Biochimica et Biophysica Acta 1861 (2016) 1719–1726

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Stearoyl-CoA desaturase-1 and adaptive stress signaling

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ARTICLE INFO

Article history:
Received 29 June 2016
Received in revised form 9 August 2016
Accepted 17 August 2016
Available online 24 August 2016

Keywords:
Stearoyl-CoA desaturase
Monounsaturated fatty acid
Lipotoxicity
Stress adaption
Endoplasmic reticulum
Lipidomics

ABSTRACT

Stearoyl-CoA desaturase (SCD), the central enzyme in the biosynthesis of monounsaturated fatty acids, introduces a *cis*-Δ9 double bond into saturated fatty acids. SCD-1 has been proposed as promising target for the treatment of cancer, skin disorders and metabolic diseases, and strong efforts have been made during the last decade to develop clinical drug candidates. While the regulation and biological implications of SCD-1 have been extensively reviewed, the molecular mechanisms through which SCD-1 mediates cellular responses remained a mystery. An important aspect seems to be that SCD-1 induces adaptive stress signaling that maintains cellular persistence and fosters survival and cellular functionality under distinct pathological conditions. Here, we will first provide an overview about the function, regulation, structure and mechanism of SCD-1 and then focus on mitogenic and stress-related signal transduction pathways orchestrated by SCD-1. Moreover, we will discuss molecular mechanisms and potential lipid factors that link SCD-1 activity with initial signal transduction.

1. Introduction

Evolutionary adaption of organisms to endogenous, dietary and environmental stress established a complex stress signaling network, which aims to maintain homeostasis through energy-consuming resistance (e.g., the DNA damage response) and energy-neutral persistence mechanisms (e.g., autophagy) [1,2]. Stress in its many facets is generally considered as harmful because biomolecules are damaged, the function of organelles impaired and cell vitality reduced [1]. However, this paradigm has been challenged. High doses of stress evoke uncontrolled destructive and inflammatory necrotic cell death, while moderate doses preferentially induce senescence, apoptosis or programmed necrosis, and low doses even enhance in some cases the vitality/functionality of cells due to the induction of adaptive stress mechanisms [1,2]. How adaptive stress signaling is regulated is far from being understood. Signaling pathways at the heart of cell growth, survival, differentiation, and metabolism apparently play a major role in balancing this sensitive network.

During recent years, stearoyl-coenzyme A desaturase (SCD)-1 emerged as key player that links lipid metabolism with adaptive stress signaling and multiple diseases such as metabolic syndrome, skin disorders, cardiovascular disease and cancer [3–9]. Large efforts have been undertaken to validate SCD-1 as drug target for the treatment of type-2 diabetes and obesity, and an increasing number of SCD-1 inhibitors have been developed and proceeded to pre-clinical and clinical studies [10,11]. However, it also became increasingly evident that inhibition of SCD-1 promotes both essential (homeostatic) and detrimental (lipotoxic) processes [3]. Understanding the balance of these mechanisms is critical for the development of safe SCD-1 inhibitors but difficult to adjust by pharmacological means because the relevance of individual signaling cascades initiated by SCD-1 strongly differs between cell types, tissues and metabolic conditions. Due to these complications, the interest of pharmaceutical companies in SCD-1 inhibitors declined during the last years, and the research focus shifted to alternative indications (e.g., cancer, acne and nonalcoholic steatohepatitis) and tissue selective drugs [10,11].

Two SCD isoenzymes have been reported in humans (SCD-1 and 5) and four in mice (SCD-1 to 4) [3]. Rodent isoforms are orthologue to human SCD-1 with mouse and human SCD-1 sharing 85% sequence homology. SCD-1 is the major isoenzyme responsible for MUFA biosynthesis in most human and rodent tissues [3,10]. MUFAs are the most abundant fatty acids in mammalian cells. The rate-limiting step in their biosynthesis essentially depends on the isoenzyme SCD-1, which catalyzes the conversion of saturated acyl-CoA into *cis*-Δ9 monounsaturated acyl-CoA [12]. CoA-activated MUFAs are either released as free fatty acids or incorporated into phospholipids, triacylglycerols and cholesteryl ester [13,14]. The isoenzyme SCD-1 is ubiquitously

Abbreviations: AMPK, AMP-activated protein kinase; ER, endoplasmic reticulum; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; MUFA, monounsaturated fatty acid; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PI3K, phosphatidylinositol-3-kinase; PPAR, peroxisomal proliferator-activated receptors; PUFA, polyunsaturated fatty acid; SCD, stearoyl-coenzyme A desaturase; SFA, saturated fatty acid; SREBP, sterol responsive element binding protein; UPR, unfolded protein response.

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http://dx.doi.org/10.1016/j.bbalip.2016.08.009
1388-1981/

expressed in rodents and humans, especially in lipogenic tissues such as liver, adipose tissue and sebaceous glands of the skin [3,15–17]. Inhibition of SCD-1 depletes MUFAs and moderately accumulates saturated fatty acids (SFAs) in major lipid classes [18–21]. Changes in the activity of SCD-1 have comprehensive consequences on the cellular lipidome (the totality of cellular lipids) due to the tight co- and counter-regulation of the lipid metabolic network [22]. For example, SCD-1-deficient mice synthesize and store significantly less neutral lipids, i.e., triacylglycerols and cholesteryl ester, in liver [20] and peripheral tissues [23,24]. Such tremendous effects on the lipid composition upon inhibition of SCD-1 are not easily understood, in particular for human, because the dietary intake of MUFAs strongly outweigh their de novo biosynthesis [3]. It has been speculated that exogenously supplied and endogenously synthesized MUFAs belong to different fatty acid pools and have divergent metabolic fates and regulatory functions.

SCD-1 is an inducible enzyme and tightly regulated by dietary and hormonal factors as described in several excellent review articles [3,22,25]. SCD-1 is induced by insulin and repressed by leptin, an adipocyte-derived proteohormone that suppresses appetite and regulates energy homeostasis and (lipid) metabolism [26]. Moreover, carbohydrates, vitamins A and D and diverse classes of lipids including SFAs, MUFAs, polyunsaturated fatty acids (PUFAs) and cholesterol modulate SCD-1 expression. Also calorie restriction, fasting and gender have strong impact on SCD-1 expression in lipogenic tissues [27,28]. SCD-1 is mainly regulated at the transcriptional level by sterol responsive element binding protein (SREBP)-1c as major transcription factor [22]. SREBP-1c induces the expression of SCD-1 along with enzymes of de novo fatty acid biosynthesis [22]. Further transcription factors controlling SCD-1 expression are liver X receptor (though apparently depending on SREBP-1c), estrogen receptor, cyclic AMP response element-binding protein 1 (CREB1) and peroxisomal proliferator-activated receptors (PPARs) [4,22,29,30]. Besides transcriptional regulation, SCD-1 activity is controlled by rapid proteolytic cleavage [31–33] and epigenetic mechanisms [34,35].

The expression, activity and substrate/product ratios of SCD-1 are associated with various diseases such as diabetes, cancer, obesity, fatty liver and atherosclerosis in humans [3,10]. SCD-1-deficient mice have skin abnormalities such as alopecia, atrophy of sebaceous glands, dermatitis and fissures [7]. Moreover, they gain less weight and have less adipose tissue despite higher food intake compared to wild-type mice [24] which was explained from an increased heat production by uncoupled oxidative phosphorylation (thermogenesis) and thus higher energy expenditure [36,37]. Although thermogenesis is enhanced, mice lacking SCD-1 develop lower core body temperatures in the cold [36], apparently due to rapid depletion of energy resources [37]. Tissue selective knockout studies ascribe the increased energy expenditure and cold intolerance to the deletion of dermal SCD-1 [37]. SCD-1-deficiency prevents mice from becoming obese and diabetic at high-fat diet and reduces liver steatosis along with increasing insulin sensitivity and improving lipid metabolic profiles [3,24,38,39]. Among others, deletion of SCD-1 impairs hepatic cholesterol ester, triglyceride and de novo fatty acid biosynthesis [20,24]. Moreover, many rodent and human cancer cell lines and tumors overexpress SCD-1 and are enriched in MUFA-containing phospholipid species [5], and selective inhibition of SCD-1 reduced tumor volumes in mouse xenograft models [40–45].

Selective SCD-1 inhibitors were originally developed against metabolic diseases (diabetes and/or obesity) and extensively characterized in cellular and animal studies. Few have been progressed to clinical trials [10,11]. For example, the liver-targeting SCD inhibitor MK-8245, developed by Merck Frosst, was advanced to phase IIa clinical studies for the treatment of type 2 diabetes mellitus and inadequate glycemic control, though clinical trials seem to have been terminated [10]. As expected from knockout studies, the clinical use of SCD-1 inhibitors is limited by apparently target-based side effects, such as fissures of the eyelid, progressive alopecia and skin inflammation [10]. Pharmaceutical companies retracted their research on SCD-1 during the last years and shifted their focus on alternative indications such as cancer, skin disorders (e.g., acne) and nonalcoholic steatohepatitis and on liver-selective and cancer-selective SCD-1 inhibitors [10,11,46]. Researchers from Novartis recently developed the potent and selective SCD-1 inhibitor XEN801, the most advanced SCD-1 inhibitor so far, which has been claimed to reduce the number and size of sebaceous glands in mice [11]. XEN801 is currently in clinical phase II for the treatment of moderate to severe acne [47]. Promising advances in the development of SCD-1 inhibitors have also been made in the field of cancer. Screening over 200,000 small molecules led to the discovery of oxalamide and benzothiazolone prodrugs, which are selectively metabolized by human cancer cell lines, expressing cytochrome P450 (CYP)4F11, into irreversible inhibitors of SCD-1 [46]. Since mouse sebocytes are not targeted, the prodrugs have been suggested to possess anti-tumoral activity without inducing skin adverse effects. Taken together, SCD-1 is critical for cellular homeostasis and dysregulated in metabolic diseases, skin disorders and cancer. Animal and human studies suggest SCD-1 as powerful therapeutic target but also revealed safety issues that have to be resolved before clinical application.

2. Structure and catalytic mechanism of SCD-1

The X-ray structure of SCD-1 has recently been resolved for the human enzyme in complex with its substrate stearoyl-CoA (at 3.25 Å) [48] and for the substrate-free mouse enzyme (at 2.6 Å) [49]. SCD-1 consists of a cytosolic domain containing a di-metal active center and four alpha-helices forming a tight hydrophobic core, which is situated in the ER membrane. Acyl-CoA substrates bind to the surface of the cytoplasmic domain by forming multiple hydrogen bonds via the adenosine group, the panthothenate group and the carbonyl-group of the fatty acid. Moreover, the substrate is fixed by ionic interactions between the phosphates of CoA and a positively charged surface of the enzyme and by a cation-π-interaction between adenosine and Lys194. The acyl-chain enters a hydrophobic tunnel extending to the interface of the cytoplasmic and transmembrane domain (Fig. 1). The substrate tunnel has a kink, which is considered to hold the substrate and thereby determining regiospecificity of the enzyme and *cis*-conformation of the product. SCD-1 has a di-metal catalytic center consisting of two iron cations (in the crystal structures replaced by zinc cations) that are coordinated by histidine residues and a single water molecule (Fig. 1). This catalytic center for dehydrogenation is located adjacent to the kink in the hydrophobic tunnel and adjacent to carbons 9 and 10 of stearoyl-CoA.

The Δ9-desaturase SCD-1 introduces a *cis*-double bond into saturated fatty acids between carbons 9 and 10 (Fig. 2) [12]. Preferred substrates of SCD-1 are long-chain acyl-CoAs with 13 to 19 carbons, among them stearoyl-CoA and palmitoyl-CoA – the most abundant saturated fatty acid-CoA ester in mammalians. Dehydrogenation of the pro-*R* hydrogens at C9 and C10 requires molecular oxygen which is activated at the di-iron center and reduced to water [48]. Two of the electrons transferred to molecular oxygen derive from the acyl-CoA substrate and two others from the di-iron center. The ferrous catalytic center is regenerated by electron transfer from cytochrome *b*5, which has been suggested to bind to a groove at the cytoplasmic domain and to transmit electrons via two histidine residues (H157 and H298) bridging the distance (Fig. 1) [49]. Ferrocytochrome *b*5 is provided by cytochrome b5 reductase using NAD(P)H as co-substrate [25].

3. Survival and stress-activated signaling pathways regulated by SCD-1

SCD-1 deficiency protects against insulin resistance and obesity but also promotes skin abnormalities and surprisingly β-cell dysfunction [3,4,11], which counteracts the observed increase in insulin sensitivity. The mechanisms behind the two faces of SCD-1 are not fully understood; the balance of stress-inducing and stress-adapting signaling

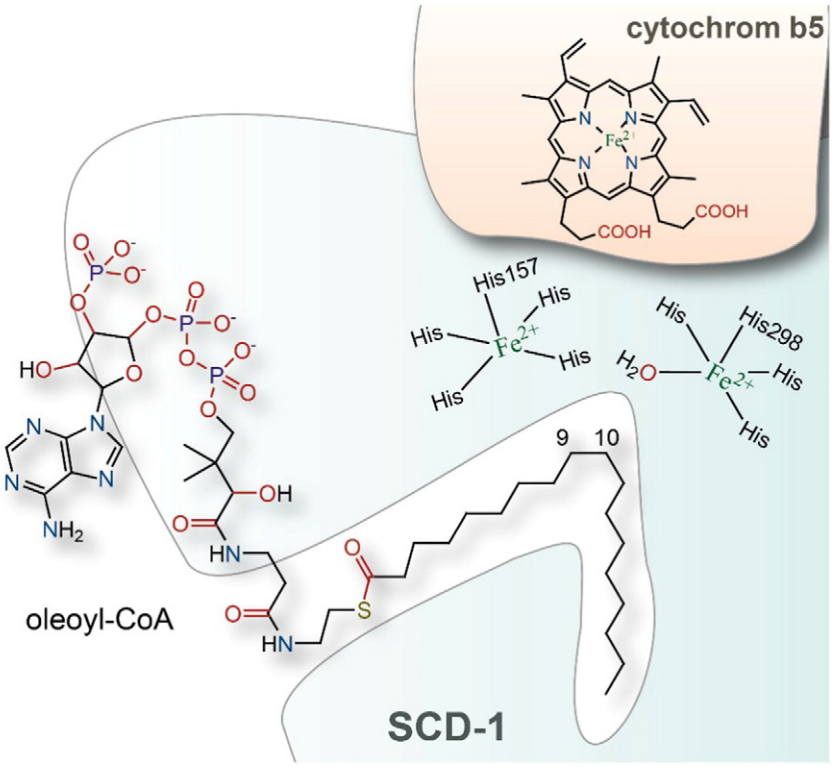

Fig. 1. Active site of SCD-1 with the substrate oleoyl-CoA, the di-iron catalytic center and the proposed binding site of the electron donor cytochrome *b*5. His157 and His298 have been suggested to be part of an electron transport chain from cytochrome *b*5 to the di-iron center. The kink in the substrate channel places C9 and C10 adjacent to the catalytic center and enforces a *cis*-configuration of the desaturated product.

pathways as well as the availability of MUFAs and SFAs seem to be essential (Fig. 3). Thus, SCD-1 knock-out mice are protected from obesity and insulin resistance at high-fat diet [24,38] but develop severe loss of body weight and hypoglycemia when dietary intake of MUFAs is restricted (at very low-fat diet), which has been attributed to the induction of hepatic ER stress [50].

3.1. Physicochemical membrane properties

Substrates (SFAs) and products (MUFAs) of SCD-1 are the most abundant fatty acids in mammalian phospholipids, triacylglycerols and cholesterol ester which suggests a strong impact of SCD-1 on membrane physiology, energy storage, membrane protein function and other membrane-associated processes such as vesicle transport. The ratio of MUFAs to SFAs critically determines the desaturation index of membranes and thus lateral fluidity, the phase transition temperature and potentially rigidity [51–53]. Whether SCD-1-mediated changes in the cellular lipid composition are translated into altered physicochemical membrane properties and thereby affect biological processes is poorly understood. Lyn et al. recently reported that inhibition of SCD-1 disrupts the integrity of membranous hepatitis C virus replication complexes [54], and Tan et al. observed an interference with lipid raft formation and signaling [55].

Loss of SCD-1 activity induces complex changes in the fatty acid composition of membrane lipids which are not restricted to the MUFA/SFA ratio. For example, PUFA levels and indices for SCD-1 activity are inversely associated in human plasma [56]. Accordingly, we and others could show that genetic and pharmacological inhibition of SCD-1 elevates the proportion of PUFAs in phospholipids [18,19,21,57], which suggests that the lack of de novo synthesized MUFAs is compensated by exogenously supplied fatty acids including essential PUFAs from the cell culture medium or diet. PUFAs are efficiently incorporated into the *sn*-2 position of phospholipids by lysophospholipid acyltransferases and elevate the fluidity of membranes [14]. Thus, it is tempting to speculate that the increased proportion of phospholipid-bound PUFAs might buffer the anticipated decrease of membrane fluidity in SCD-1-deficient cells, previously postulated from the lower MUFA/SFA ratio. Moreover, phospholipid-bound

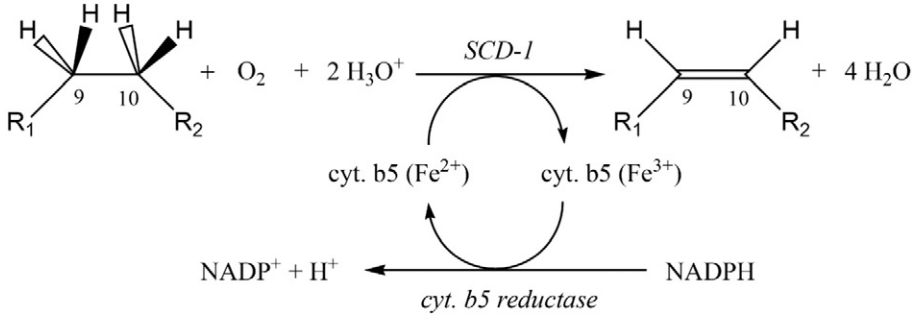

Fig. 2. SCD-1 catalyzes the formation of a *cis*-Δ9-double bond using cytochrome (cyt.) b5 as redox-active co-substrate and reducing molecular oxygen to water. Ferrocytochrome b5 [cyt. b5 (Fe^{2+})] is regenerated by reduction of ferricytochrome b5 [cyt. b5 (Fe^{3+})] through cyt. b5 reductase using NADPH as electron donor.

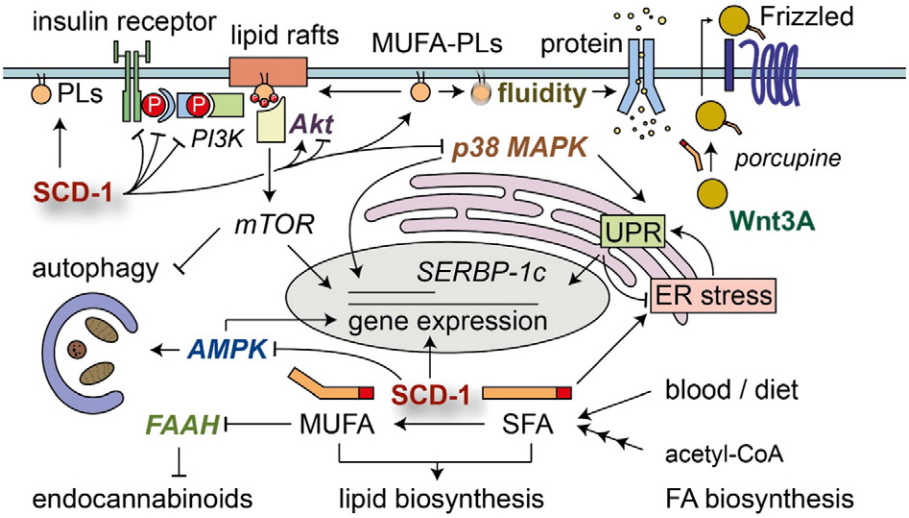

Fig. 3. Schematic overview about major stress- and survival-related signaling pathways regulated by SCD-1. SFAs, either taken up by diet or produced by de novo fatty acid (FA) biosynthesis, are converted to MUFAs by SCD-1. MUFAs are efficiently incorporated into cellular lipids including phospholipids (PLs), directly inhibit fatty acid amide hydrolase (FAAH) and thus the degradation of endocannabinoids and are covalently coupled to Wnt3A with impact on Wnt/β-catenin signaling. Moreover, SCD-1 i) regulates gene expression, ii) suppresses the activation of AMPK, p38 MAPK and insulin signaling, iii) induces or represses Akt signaling, iv) promotes SFA-dependent lipotoxicity, ER stress, the UPR, and autophagy v) facilitates the formation of lipid rafts and vi) potentially affects protein structure and function by altered biophysical membrane properties such as fluidity.

PUFAs are converted to structurally diverse bioactive lipids [58] and directly interfere with signaling molecules, e.g. Akt [59], which might further contribute to the pleiotropic effects of SCD-1 on cell signaling.

Although it is widely accepted that SCD-1 influences biophysical membrane properties, the physiological importance of such a mechanism has not yet been confirmed and is meanwhile controversially discussed [60,61]. On the one hand, changes in physicochemical membrane properties are expected to have broad, unspecific effects on membrane-associated processes. On the other hand, SCD-1 regulates multiple but clearly defined downstream signaling pathways in a selective manner as described in the following.

3.2. Insulin/Akt signaling

Insulin is not only involved in metabolic regulation but also acts as growth factor by inducing mitogenic signaling pathways, such as protein kinase B (Akt) and extracellular signal-regulated kinase (ERK)1/2 [62], that promote cellular vitality under stress conditions and counteract mechanisms of programmed cell death [63]. SCD-1 deficiency induces insulin signaling in peripheral tissues, namely phosphorylation of insulin receptor and insulin receptor substrates (IRS)1 and 2 [64]. Association of IRS isoforms with the regulatory subunit of phosphatidylinositol-3-kinase (PI3K) [64] promotes the synthesis of phosphatidylinositol-3,4,5-trisphoshates (PIP_3) as membrane anchor sites for the serine/threonine kinase Akt [63]. Membrane translocation of Akt is followed by phosphorylation and thus activation by co-recruited kinases [64]. After dissociation from the membrane, Akt facilitates the membrane translocation of glucose transporter type (GLUT)4 [64] and regulates pleiotropic signaling and transcription factors that are involved in cell cycle control, apoptosis and differentiation [63]. The enhanced phosphorylation of IRS1 in SCD-1 knockout mice was ascribed, at least partially, to the moderate repression of protein tyrosine phosphatase 1B (PTB-1B), which rapidly dephosphorylates IRS1 and 2 [64]. Dobrzyn et al. suggested that the insulin-sensitizing effect of SCD-1 deficiency in skeletal muscle depends on an accumulation of lipids [61]. In fact, lipids are critical factors promoting insulin resistance and not only enriched in adipose tissue but also in liver and muscle of insulin-resistant patients [65]. However, the exact mechanisms how SCD-1-mediated lipid accumulation might affect insulin receptor signaling are not known.

In multiple cancer cell lines, SCD-1 inhibition downregulates the PI3K/Akt/mechanistic target of rapamycin (mTOR)-axis along with reducing cell proliferation and viability [5,66], potentially by disrupting lipid raft formation [55]. In fact, genetic and pharmacological inhibition of SCD-1 in tsc2(−/−) mouse embryonic fibroblasts reduced the cellular staining of lipid rafts as well as binding of Akt to these domains [55]. Translocation of Akt from the cytosol to membrane lipid domains is essential for its activation by co-recruited kinases [63].

3.3. Metabolism and energy homeostasis

SCD-1 is critical for cell proliferation, especially in hyperproliferative cells, such as cancer cells [5]. Reasons discussed are i) the restricted supply of MUFAs for membrane biogenesis, which is essential for cell division, ii) the induction of mitogenic signal transduction pathways (e.g., the PI3K/Akt signaling cascade described above) and iii) the regulation of cellular metabolism and energy homeostasis with AMP-activated protein kinase (AMPK) as a major sensor. AMPK is activated at low energy states and maintains energy balance by inducing catabolic ATP production, e.g., through glucose uptake, glycolysis and β-oxidation of fatty acids [67]. Energy-consuming processes such as glucose and lipid biosynthesis are instead downregulated. Moreover, AMPK elicits insulin-sensitizing effects and has been proposed as therapeutic target of type 2 diabetes [67,68]. Knockout of SCD-1 activates AMPK in mouse liver [69] and skeletal muscle [70] and accordingly enhances fatty acid oxidation, diminishes lipid biosynthesis and increases thermogenesis [61].

Another mechanism by which SCD-1 modulates overall lipid metabolism depends on the negative regulation of the lipogenic transcription factor SREBP-1c, thereby reducing lipid biosynthesis and enhancing β-oxidation of fatty acids [61,71]. Examples for lipid metabolic enzymes regulated by SCD-1 activity are hepatic fatty acid synthase, glycerol-3-phosphate acyltransferase, carnitine palmitoyltransferase (CPT)1, and very long chain acyl-CoA dehydrogenase [24]. The comprehensive effect of SCD-1 deficiency on lipid metabolism might represent a feed-back mechanism that aims to maintain the relative composition of cellular lipids despite the restriction of MUFAs. In addition, knockout of SCD-1 suppresses the expression of gluconeogenetic enzymes, including the rate-limiting enzyme phosphoenolpyruvate carboxykinase [38]. How SCD-1 blockade regulates AMPK and SREBP-1c expression is not known so far.

3.4. Endoplasmic reticulum (ER)-stress, unfolded protein response (UPR) and autophagy

Many physiological and pathophysiological stress conditions, including lipotoxic stress, lead to an accumulation of misfolded proteins in the ER [72]. To cope with ER stress, cells engage an adaptive signaling cascade called UPR, which coordinates the recovery of homeostasis or drives cells into apoptosis if the damage is irremediable. Three UPR sensors located in the ER membrane have been discovered in mammalians: endoribonuclease inositol-requiring enzyme (IRE)1α, protein kinase RNA-like endoplasmic reticulum kinase (PERK) and activating transcription factor (ATF)6α [72]. Inhibition of SCD-1 enhances prolonged ER stress and activates the UPR in pre-stressed cells in line with the hypothesis of SCD-1 being part of an adaptive stress response [4,21,73–75]. Focus has been placed on stress conditions related to an excess of SFAs or a lack of dietary unsaturated fat [4,73–75]. The role of SCD-1 under non-lipotoxic stress conditions is poorly understood. We have recently shown that inhibition of SCD-1 augments the UPR during cell cycle stress (arrest in G2/M phase) [21], which might be indirectly linked to lipotoxic stress because multiple enzymes of lipid biosynthesis, including acetyl CoA carboxylase, are cell cycle-dependently regulated [76]. Moreover, mechanical shear stress has been shown to induce SCD-1 expression in human umbilical vein endothelial cells [77]. However, it remains elusive whether upregulation of SCD-1 is actually relevant for the cellular adaption to shear stress, e.g., by adjusting membrane elasticity and deformability. Inhibition of SCD-1 does not induce ER stress and the UPR under basal, non-stressed conditions as shown in vitro for insulin-producing mouse insulinoma MIN6 cells and mouse RAW264.7 macrophages and in vivo in mouse liver [4,21,73–75]. Although the underlying mechanisms are a matter of dispute as discussed below (chapter 4), SCD-1 protects cells from SFA-induced lipotoxicity, and its induction represents an important adaption mechanism against SFA-induced lipotoxic stress in most cell types [4] with only few exceptions [78]. For example, i) expression of SCD-1 in palmitate-stressed primary human monocytes inversely correlates with the ER stress response and apoptosis [79], ii) pancreatic β-cells induce SCD-1 expression when challenged with SFAs while inhibition of SCD-1 diminishes palmitate resistance [80] and iii) human arterial endothelial cells, which do not induce SCD-1 expression in response to SFAs, are sensitive to lipotoxicity, while concomitant overexpression of SCD-1 has a protective function [81]. Based on these findings, the substantially impaired insulin secretion of SCD-1-deficient β-cells from leptin-deficient obese mice has been attributed to the lipotoxic loss of β-cell function [75].

Another strategy to mitigate ER stress is the induction of autophagy [82], which is dynamically interconnected with ER stress and the UPR by so far incompletely understood positive and negative regulatory mechanisms [83]. Autophagy is a major pathway for the clearance of intracellular protein aggregates and damaged organelles [82]. Cytoplasmic components are sequestered into autophagosomes by enclosing portions of the cytoplasm into an isolation membrane [83], which is formed at ER/mitochondria contact sites [84] and characterized by a high content of unsaturated fatty acids [85]. Autophagosomes subsequently fuse with endosomes and lysosomes to form autolysosomes which degrade cytoplasmic macromolecules by lysosomal hydrolases [82]. Since degradation products such as amino acids and fatty acids are recycled, autophagy gains importance at low energy states as persistence mechanism. Autophagy is essential for cellular homeostasis at a basal level and upregulated under diverse stress conditions including starvation, immune cell activation, β-cell activity and cell death [82]. The multicomponent core autophagy machinery tightly regulates autophagy together with a variety of additional factors. The PI3K/Akt/mTOR-axis is a principle negative and AMPK a positive regulator of autophagy [82]. Inhibition of SCD-1 has been shown to enhance autophagy in tsc2(−/−) mouse embryonic fibroblasts (possessing constitutively active MTORC1) [55] and hepatocellular carcinoma cells (characterized by increased de novo biosynthesis of fatty acids) [86] either by diminishing Akt activation followed by forkhead-box-protein O (FOXO)1 nuclear translocation and transcription of genes involved in autophagy [55] or by activation of AMPK [86]. On the other hand, SCD-1 inhibition suppressed starvation-induced autophagy in mouse embryonic fibroblasts [87] and palmitate-induced autophagy in rat pancreatic β-cells apparently by disturbing autophagosome-lysosome fusion [88]. Taken together, SCD-1 has a dual function in the regulation of autophagy by either promoting or inhibiting autophagy depending on the experimental settings and stress conditions.

3.5. Stress-activated protein kinases

The stress-activated protein kinases p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) are key enzymes at the interface of stress signaling, metabolic control, survival and differentiation [89]. Since these kinases are downstream targets of the UPR, it is not surprising that inhibition of SCD-1 and subsequent enhancement of ER stress in stressed fibroblasts results in their phosphorylation and thus activation [72,90]. However, p38 MAPK is also activated independently of the UPR by inhibition of SCD-1 [21], and then promotes the UPR in a feed-forward mechanism [91,92]. The counter-regulation of p38 MAPK by SCD-1 is critical for ER homeostasis: ER stress is prevented, the UPR suppressed and ER morphology maintained under stress conditions such as lipotoxic stress and cell cycle arrest [21]. Inhibition of SCD-1 activates upstream kinases of p38 MAPK, among others mixed-lineage protein kinase (MLK)3 and mitogen-activated protein kinase kinase (MKK)3/6 (Thürmer and Koeberle, 2016, unpublished data). Key for the activation of p38 MAPK signaling seems to be a lack of SCD-1-derived MUFAs rather than an accumulation of SFAs [21].

3.6. Other signaling pathways

Due to the central role of SFAs and MUFAs for cell function and viability, interference with SCD-1 has complex, often indirect effects on mitogenic signaling pathways. For example, silencing of SCD-1 in breast cancer cells decreases extracellular signal-regulated kinase (ERK)1/2 activation and the expression of cell cycle genes along with activation of glycogen synthase kinase (GSK)-3 and suppression of mitogenic β-catenin signaling [93]. Rios-Esteves et al. recently described a mechanism that might explain the suppressive effect of SCD-1 inhibition on Wnt/β-catenin signaling [94]. They show that SCD-1 activity is required for the production of MUFA-CoA, a substrate of the membrane-bound O-acyltransferase (MBOAT) family member porcupine that posttranslationally adds a palmitoleoyl group to serine 209 of Wnt3A [95]. This lipid modification is essential for secretion of Wnt3A and the interaction with its receptor Frizzled [96,97]. Moreover, SCD-1-derived MUFAs directly inhibit fatty acid amide hydrolase, which degrades the endocannabinoid arachidonoylethanolamide, an endogenous ligand of cannabinoid receptors [98]. Inhibition of fatty acid amide hydrolase has been shown to protect from insulin resistance [99].

4. Molecular link between SCD-1 activity and cell signaling

SCD-1 orchestrates multiple stress- and survival-related signal transduction pathways, though the exact molecular mechanisms that trigger SCD-1 activity with early signaling events are diffuse; most hypotheses are based on correlations and lack confirmation. For example, a plethora of molecular targets have been reported for SCD-1 substrates (SFAs) and products (MUFAs), including free fatty acid receptors [100], PPARs [101], ion channels [102], toll-like receptors [103], mitogenic kinases [104], sensor proteins of the UPR [105], pro-inflammatory factors [106] and lipid metabolic enzymes [107]. Moreover, SFAs and MUFAs represent important building blocks for membrane biogenesis, influence biophysical membrane properties, and have been, in case of palmitoleate, proposed as lipokines [60,108].

On the other hand, i) SCD-1 has broad but still specialized functions in cell signaling, which are not simply reflected by those described for SFAs and MUFAs, and ii) mechanisms of action reported for these fatty acids often require much higher concentrations as can be expected from the regulation of SCD-1 [3–5,8,61,109]. For example, the increase of phospholipid saturation upon inhibition of SCD-1 has been proposed to enhance the UPR in presence of an excess of SFAs [18] either through disturbing Ca^{2+} homeostasis [110], activating PERK [105] or autophosphorylating inositol-requiring 1α (IRE1α) [111]. This hypothesis seems reasonable because SFAs are well-established inducers of lipotoxic ER stress at high, physiological concentrations, and SFA-induced lipotoxicity has been associated with ER stress, e.g., in pancreatic β-cells with apparent consequence on insulin resistance [3,80]. However, neither deletion nor inhibition of SCD-1 is sufficient to evoke the required dramatic changes in the proportion of saturated phospholipids (SCD-1: up to 3–12 mol% [18–20]; required: ≥20 mol% [105,110]). Alternative mechanisms apparently exist, which might be based on spatially and/or time-resolved pools of MUFAs with different function.

The nature of these mechanisms is only starting to be understood and represents one of the most fascinating but also challenging questions of current SCD-1 research. SCD-1 has recently been shown to be essential for the proper organization and function of lipid rafts, specialized lipid domains that accommodate distinct membrane receptors and signaling factors, such as Akt [55]. Moreover, SCD-1-derived MUFAs are required for palmitoleylation of Wnt3A and subsequent β-catenin signaling [95] and they have been reported to directly inhibit fatty acid amide hydrolase, an endocannabinoid hydrolyzing enzyme [98]. These mechanisms only account for a small proportion of the pleiotropic bioactivities of SCD-1. Multiple so far unknown direct molecular targets apparently exist, but both their nature and the precise identity of lipid factors responsible for mediating the biological effects of SCD-1 remain a mystery. Potential lipid factors besides free fatty acids and acyl-CoA ester are MUFA-containing phospholipids, such as phosphatidylinositols, which respond sensitive to changes in SCD-1 activity (as shown for mouse fibroblasts) and play a key role in cell signaling as phosphoinositides [60]. Further candidates are lipid mediators such as ceramides, diacylglycerols and fully saturated phosphatidic acids [57,70,112,113] but also storage lipids like triacylglycerols and cholesteryl ester [20], possibly by modulating the function of lipid droplets [114]. The content of these lipids is significantly altered in liver and other tissues of SCD-1-deficient mice. In fact, Chen et al. recently confirmed by rescue experiments that the increase of ceramide levels upon inhibition of SCD-1 promotes apoptosis of colorectal cancer cells and delays tumor growth in a mouse xenograft of colorectal cancer [42].

5. Conclusion

The development of SCD-1 inhibitors is hampered by the fragmentary knowledge about how SCD-1 mediates biological responses. In particular, the link between SCD-1 and major cellular signaling cascades remained diffuse despite enormous efforts during the last decade. Major hurdles are i) the unknown identity and likely diversity of bioactive lipid factors that mediate the cellular effects of SCD-1, ii) the apparent existence of defined pools of SCD-1-derived MUFAs, and iii) the broad (though specific) interference of SCD-1 inhibition with cell metabolism and signaling. It is meanwhile widely accepted that SCD-1 mediates its pleiotropic functions through multiple mechanisms, including stress-inductive, stress-adaptive and mitogenic signaling pathways that essentially contribute to cellular homeostasis, vitality and functionality. Less understood is how the regulation of these signaling pathways may induce defined biological responses. From a network science perspective, the interference with key nodes (e.g., the inhibition of SCD-1) may produce different responses in tightly controlled signaling networks depending on system-specific factors, e.g., metabolic enzymes that convert MUFAs into bioactive signaling molecules [115,116]. Since the expression and activity of these factors substantially differs between cell types and metabolic conditions, changes in SCD-1 activity may have diverse effects on cell function depending on the experimental settings. In fact, an expanding body of knockout and inhibitor studies shows that SCD-1 differentially and even contrarily regulates biological outputs depending on species, diet, tissue, cell type and further experimental parameters [3–9]. Hence, comprehensive lipidomics analysis together with functional genomic, transcriptomic and (phospho)proteomic approaches might be valuable to gain in-depth insights into the signaling mechanisms of SCD-1 especially when combined with system biological network analysis and when applied to relevant disease models. The detailed knowledge of these interrelations will help to estimate the pros and cons of targeting SCD-1 under different pathological states and might direct the development of tissue-selective SCD-1 inhibitors.

Transparency document

The Transparency document associated with this article can be found, in the online version.

Acknowledgements

We kindly acknowledge the support from DFG Research Grant KO 4589/4-1 and RTG 1715.

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