substrates, which are converted to palmitoleoyl-CoA (16:1) and oleoyl-CoA (18:1), respectively [13]. Monounsaturated fatty acids are important substrates for the synthesis of

triglycerides (TGs), cholesterol esters, phospholipids, and wax esters [14]. Intracellular levels of MUFAs influence membrane fluidity, signal transduction, cell growth, and cell differentiation [15]. Excessively high levels of MUFAs can induce tumorigenesis [16]. Stearoyl-CoA desaturase has three conserved histidine motifs that are responsible for binding Fe^{2+}, which is required for electron flow [17,18]. Desaturation is an aerobic process that requires oxygen as a final electron acceptor and NAD(P)H as a donor of electrons. The electrons flow through cytochrome b5 reductase (FADH2), to cytochrome b5, to SCD, and finally to O_2, which is reduced to H_2O [18] (Fig. 1).

Studies of mouse strains that have a mutation of the SCD1 gene provided evidence that SCD1 is an important control point in lipid metabolism and body weight regulation [19]. Mice with targeted disruption of the SCD1 gene exhibited higher energy expenditure, lower body adiposity, and higher insulin sensitivity and were resistant to diet-induced obesity [18]. SCD1 was found to be specifically repressed during leptin-mediated weight loss. Leptin-deficient ob/ob mice that lacked SCD1 exhibited markedly lower adiposity, despite higher food intake [20]. Additionally, SCD1 deficiency completely reversed the hypometabolic phenotype and hepatic steatosis in ob/ob mice [20] and attenuated fasting-induced liver steatosis in peroxisome proliferator-activated receptor-α (PPARα)-deficient mice [21]. The lack of SCD1 expression also improved the action of insulin in skeletal muscles and prevented diet-induced hepatic insulin resistance in mice [22]. Much evidence indicates that the direct anti-steatotic and anti-diabetic effects of SCD1 deficiency result from lower tissue lipid content that is caused by higher FA oxidation and lower lipid synthesis [23].

ISOFORMS OF STEAROYL-COA DESATURASE

Four isoforms of murine SCD have been characterized, the genes for which are localized on chromosome 19 and span six exons. SCD1 (transcript 4844 bp → 355 aa) and SCD2 (transcript 5453 bp → 358 aa) are expressed in almost all tissues, especially in white adipose tissue, brown adipose tissue, the eyelids, the skin, the Harderian gland, the preputial gland, and the liver, whereas SCD2 is not expressed in the liver in adult mice [24-27]. The nucleotide sequences of murine SCD1 and SCD2 have 85% and 82% homology, respectively, with human SCD1 (i.e., one of two isoforms [SCD1 and SCD5] that have been characterized in humans [28]. SCD3 (transcript 3470 bp → 359 aa) is expressed in the skin, Harderian gland, and preputial gland [17,29,30]. SCD4 (transcript 3072 bp → 353 aa) is expressed exclusively in the murine heart [29,30]. The SCD4 amino acid sequence has over 77% sequence homology with the other SCD isoforms, and SCD4 shares 100% identity with the other SCD isoforms with its three histidine motifs [13,26]. The reason for the expression of several SCD isoforms is still not well understood, but different physiological roles for these isoforms have been suggested. Three SCD isoforms are expressed in the heart, where only SCD4 is repressed by leptin, whereas SCD1 and SCD2 are not [13,26]. The regulation of SCD expression also appears to be tissue-specific. For example, PUFAs repress the expression of SCD1 and SCD2 but not SCD4 in the heart, and all of these isoforms are induced by the liver X receptor α agonist [26]. More research is needed to confirm tissue-specific regulation of the actions of SCD.

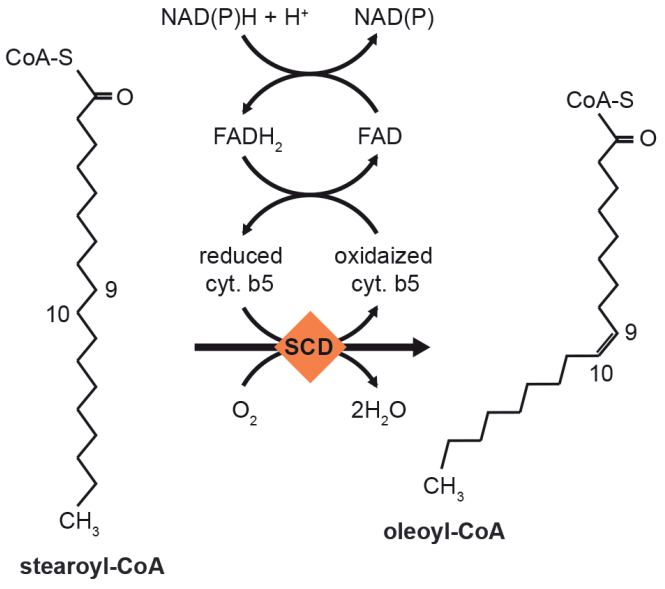

Figure 1. Reaction catalyzed by SCD. Electrons flow from the donor ($NADPH+H^+$) *via* FAD, cytochrome b5 to SCD, and to the final acceptor O_2, which is reduced to H_2O.

SCD1 REGULATES CARDIAC SUBSTRATE UTILIZATION

The work that the heart performs requires a large amount of adenosine triphosphate, which derives from oxidative phosphorylation in mitochondria and glycolysis and guanosine triphosphate formation in the citric acid cycle. Different energy substrates can be consumed by the heart, including FAs, glucose, lactate, ketones, pyruvate, and amino acids. A shift of substrate preference is a key factor for maintaining cardiac function, which is tightly controlled by the activity of several enzymes and transporters. The specific types of substrates that are utilized and their metabolic by products affect cardiac efficiency [31]. Although FAs are a plentiful source of energy, they are also very inefficient because more oxygen is utilized for their oxidation relative to glucose oxidation. This suggests the possibility of applying pharmacological agents to shift substrate preference toward glucose as an energy substrate to preserve or improve the mechanics of the heart [32,33].

SCD1 influences myocardial substrate utilization. Higher glucose oxidation and lower fat oxidation were observed in the heart in $SCD1^{-/-}$ mice [34] (Fig. 2). These effects were related to the upregulation of insulin signaling and an increase in glucose uptake that was caused by an increase in tyrosine phosphorylation of the insulin receptor and the activation of downstream molecules [34]. SCD1 deficiency also altered the availability of FAs, reflected by a decrease in FA uptake in the cytosol and transport across the mitochondrial membrane (Fig. 2). The uptake of FAs is facilitated by transport proteins, including FA translocase (CD36) and FA transport protein (FATP), the levels of which were lower in the heart in $SCD1^{-/-}$ mice compared with controls. Similarly, SCD1 inhibition decreased FATP1 protein levels in HL-1 cardiac muscle cells [35]. SCD1 deficiency also resulted in

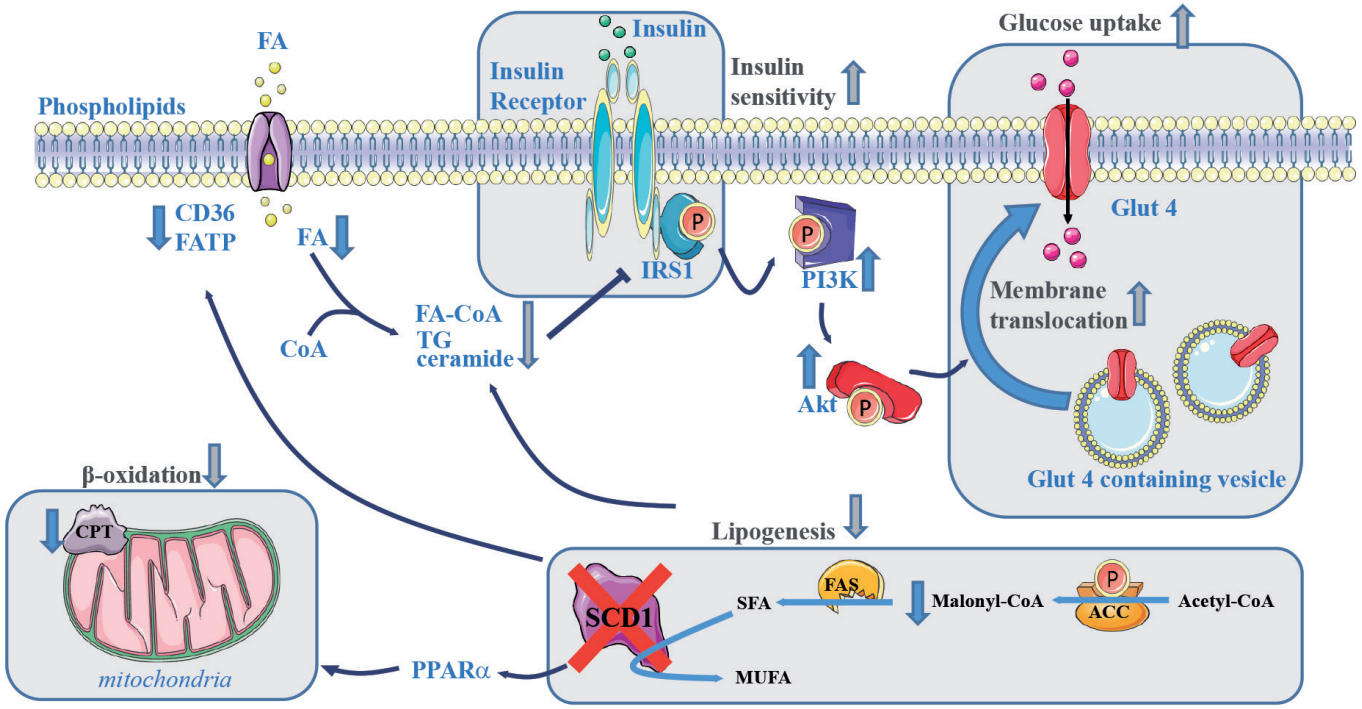

Figure 2. Effect of SCD1 deficiency on fatty acid and glucose oxidation pathways in the heart.

The loss of SCD1 decreases the uptake of FA and the accumulation of FA, FA-CoA, TG, and ceramide in cardiomyocytes. Stearoyl-CoA desaturase ablation causes a drop in the rate of lipogenesis and a decrease in the expression of genes that are involved in β-oxidation. Changes in lipid metabolism and the upregulation of IRS, Akt kinase, and PI3K lead to an increase in GLUT4 membrane translocation and greater glucose uptake. CD36 – fatty acid translocase CD36; CPT1 – carnitine palmitoyltransferase 1; FA – fatty acid; FA-CoA – fatty acyl-CoA; FATP – fatty acid transport protein; GLUT4 – glucose transporter 4; IRS – insulin receptor substrate; PI3K – phosphatidylinositol 3-kinase; PPAR – peroxisome proliferator-activated receptor; SCD – stearoyl-CoA desaturase; TG – triglyceride.

a disturbance of mitochondrial FA transport, reflected by lower levels of carnitine palmitoyltransferase (CPT1) at both the mRNA and protein levels [34]. Importantly, free FAs must be conjugated to carnitine by CPT1 before entering mitochondria [36]. Energy metabolism in the heart has been shown to be regulated by the activity of adenosine monophosphate-activated protein kinase (AMPK). AMPK phosphorylation results in increases in FA oxidation, glucose uptake, and glycolysis [37]. An increase in AMPK phosphorylation was found in the liver and skeletal muscle in SCD1-deficient mice, whereas no such activation was observed in the heart. This indicates that AMPK does not play a role in metabolic changes that are observed in the heart in SCD1-deficient mice [34]. Moreover, in HL-1 cardiomyocytes, SCD inhibition did not alter the phosphorylation of either AMPK or its downstream target acetyl-CoA carboxylase (ACC) [35].

Metabolic pathways in the heart are rapidly regulated by the activity of enzymes and transporters and can be regulated on a long-term basis. Such long-term regulation occurs through modulation of the rate of transcription by specific transcription factors, such as PPARs. Upon their activation, PPARs can promote FA oxidation together with ketone body synthesis in the heart [38]. An increase in cardiac lipid oxidation and alterations of glucose metabolism and insulin resistance were found in transgenic mice with the heart-specific overexpression of PPARα. Notably, these mice developed a cardiac phenotype that resembled cardiomyopathy that is seen in obesity and diabetes, reflected by specific ventricular hypertrophy and lipid accumulation [39]. This lipotoxic form of cardiomyopathy that was caused by PPARα overexpression was ablated by CD36 knockout [40]. The expression of PPARα significantly decreased in the myocardium in SCD1$^{-/-}$ mice. This decrease was accompanied by a significant drop in the mRNA levels of CPT1 and acyl-CoA oxidase, whose genes are targets for PPARα [34]. A similar effect was found in HL-1 cells that were treated with a SCD inhibitor [35]. These results suggest a link between SCD1 and PPARα. Palmitoleic acid, which is a product of the SCD1-mediated desaturation of palmitic acid, led to PPARα activation in peripheral tissues through an increase in PPARα binding to its DNA consensus sequence (PPRE) [41]. Furthermore, PPARα activity in the heart can be regulated by oleate, which is *de novo*-produced by SCD [42]. Thus, the observed decrease in intracellular PUFA content in SCD1-deficient mice [34] might cause the downregulation of PPARα, in which PUFAs were shown to influence SCD1 expression [43]. A study of SCD1$^{-/-}$ and PPARα$^{-/-}$ double-knockout mice suggested that SCD1 can act independently of PPARα [35].

SCD1 REGULATES LIPID METABOLISM IN THE HEART

Both circulating non-esterified FAs and those that are bound to lipoproteins are the main source of lipids in the heart, because *de novo* FA synthesis in the myocardium is very limited. Fatty acid uptake and oxidation are tightly regulated, any imbalance of which results in the accumulation of long-chain FAs and an increase in intracellular TGs

and toxic derivatives of unoxidized palmitoyl-CoA, such as ceramide [44]. Lower levels of free FAs (FFAs) and ceramide were reported in the heart in SCD1$^{-/-}$ mice compared with wildtype mice [34]. Similarly, the inhibition of SCD1 in HL-1 cells resulted in a decrease in FFA, TG, and ceramide levels. These changes were accompanied by lower levels of lipogenic proteins, such as ACC and fatty acid synthase (FAS). Decreases in the expression of these two enzymes were also found in the heart in SCD1$^{-/-}$ mice [35].

Acetyl-CoA carboxylase- and FAS-encoding genes are under the control of sterol regulatory element binding proteins (SREBPs). Inactive SREBP precursors undergo proteolytic cleavage when intercellular lipid levels drop. Following cleavage, the amino terminus enters the nucleus and enhances the expression of genes that participate in lipid synthesis, including ACC and FAS [45]. A significant drop in the expression of SREBP1c was observed in SCD1$^{-/-}$ mice, with a consequent decrease in the expression of lipogenic genes. Likewise, in an *in vitro* model that employed HL-1 cells, SCD1 inhibition decreased SREBP1, FAS, and ACC protein levels [35].

In addition to influencing lipogenesis, SCD1 can also influence lipolysis (i.e., TG hydrolysis to DAG). SCD1 inhibition in cardiomyocytes decreased the levels of adipose triglyceride lipase (ATGL) protein, which initiates the intracellular catabolism of TAG. Concurrently, a significant drop in G0/G1 switch 2 (G0S2) protein levels was observed in HL-1 cells after SCD1 inhibition [35]. G0S2 acts as an inhibitor of ATGL, and G0S2 deficiency evokes the de-repression of cardiac lipolysis [46]. The effect of SCD inhibition on G0S2 expression was confirmed in an *in vivo* study in SCD1$^{-/-}$ mice, in which a decrease in G0S2 transcript levels was found [35]. SCD1 also appears to play an important role in regulating subsequent steps of lipolysis, including DAG hydrolysis. This process is mediated by hormone-sensitive lipase (HSL) [46]. SCD1 inhibition in cardiomyocytes resulted in an increase in the enzymatic activity of HSL, thus confirming the importance of SCD protein in regulating lipid metabolism in the heart [35].

ROLE OF SCD1 IN MAINTAINING HEART FUNCTION AND STRUCTURE

The effect of alterations of substrate utilization that are caused by SCD1 deficiency on excitation-contraction coupling machinery in the heart has been investigated. Metabolic alterations in the heart in SCD1$^{-/-}$ mice did not induce any changes in cardiac function [34]. However, further studies of the structure of the heart that performed transthoracic echocardiography and Doppler flow analysis indicated some structural changes in the heart in SCD1$^{-/-}$ mice compared with wildtype mice. SCD1 ablation increased the weight of the left ventricle (LV) by 15% and enlarged the diameter of the LV. Nevertheless, the thicknesses of the LV posterior and anterior walls were not significantly affected by SCD1 deficiency. Moreover, no differences in heart rate, systolic/diastolic function, the myocardial performance index, or blood flow velocity across the mitral valve in early diastole were observed between SCD1$^{-/-}$ and wildtype mice. Importantly, excitation-contraction coupling is energy-dependent, and any uncontrolled shift in substrate utilization can disturb heart function.

Slight changes in ectopic intracellular myocardial and pericardial lipid deposition are associated with alterations of cardiac performance. Functional alterations of the myocardium were described in obese leptin-resistant Zucker diabetic rats [47], db/db mice, and leptin-deficient ob/ob mice [48]. Hypertrophic remodeling in the LV was shown to be accompanied by increases in TG and ceramide levels and cardiomyocyte apoptosis [34,48]. SCD1 was shown to be a crucial enzyme that regulates cardiomyocyte metabolism in the pathogenesis of lipid-induced heart disease. Significant increases in SCD1 expression and activity were observed in the myocardium in ob/ob and db/db mice and obese diabetic rats [49]. Moreover, increases in SCD1 expression were shown to favor lipid droplet accumulation in isolated neonatal rat cardiac myocytes that were incubated with palmitate [50]. Studies of acyl-CoA synthase transgenic mice, which are prone to the development of severe lipotoxic cardiomyopathy [51], reported increases in SCD1 and SCD4 expression. Significant decreases in LV diameter and LV mass were found in ob/ob/SCD1$^{-/-}$ double mutant mice compared with ob/ob mice, with no alterations of LV wall thickness [19]. However, the LV mass/body weight ratio was significantly increased in double knockout mice. Measurements of the myocardial performance index showed significant differences between ob/ob mice and ob/ob;SCD1$^{-/-}$ mice. Moreover, a Doppler flow analysis revealed a 57% decrease in the E/Ea ratio in ob/ob mice compared with wildtype mice, indicating diastolic dysfunction in ob/ob mice [19]. The E/Ea ratio in the heart in ob/ob;SCD1$^{-/-}$ decreased compared with wildtype mice, and SCD1 deficiency increased the E/Ea ratio by 27% in the heart in these mice compared with ob/ob mice. Altogether, SCD1 ablation was shown to improve cardiac function in obese leptin-deficient ob/ob mice.

Higher levels of ceramide cause the apoptosis of cardiac myocytes, which can result in LV chamber expansion, contractile dysfunction, and impairments in diastolic filling, thus contributing to cardiomyopathy that is observed in the setting of obesity and diabetes [47]. The accumulation of intramyocardial ceramide and TGs was also observed in obese leptin-deficient ob/ob mice [19]. Interestingly, SCD1 gene knockout resulted in a decrease in TG and ceramide content in the heart in ob/ob;SCD1$^{-/-}$ mice compared with control ob/ob mice [19]. The decrease in ceramide levels in the SCD1-deficient heart appeared to be attributable to a decrease in *de novo* synthesis, reflected by decreases in serine palmitoyltransferase activity and gene expression and a reduction of the incorporation of [^{14}C]palmitate into ceramide [19].

The ceramide pathway is one of the most important lipoapoptotic routes in cardiomyocytes [52]. A decrease in ceramide content that was caused by SCD1 deficiency resulted in a lower rate of apoptosis in the heart in ob/ob mice. Two key markers of ceramide-induced apoptosis—nitric oxide (NO) production (measured by inducible nitric oxide synthase [iNOS] activity) and caspase-3 activity—were significantly reduced in the heart in ob/ob;SCD1$^{-/-}$ double knockout mice [19]. Decreases in the activity of iNOS and caspase-3 might result from the inhibition of *de novo* ceramide synthesis that is caused by SCD1 deficiency. Bielawska *et al.* [53] proposed that ceramide upregulates iNOS expression and increases NO production, which causes

an increase in apoptosis. The downregulation of caspase-3 was linked with the action of ceramide [54,55]. Ravid *et al.* [55] showed that ceramide-mediated apoptosis was blocked by the general caspase inhibitor Boc-D-fluoromethylketone. Ruvolo *et al.* [56] found that exogenous ceramide can downregulate antiapoptotic factor Bcl-2 expression and phosphorylation, thereby activating caspase-3 and apoptosis. The antiapoptotic effect of Bcl-2 may occur *via* the modulation of ceramide production and prevention of ceramide-mediated caspase activation [56,57]. An increase in Bcl-2 mRNA levels was observed in the heart in ob/ob;SCD1$^{-/-}$ double mutant mice compared with ob/ob controls. Thus, an increase in Bcl-2 gene expression could be another factor that contributes to the downregulation of caspase-3 activity and a lower rate of apoptosis in the heart in ob/ob;SCD1$^{-/-}$ mice.

An increase in the oxidation of palmitate through CPT1 is involved in the production of apoptosis in cardiomyocytes. Palmitate-induced cell death was enhanced by carnitine, a cofactor that is required for palmitate transport into mitochondria *via* CPT1 [58]. CPT1 mRNA levels decreased in the heart in ob/ob;SCD1$^{-/-}$ mice compared with ob/ob mice [19]. Therefore, lower FA mitochondrial oxidation could account for the decrease in apoptosis in the heart in SCD1-deficient ob/ob mice. A reduction of cardiomyocyte apoptosis was shown to improve cardiac function [48], and the inhibition of lipid-induced apoptosis that is caused by SCD1 deficiency might be directly responsible for the improvement in heart function in ob/ob mice.

A reduction of SCD1 activity was also shown to exert beneficial effects on heart function in animal models of diet-induced obesity. Rats that were fed a high-carbohydrate, high-fat diet developed eccentric hypertrophy, which is characteristic of higher preload, defined by an increase in the internal diameter on the LV in diastole without changes in the relative wall thickness [59]. Consequently, these rats exhibited impairments in systolic function. Additionally, diastolic, systolic, and stroke volumes and cardiac output were all elevated in high-carbohydrate, high-fat diet fed rats, with no changes in heart rate [59]. These detrimental changes in cardiac function were accompanied by an increase in SCD activity and reversed by α-linoneic acid, docosahexaenoic acid, and eicosapentenoic acid, all of which suppress SCD1 expression [60]. These findings emphasize the importance of SCD for the regulation of heart function.

LIPIDS IN THE DEVELOPMENT OF PHYSIOLOGICAL AND PATHOLOGICAL LEFT VENTRICULAR HYPERTROPHY

Cardiac hypertrophy is the abnormal enlargement or thickening of the heart muscle, associated with extensive physiological or pathological remodeling of the heart structure. Pathological remodeling is typically characterized by cardiac myocyte loss, fibrosis, and cardiac dysfunction [61,62]. In contrast, physiological remodeling is characterized by cardiac enlargement, associated with cell survival and normal heart function [63]. Lipidomic profiling revealed that significant changes in lipid content and composition and the regulation of lipid metabolism pathways between physiological and pathological cardiac hypertrophy [63].

Our group found increases in the expression of SCD1- and SCD2-encoding genes and other lipogenic protein-encoding genes, together with the activation of SREBP-1 and Akt signaling pathways, under conditions of physiological hypertrophy that was induced by endurance training, in contrast to the heart that presented pathological hypertrophy that was induced by abdominal aortic banding [61]. These data indicate that although the myocardium has a low capacity for *de novo* lipogenesis, lipogenic genes play significant roles in the control of cardiac metabolism and remodeling. The effects of physiological and pathological hypertrophy on cardiac lipid metabolism are more complex. Although the expression of lipogenic genes and the levels of FA transport proteins (e.g., CD36 and FATP1) were unaltered or reduced, pathological hypertrophy led to cardiac TG and DAG accumulation compared with the sham group. A possible explanation for this phenomenon is a decrease in lipolysis, reflected by an increase in G0S2 protein content (i.e., a small basic protein that functions as an endogenous inhibitor of adipose triglyceride lipase, a key enzyme in intracellular lipolysis), an increase in the phosphorylation of hormone-sensitive lipase at Ser565, and decreases in the protein levels of DAG lipase α (DAGLα) and DAGLβ, which attenuate TG and DAG content [61]. Taken together, all of these data show that activation of lipogenesis and reduction of lipolysis may play a role in the mechanism underlying the differences between physiological and pathological cardiac hypertrophy.

FUTURE REMARKS

The available data from SCD1-deficient mice highlight the importance of SCD in cardiac metabolic reprogramming. The shift of substrate utilization toward glucose that is evoked by the loss of SCD appears to be favorable in terms of cardiomyocyte protection against apoptosis and improvements in heart function in obese mouse models. Future research should focus on elucidating the mechanisms by which SCD plays a role in the heart with regard to both physiology and pathology. Myocardial substrate utilization affects the development and progression of heart failure. One intriguing possibility is to employ SCD inhibitors to regulate myocardial metabolism and improve cardiac function. Such a possibility, however, remains to be investigated. The role of SCD4, which is a cardiac-specific isoform of SCD, also requires further investigation.

REFERENCES

1. Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N (2017) European Cardiovascular Disease Statistics 2017 Edition
2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, De Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jim'nez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, *et al.* (2017) Heart Disease and Stroke Statistics'2017 Update: A Report from the American Heart Association. Circulation 135: e146-e603
3. Anand SS, Hawkes C, De Souza RJ, Mente A, Dehghan M, Nugent R, Zulyniak MA, Weis T, Bernstein AM, Krauss RM, Kromhout D, Jenkins DJA, Malik V, Martinez-Gonzalez MA, Mozaffarian D, Yusuf S, Willett WC, Popkin BM (2015) Food consumption and its impact on cardiovascular disease: importance of solutions focused on the globalized food system a report from the workshop convened by the world heart federation. J Am Coll Cardiol 66: 1590-1614

4. Nettleton JA, Brouwer IA, Geleijnse JM, Hornstra G (2017) Saturated fat consumption and risk of coronary heart disease and ischemic stroke: a science update. Ann Nutr Metab 70: 26-33
5. Jula A, Marniemi J, Rönnemaa T, Virtanen A, Huupponen R (2005) Effects of diet and simvastatin on fatty acid composition in hypercholesterolemic men: A randomized controlled trial. Arterioscler Thromb Vasc Biol 25: 1952-1959
6. Mayneris-Perxachs J, Guerendiain M, Castellote AI, Estruch R, Covas MI, Fitó M, Salas-Salvadó J, Martínez-González MA, Aros F, Lamuela-Raventós RM, López-Sabater MC (2014) Plasma fatty acid composition, estimated desaturase activities, and their relation with the metabolic syndrome in a population at high risk of cardiovascular disease. Clin Nutr 33: 90-97
7. Warensjö E, Risérus U, Gustafsson IB, Mohsen R, Cederholm T, Vessby B (2008) Effects of saturated and unsaturated fatty acids on estimated desaturase activities during a controlled dietary intervention. Nutr Metab Cardiovasc Dis 18: 683-690
8. Djoussé L, Weir NL, Hanson NQ, Tsai MY, Gaziano JM (2012) Plasma phospholipid concentration of cis-palmitoleic acid and risk of heart failure. Circ Hear Fail 5: 703-709
9. Ebbesson SE, Lopez-Alvarenga JC, Okin P, Devereux RB, Elizabeth Tejero M, Harris W, Ebbesson LE, MacCluer J, Wenger C, Laston S, Fabsitz R, Kennish J, Howard WJ, Howard B, Umans J, Comuzzie AG (2012) Heart rate is associated with markers of fatty acid desaturation: the GOCADAN study. Int J Circumpolar Health 71: 17343
10. Yang B, Ding F, Wang F-L, Yan J, Ye X-W, Yu W, Li D (2016) Association of serum fatty acid and estimated desaturase activity with hypertension in middle-aged and elderly Chinese population. Sci Rep 6: 23446
11. Aristizabal JC, González-Zapata LI, Estrada-Restrepo A, Monsalve-Alvarez J, Restrepo-Mesa SL, Gaitán D (2018) Concentrations of plasma free palmitoleic and dihomo-gamma linoleic fatty acids are higher in children with abdominal obesity. Nutrients 10: 1-11
12. Karpe F, Hodson L (2008) Caution on the interpretation of plasma fatty acid composition as a proxy marker for SCD1 activity: particular implications for using the 16:1/16:0 ratio in QTL studies involving hyperlipidemic patients. Arterioscler Thromb Vasc Biol 28: e152-e152
13. Dobrzyn P, Bednarski T, Dobrzyn A (2015) Metabolic reprogramming of the heart through stearoyl-CoA desaturase. Prog Lipid Res 57: 1-12
14. Dobrzyn A, Natambi JM (2004) The role of stearoyl-CoA desaturase in body weight regulation. Trends Cardiovasc Med 14: 77-81
15. Ntambi JM (1999) Regulation of stearoyl-CoA desaturase by polyunsaturated fatty acids and cholesterol. J Lipid Res 40: 1549-1558
16. Lai KKY, Kweon S, Chi F, Hwang E, Kabe Y, Higashiyama R, Qin L, Yan R, Wu RP, Lai K, Fujii N, French S, Xu J, Wang J, Murali R, Mishra L, Lee J, Ntambi JM, Tsukamoto H (2017) Stearoyl-CoA desaturase promotes liver fibrosis and tumor development in mice *via* a wnt positive-signaling loop by stabilization of low-density lipoprotein-receptor-related proteins 5 and 6. Gastroenterology 152: 1477-1491
17. Zheng Y, Prouty SM, Harmon A, Sundberg JP, Stenn KS, Parimoo S (2001) Scd3 - A novel gene of the stearoyl-CoA desaturase family with restricted expression in skin. Genomics 71: 182-191
18. Paton CM, Ntambi JM (2010) Loss of stearoyl-CoA desaturase activity leads to free cholesterol synthesis through increased Xbp-1 splicing. Am J Physiol Endocrinol Metab 299: 1066-1075
19. Dobrzyn P, Dobrzyn A, Miyazaki M, Ntambi JM (2010) Loss of stearoyl-CoA desaturase 1 rescues cardiac function in obese leptin-deficient mice. J Lipid Res 51: 2202-2210
20. Cohen P, Miyazaki M, Socci ND, Hagge-Greenberg A, Liedtke W, Soukas AA, Sharma R, Hudgins LC, Ntambi JM FJ (2002) Role for Stearoyl-CoA Desaturase-1 in Leptin-Mediated Weight Loss. Science 297: 240-243
21. Miyazaki M, Dobrzyn A, Sampath H, Lee SH, Weng CM, Chu K, Peters JM, Gonzalez FJ, Ntambi JM (2004) Reduced adiposity and liver steatosis by stearoyl-CoA desaturase deficiency are independent of peroxisome proliferator-activated receptor-α. J Biol Chem 279: 35017-35024
22. Dobrzyn A, Dobrzyn P, Lee S-H, Miyazaki M, Cohen P, Asilmaz E, Hardie DG, Friedman JM, Ntambi JM (2005) Stearoyl-CoA desaturase-1 deficiency reduces ceramide synthesis by downregulating serine palmitoyltransferase and increasing beta-oxidation in skeletal muscle. Am J Physiol Endocrinol Metab 288: E599-607
23. Dobrzyn P, Jazurek M, Dobrzyn A (2010) Stearoyl-CoA desaturase and insulin signaling - What is the molecular switch? Biochim Biophys Acta - Bioenerg 1797: 1189-1194
24. Ntambi JM, Buhrow SA, Kaestner KH, Christy RJ, Sibley E, Kelly TJ, Lane MD (1988) Differentiation-induced gene expression in 3T3-L1 preadipocytes. Characterization of a differentially expressed gene encoding stearoyl-CoA desaturase. J Biol Chem 263: 17291-300
25. Kaestner KH, Ntambi JM, Kelly TJ, Lane MD (1989) Differentiation-induced gene expression in 3T3-L1 preadipocytes. A second differentially expressed gene encoding stearoyl-CoA desaturase. J Biol Chem 264: 14755-61
26. Miyazaki M, Jacobson MJ, Man WC, Cohen P, Asilmaz E, Friedman JM, Ntambi JM (2003) Identification and characterization of murine SCD4, a novel heart-specific stearoyl-CoA desaturase isoform regulated by leptin and dietary factors. J Biol Chem 278: 33904-33911
27. Miyazaki M, Dobrzyn A, Elias PM, Ntambi JM (2005) Stearoyl-CoA desaturase-2 gene expression is required for lipid synthesis during early skin and liver development. Proc Natl Acad Sci USA 102: 12501-12506
28. Zhang L, Ge L, Parimoo S, Stenn K, Prouty SM (1999) Human stearoyl-CoA desaturase: alternative transcripts generated from a single gene by usage of tandem polyadenylation sites. Biochem J 340: 255-264
29. Miyazaki M, Kim HJ, Man WC, Ntambi JM (2001) Oleoyl-CoA is the major de novo product of stearoyl-CoA desaturase 1 gene isoform and substrate for the biosynthesis of the harderian gland 1-alkyl-2,3-diacylglycerol. J Biol Chem 276: 39455-39461
30. Miyazaki M, Gomez FE, Ntambi JM (2002) Lack of stearoyl-CoA desaturase-1 function induces a palmitoyl-CoA Δ6 desaturase and represses the stearoyl-CoA desaturase-3 gene in the preputial glands of the mouse. J Lipid Res 43: 2146-2154
31. Lopaschuk GD, Ussher JR, Folmes CDL, Jaswal JS, Stanley WC (2010) Myocardial fatty acid metabolism in health and disease. Physiol Rev 90: 207-258
32. Wambolt RB, Lopaschuk GD, Brownsey RW, Allard MF (2000) Dichloroacetate improves postischemic function of hypertrophied rat hearts. J Am Coll Cardiol 36: 1378-1385
33. Fillmore N, Mori J, Lopaschuk GD (2014) Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy. Br J Pharmacol 171: 2080-2090
34. Dobrzyn P, Sampath H, Dobrzyn A, Miyazaki M, Ntambi JM (2008) Loss of stearoyl-CoA desaturase 1 inhibits fatty acid oxidation and increases glucose utilization in the heart. Am Jounal Physiol Endocrinol Metab 294: 357-364
35. Bednarski T, Olichwier A, Opasinska A, Pyrkowska A, Gan AM, Ntambi JM, Dobrzyn P (2016) Stearoyl-CoA desaturase 1 deficiency reduces lipid accumulation in the heart by activating lipolysis independently of peroxisome proliferator-activated receptor α. Biochim Biophys Acta - Mol Cell Biol Lipids 1861: 2029-2037
36. Longo N, Frigeni M, Pasquali M (2016) Carnitine transport and fatty acid oxidation. Biochim Biophys Acta - Mol Cell Res 1863: 2422-2435
37. Towler MC, Hardie DG (2007) AMP-activated protein kinase in metabolic control and insulin signaling. Circ Res 100: 328-341
38. Madrazo JA, Kelly DP (2008) The PPAR trio: Regulators of myocardial energy metabolism in health and disease. J Mol Cell Cardiol 44: 968-975
39. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, Han X, Gross RW, Kozak R, Lopaschuk GD, Kelly DP (2002) The cardiac phenotype induced by PPARα overexpression mimics that caused by diabetes mellitus. J Clin Invest 109: 121-130
40. Yang J, Sambandam N, Han X, Gross RW, Courtois M, Kovacs A, Febbraio M, Finck BN, Kelly DP (2007) CD36 deficiency rescues lipotoxic cardiomyopathy. Circ Res 100: 1208-1217

41. Bolsoni-Lopes A, Festuccia WT, Farias TSM, Chimin P, Torres-Leal FL, Derogis PBM, de Andrade PB, Miyamoto S, Lima FB, Curi R, Alonso-Vale MIC (2013) Palmitoleic acid (n-7) increases white adipocyte lipolysis and lipase content in a PPAR -dependent manner. AJP Endocrinol Metab 305: E1093-E1102
42. Dobrzyn P, Pyrkowska A, Jazurek M, Dobrzyn A (2012) Increased availability of endogenous and dietary oleic acid contributes to the up-regulation of cardiac fatty acid oxidation. Mitochondrion 12: 132-137
43. Sampath H, Ntambi JM (2005) Polyunsaturated fatty acid regulation of genes of lipid metabolism. Annu Rev Nutr 25: 317-340
44. Park HJ, Georgescu SP, Du C, Madias C, Aronovitz MJ, Welzig CM, Wang B, Begley U, Zhang Y, Blaustein RO, Patten RD, Karas RH, Van Tol HH, Osborne TF, Shimano H, Liao R, Link MS, Galper JB (2008) Parasympathetic response in chick myocytes and mouse heart is controlled by SREBP. J Clin Invest 118: 259-271
45. Shao W, Espenshade PJ (2012) Expanding roles for SREBP in metabolism. Cell Metab 16: 414-419
46. Heier C, Radner FPW, Moustafa T, Schreiber R, Grond S, Eichmann TO, Schweiger M, Schmidt A, Cerk IK, Oberer M, Christian Theussl H, Wojciechowski J, Penninger JM, Zimmermann R, Zechner R (2015) G0/G1 switch gene 2 regulates cardiac lipolysis. J Biol Chem 290: 26141-26150
47. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L, Unger RH (2000) Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci USA 97: 1784-1789
48. Barouch LA, Gao D, Chen L, Miller KL, Xu W, Phan AC, Kittleson MM, Minhas KM, Berkowitz DE, Wei C, Hare JM (2006) Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. Circ Res 98: 119-124
49. Ge F, Hu C, Hyodo E, Arai K, Zhou S, Lobdell Iv H, Walewski JL, Homma S, Berk PD (2012) Cardiomyocyte triglyceride accumulation and reduced ventricular function in mice with obesity reflect increased long chain fatty acid uptake and *de novo* fatty acid synthesis. J Obes 2012: 1-12
50. Matsui H, Yokoyama T, Sekiguchi K, Iijima D, Sunaga H, Maniwa M, Ueno M, Iso T, Arai M, Kurabayashi M (2012) Stearoyl-Coa desaturase-1 (SCD1) augments saturated fatty acid-induced lipid accumulation and inhibits apoptosis in cardiac myocytes. PLoS One 7: e33283
51. Lee Y, Naseem RH, Duplomb L, Park B-H, Garry DJ, Richardson JA, Schaffer JE, Unger RH (2004) Hyperleptinemia prevents lipotoxic cardiomyopathy in acyl CoA synthase transgenic mice. Proc Natl Acad Sci USA 101: 13624-13629
52. Shimabukuro M, Higa M, Zhou Y, Wang M, Newgard CB, Unger RH (1998) Lipoapoptosis in Beta-cells of Obese Prediabetic fa / fa Rats. J Biol Chem 273: 32487-32490
53. Bielawska AE, Shapiro JP, Jiang L, Melkonyan HS, Piot C, Wolfe CL, Tomei LD, Hannun YA, Umansky SR (1997) Ceramide is involved in triggering of cardiomyocyte apoptosis induced by ischemia and reperfusion. Am J Pathol 151: 1257-1263
54. Castillo SS, Levy M, Wang C, Thaikoottathil J V., Khan E, Goldkorn T (2007) Nitric oxide-enhanced caspase-3 and acidic sphingomyelinase interaction: A novel mechanism by which airway epithelial cells escape ceramide-induced apoptosis. Exp Cell Res 313: 816-823
55. Ravid T, Tsaba A, Gee P, Rasooly R, Medina E a, Goldkorn T (2003) Ceramide accumulation precedes caspase-3 activation during apoptosis of A549 human lung adenocarcinoma cells. Am J Physiol Lung Cell Mol Physiol 284: L1082-L1092
56. Ruvolo PP, Clark W, Mumby M, Gao F, Stratford May W (2002) A functional role for the B56 α-subunit of protein phosphatase 2A in ceramide-mediated regulation of Bcl2 phosphorylation status and function. J Biol Chem 277: 22847-22852
57. Sawada M, Nakashima S, Banno Y, Yamakawa H, Takenaka K, Shinoda J, Nishimura Y, Sakai N, Nozawa Y (2000) Influence of Bax or Bcl-2 overexpression on the ceramide-dependent apoptotic pathway in glioma cells. Oncogene 19: 3508-3520
58. Kong JY, Rabkin SW (2002) Palmitate-induced cardiac apoptosis is mediated through CPT-1 but not influenced by glucose and insulin. Am J Physiol Heart Circ Physiol 282: H717-H725
59. Poudyal H, Panchal SK, Waanders J, Ward L, Brown L (2012) Lipid redistribution by α-linolenic acid-rich chia seed inhibits stearoyl-CoA desaturase-1 and induces cardiac and hepatic protection in diet-induced obese rats. J Nutr Biochem 23: 153-162
60. Poudyal H, Panchal SK, Ward LC, Brown L (2013) Effects of ALA, EPA and DHA in high-carbohydrate, high-fat diet-induced metabolic syndrome in rats. J Nutr Biochem 24: 1041-1052
61. Dobrzyn P, Pyrkowska A, Duda MK, Bednarski T, Maczewski M, Langfort J, Dobrzyn A (2013) Expression of lipogenic genes is up-regulated in the heart with exercise training-induced but not pressure overload-induced left ventricular hypertrophy. AJP Endocrinol Metab 304: E1348-E1358
62. Tham YK, Bernardo BC, Ooi JYY, Weeks KL, McMullen JR (2015) Pathophysiology of cardiac hypertrophy and heart failure: signaling pathways and novel therapeutic targets. Arch Toxicol 89: 1401-1438
63. Tham YK, Huynh K, Mellett NA, Henstridge DC, Kiriazis H, Ooi JYY, Matsumoto A, Patterson NL, Sadoshima J, Meikle PJ, McMullen JR (2018) Distinct lipidomic profiles in models of physiological and pathological cardiac remodeling, and potential therapeutic strategies. Biochim Biophys Acta - Mol Cell Biol Lipids 1863: 219-234

Rola desaturazy stearoilo-CoA w regulacji metabolizmu serca

Sabina Tabaczar, Marcin Wołosiewicz, Anna Filip, Adam Olichwier, Paweł Dobrzyń✉

Pracownia Molekularnej Biochemii Medycznej, Instytut Biologii Doświadczalnej im. M. Nenckiego, PAN, ul. Pasteura 3, 02-093 Warszawa

✉e-mail: p.dobrzyn@nencki.gov.pl

Słowa kluczowe: kwasy tłuszczowe, utylizacja glukozy, niewydolność serca, przerost mięśnia sercowego, ceramidy

STRESZCZENIE

Metabolizm energetyczny serca jest ściśle regulowany, a zaburzenia w zużyciu substratów energetycznych w kardiomiocytach prowadzą do zaburzeń funkcji skurczowej oraz powodują przebudowę lewej komory o charakterze patologicznym. Desaturaza stearoilo-CoA (SCD) katalizuje biosyntezę jednonienasyconych kwasów tłuszczowych. Preferowanymi substratami SCD są kwasy: palmitynowy i stearynowy, które są przekształcane odpowiednio do kwasu palmitooleinowego i oleinowego. Przeprowadzone badania wykazały, że wyciszanie ekspresji SCD1 prowadzi do obniżenia tempa utleniania kwasów tłuszczowych, przy jednoczesnym zwiększeniu zużycia glukozy w kardiomiocytach w celu pozyskania energii. Poza tym stwierdzono, że obniżenie ekspresji SCD1 poprawia funkcję skurczową i rozkurczową lewej komory serca w przypadku dysfunkcji mięśnia sercowego związanego z otyłością. Badania przeprowadzone na populacji ludzkiej wykazały korelację pomiędzy stopniem desaturacji kwasów tłuszczowych w osoczu a ryzykiem rozwoju chorób serca, dlatego też zasugerowano, że poznanie roli SCD w regulacji funkcji serca może przyczynić się do rozwoju nowych terapii. W niniejszej pracy przedstawiono aktualny stan wiedzy dotyczący roli SCD1 w regulacji metabolizmu serca.