Progress in Lipid Research 57 (2015) 1–12

Contents lists available at ScienceDirect

Progress in Lipid Research

journal homepage: www.elsevier.com/locate/plipres

Review

Metabolic reprogramming of the heart through stearoyl-CoA desaturase

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ARTICLE INFO

Article history:
Received 22 July 2014
Received in revised form 25 November 2014
Accepted 25 November 2014
Available online 5 December 2014

Keywords:
Heart function
Fatty acids
Metabolism
Stearoyl-CoA desaturase (SCD)
Hypertrophy
Atherosclerosis

ABSTRACT

Stearoyl-CoA desaturase (SCD), a central enzyme in lipid metabolism that synthesizes monounsaturated fatty acids, has been linked to tissue metabolism and body adiposity regulation. Recent studies showed that SCD has the ability to reprogram cardiac metabolism, thereby regulating heart function. In the heart, the lack of SCD1 enhances glucose transport and metabolism at the expense of fatty acid (FA) uptake and oxidation. The metabolic changes associated with SCD1 deficiency protect cardiac myocytes against both necrotic and apoptotic cell death and improve heart function. Furthermore, SCD4, a heart-specific isoform of SCD, is specifically repressed by leptin and the lack of SCD1 function in leptin-deficient ob/ob mice results in a decrease in the accumulation of neutral lipids and ceramide and improves the systolic and diastolic function of a failing heart. Large-population human studies showed that the plasma SCD desaturation index is positively associated with heart rate, and cardiometabolic risk factors are modulated by genetic variations in SCD1. The current findings indicate that SCD may be used to reprogram myocardial metabolism to improve cardiac function. Here, we review recent advances in understanding the role of SCD in the control of heart metabolism and its involvement in the pathogenesis of lipotoxic cardiomyopathies.

Contents

Abbreviations: AMPK, AMP-activated protein kinase; CD36, fatty acid translocase CD36; CPT1, carnitine palmitoyltransferase; CVD, cardiovascular disease; DAG, diacylglycerol; DAGL, diacylglycerol lipase; FA, fatty acid; FAS, fatty acid synthase; FATP, fatty acid transport protein; GLUT4, glucose transporter 4; GPAT, glycerol-3-phosphate acyltransferase; IL, interleukin; iNOS, inducible nitric oxide synthase; IR, insulin receptor; IRS, insulin receptor substrate; LV, left ventricle; MUFA, monounsaturated fatty acids; NO, nitric oxide; PI3K, phosphatidylinositol 3-kinase; PLs, phospholipids; PPAR, peroxisome proliferator-activated receptors; PUFA, polyunsaturated fatty acids; SCD, stearoyl-CoA desaturase; SFA, saturated fatty acids; SREBP, sterol regulatory element-binding protein; TG, triacylglycerol; TO, trioleate; TS, tristearate.

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http://dx.doi.org/10.1016/j.plipres.2014.11.003
0163-7827/

1. Introduction

Myocardial metabolism plays an important role in maintaining proper heart function and therefore is strictly regulated. Under aerobic conditions, the heart derives 60–90% of the energy necessary for contractile function from fatty acid (FA) oxidation, whereas the remainder is obtained mainly from carbohydrates (glucose and lactate) [1,2]. Evidence suggests that impaired cardiomyocyte metabolism contributes to contractile dysfunction and the progressive left-ventricular remodeling that is characteristic of heart failure. In disease states, such as ischemia-reperfusion, diabetes, and obesity, cardiac substrate utilization shifts to the excessive use of FAs in place of glucose [1–3]. This shift in metabolism has been suggested to play a role in the development of cardiomyopathy, leading to both impaired contractile function and ischemic injury [2,4]. In contrast, readjusting cardiomyocyte metabolic pathways to favor glucose oxidation leads to ischemia resistance in the heart [5] and protects against lipotoxic heart disease [6]. Patients with congenital lipodystrophy, a rare disorder in which the absence of adipocytes results in the accumulation of lipid in non-adipose tissues, or with inherited mitochondrial fatty acid oxidation defects develop premature cardiomyopathy [7]. In animal models of obesity and diabetes, such as leptin-deficient ob/ob mice, leptin receptor-deficient db/db mice and Zucker Diabetic Fatty rats, lipid accumulation within cardiomyocytes and dysregulation in cardiac metabolism are associated with impaired contractile function [7]. To date, metabolic alterations in the failing heart have been considered a part of the phenotype (i.e., a consequence of the development of cardiac dysfunction). However, some observations suggest the intriguing possibility that the disruption of normal glucose or FA metabolism may indeed be a primary factor responsible for the development of heart failure. Thus, understanding the regulatory mechanisms that are responsible for reprogramming cardiomyocyte metabolism is imperative to discover new treatments to improve cardiac function.

Many studies underscore the important role of lipogenic enzymes in the regulation of cardiac metabolism and function and suggest that the role of lipogenic genes in cardiomyocytes may be distinct from other tissues. Cardiac sterol regulatory element-binding protein 1 (SREBP1), a key lipogenic transcription factor, was shown to activate G-protein-coupled inwardly reflecting K^+ channels, leading to enhanced acetylcholine-sensitive K^+ currents and reduced arrhythmias postmyocardial infraction [8]. The transgenic overexpression of fatty acid transport protein 1 (FATP1) in the heart has also been shown to cause lipotoxic cardiomyopathy [9]. The heart-specific knockdown of peroxisome proliferator-activated receptor γ (PPARγ) [10] and acyl-CoA synthase 1 (ACS-1) [11] induces cardiac hypertrophy. Fatty acid synthase (FAS), the enzyme that catalyzes *de novo* FA synthesis, is involved in the regulation of the ability of the heart to respond to stress through the activation of Ca^{2+}/calmodulin-dependent protein kinase II [12]. Diacylglycerol acyltransferase 1 overexpression improves heart function in long-chain acyl-CoA synthetase-expressing mice, which develop lipotoxic cardiomyopathy, by reducing the levels of cardiac ceramide and diacylglycerol (DAG), decreasing cardiomyocyte apoptosis, but increasing FA oxidation [13].

Recent studies showed that stearoyl-CoA desaturase (SCD), an enzyme involved in the biosynthesis of monounsaturated fatty acids (MUFAs), induces the reprogramming of cardiomyocyte metabolism, thereby playing an important role in the regulation of cardiac function [6,14,15]. The lack of SCD1 expression decreases FA uptake and oxidation and increases glucose transport and oxidation in the heart [14]. Disruption of the SCD1 gene improves cardiac function in obese leptin-deficient ob/ob mice by correcting systolic and diastolic dysfunction [6]. The improvement is associated with a reduction of the expression of genes involved in FA transport and lipid synthesis within the heart, together with decreases in cardiac free fatty acid (FFA), DAG, triacylglycerol (TG), and ceramide levels and reduced cardiomyocyte apoptosis [6]. Additionally, recent studies showed that physiological hypertrophy induced by endurance training is accompanied by the increased expression of SCD1 and SCD2 [15]. Here, we review recent advances in understanding the role of SCD in the control of heart metabolism and its involvement in the pathogenesis of lipotoxic cardiomyopathy.

2. Stearoyl-CoA desaturase (SCD): what does it do?

SCD is the rate-limiting enzyme that catalyzes the synthesis of MUFAs, mainly oleate and palmitoleate (Fig. 1), which are used as substrates for the synthesis of TG, wax esters, cholesteryl esters, and phospholipids (PLs) [16]. The degree of the unsaturation of cellular lipids can also play a role in membrane fluidity and cell signaling. Therefore, SCD is highly conserved, with multiple isoforms that provide overlapping but distinct tissue and substrate specificity. Four isoforms of SCD have been identified in the mouse (SCD1-4) [17–20], and two isoforms (SCD1 and 5) have been identified in the human genome [21,22]. Human SCD1 shows 85% homology with murine SCD1 [21]. In the adult mouse, SCD1 is expressed in lipogenic tissues, including the liver and adipose tissue. SCD2 is ubiquitously expressed in most tissues except the liver, where it is only expressed at early stages of life (embryonic and neonatal); at weaning, it is replaced by SCD1 [23]. SCD3 expression is restricted to sebocytes in the skin, harderian gland, and preputial gland [24]. SCD4 is expressed exclusively in the heart [20]. Human SCD1 is expressed in adult adipose tissue, the liver, the lungs, the brain, the heart, the pancreas, and skeletal muscles [25]. Human SCD5 is expressed predominantly in the brain and pancreas, with some limited expression in the heart, kidneys, lungs, and placenta [22,25,26]. The physiological role of each SCD isoform and the reason for having multiple SCD gene isoforms that share considerable sequence homology and catalyze the same biochemical reactions are currently under investigation.

Although MUFA products of SCD are abundant in the diet, SCD1 is highly regulated, indicating a critical role for endogenously synthesized MUFAs. The regulation of SCD1 has been reviewed elsewhere [27]. Briefly, the SCD1 gene is positively regulated by insulin, transcription factor SREBP1c, the liver X receptor, and numerous dietary and cellular factors, including glucose, fructose, and saturated FA (SFA). Negative regulation of the SCD1 gene is affected by the actions of polyunsaturated fatty acids (PUFA) and leptin [28]. SCD1 may also be regulated at the protein level and subjected to degradation by proteases and through the proteasomal pathway [29,30].

Research over the past decade has identified SCD as an important regulator of body adiposity and lipid partitioning. High SCD activity favors fat storage, whereas the suppression of the enzyme activates metabolic pathways that promote the burning of fat and