Biochimie 93 (2011) 78–86

Contents lists available at ScienceDirect

Biochimie

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

Mini-review

Hormonal and nutritional regulation of SCD1 gene expression

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ARTICLE INFO

Article history:
Received 26 May 2010
Accepted 3 August 2010
Available online 14 August 2010

Keywords:
Stearoyl-Coa desaturase 1
Hormonal regulation
Nutritional regulation
Transcription factors

ABSTRACT

Stearoyl-CoA Desaturase 1 (SCD1) is the rate limiting enzyme catalyzing the biosynthesis of monounsaturated fatty acids preferentially from palmitoyl-CoA and stearoyl-CoA forming respectively palmitoleyl-CoA and oleyl-CoA. These monounsaturated fatty acids are the key components of triglycerides and membrane phospholipids. Studying the regulation of SCD1 is of particular interest since alterations in phospholipids composition have been implicated in a variety of diseases including cancers, diabetes and cardiovascular disorders. Furthermore, oleic acid, the main product of SCD1 reaction, is the predominant fatty acid of human adipose tissue triacylglycerols, associating SCD1 with the development of obesity and the metabolic syndrome. In light of the key role of SCD1 in general metabolism, it is not surprising to observe a very tight and complex regulation of SCD1 gene expression in response to various parameters including hormonal and nutrient factors. In this review we analyze the anatomy and index the transcription factors that have been characterized to bind the SCD1 promoter. Then we present the current knowledge on how hormones regulate SCD1 expression with a particular interest on the role of insulin and leptin. We also describe how nutrients especially polyunsaturated fatty acids and carbohydrates modulate SCD1 gene expression.

1. Introduction

The stearoyl-CoA Desaturase 1 (SCD1) is a 40 kDa intrinsic membrane protein anchored in the endoplasmic reticulum. This iron-containing enzyme catalyzes the biosynthesis of monounsaturated fatty acids that requires acyl-CoA, NADH, NADH-reductase, cytochrome b5, phospholipid, and oxygen [1]. SCD1 introduces a *cis* double bond in the Δ9 position of fatty acyl-CoA substrates. SCD can act on chain lengths from C12:0 to C19:0 [2]. However SCD1 preferred desaturation substrates are palmitoyl-CoA (C16:0) and stearoyl-CoA (C:18:0), which are converted to palmitoleoyl-CoA (C16:1) and oleoyl-CoA (C18:1) respectively [3]. These monounsaturated fatty acids are key substrates for the formation of phospholipids, triacylglycerols, cholesterol and wax esters. Phospholipid composition is important in the maintenance of membrane fluidity necessary for a normal cellular function. Moreover triacylglycerols which are predominant fatty acids in human adipose tissue are principally formed from oleic acid, the main product of SCD1 reaction [4]. Furthermore alterations in phospholipids composition have been implicated in a variety of diseases including cancers [5,6] type II diabetes [7,8] and cardiovascular disorders [9,10], thus associating SCD1 with these diseases.

SCD1 regulation is a very complex phenomena as the intracellular concentration of desaturases fluctuates in response to a very large number of effectors including hormonal and dietary factors : SCD1 is the principal target of these stimuli [11]. SCD1 is also very tightly regulated as the regulation of SCD occurs through a regulation at the transcriptional level but also through a rapid protein degradation [12–14] producing variation of enzymatic activities in response to various physiologic demands.

In the present review we analyze data on the regulation of SCD1 gene expression mainly in liver and adipose tissue. A first focus will be made on the anatomy of the SCD1 promoter and on the transcription factors binding on this regulatory region. A section will then describe the association of SCD1 with cancer and obesity. Thereafter, we will present the current knowledge on how

Abbreviations: AA, arachidonic acid; Akt, protein kinase B; AP-1, Activated Protein-1; C/EBP, CCAAT-enhancer-binding protein; ChREBP, Carbohydrates response element binding protein; CLA, Conjugated Linoleic Acid; DHA, Docosahexaenoic Acid; EGF, Epidermal Growth Factor; EPA, Eicosapentaenoic Acid; ERK1/2, Extracellular Regulated Kinase 1/2; IRE, Insulin Response Element; Jak2, Janus kinase 2; KGF, Keratinocyte Growth Factor; LepRE, Leptin Response Element; LXR, Liver X Receptor; MAPK, Mitogen Activated Protein Kinase; mTOR, mammalian Target Of Rapamycin; NF-1, NF-Y: Nuclear Factor 1/Y; PDGF, Platelet-Derived Growth Factor; PI3K, Phosphoinositide-3-kinase; PPAR, Peroxisome Proliferator-Activated Receptor; PGC-1, peroxisome proliferator-activated receptor co-activator-1; PUFA, Polyunsaturated Fatty Acid; p90RSK, p90 Ribosomal S6 Kinase; SCD, Stearoyl-CoA Desaturase; SREBP, Sterol Regulatory Element Binding Protein; STAT3, Signal Transducer and Activator of Transcription 3; TGF, Tumor Growth Factor; VLDL, Very Low Density Lipoprotein.

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doi:10.1016/j.biochi.2010.08.001

hormones regulate the SCD1 promoter with a particular focus on the role of insulin and leptin. The last part of this review will describe how nutrients, especially polyunsaturated fatty acids (PUFAs) and carbohydrates, modulate SCD1 gene expression.

2. Stearoyl-CoA desaturase gene

The entire coding sequences of the SCD genes as well as their promoter regions have been characterized in different species. Four SCD isoforms have been identified in mice [15–18]. The mSCD1 gene is expressed in various tissues including liver and adipose tissue. The mSCD2 is mainly expressed in brain while mSCD3 expression is restricted to the harderian gland. The expression of the mSCD4 appears to be restricted to the heart. Two SCD isoforms have been isolated in rat (SCD1 and SCD2) [19], and in human (SCD1 and SCD5) [20,21]. The hSCD1 shares a high homology with the rat and mouse genes, however, the hSCD5, which is mainly expressed in brain and pancreas, appears to be specific of primates. To date, in birds (chicken [22] and goose [23]), only one isoform has been isolated. It is ubiquitously expressed with a higher expression observed in hypothalamus, kidney, liver, and adipose tissue [24].

The human SCD1 gene spans 24 kb and contains 6 exons [20]. The exon 1 contains the ATG while the exon 6 encodes for a very long (around 2 kb) 3′-untranslated region. This unusual long 3′-untranslated region, also observed in yeast, contains several structural motifs UUAUUUA(U/A)(U/A) [15,19,20,25] characteristics of mRNA destabilization motifs [26]. A similar gene organization is observed in rat and mouse.

Promoter regions of SCD1 genes have been characterized in various species including mice [27], human [28], chicken [29], goose [23] and bovine [30]. High carbohydrate diet [31–33], insulin [22,31–34], peroxisome proliferators and cholesterol were identified as positive effectors of SCD1 transcription [34–36] whereas, triiodothyronine (T3), estrogen, PUFAs and leptin were described as inhibitors [37–41]. Numerous transcription factors bind to the SCD1 promoter suggesting a fine regulation of SCD1 expression. This includes SREBP-1c, LXR, PPAR-α, C/EBP-α, NF-1, NF-Y, AP-1, Sp1, TR and PGC1-α (Fig. 1).

3. Role of SCD1 in obesity and cancer

Increased expression of SCD1 may be implicated in cancer development [6,42,43], however no general trend among cancer types has been observed. Indeed, Scaglia et al. links upregulation of SCD1 to increased neoplastic cell transformation [44]. In various studies, they showed that SCD1 inhibition has been associated with impairs cell survival in human lung carcinoma cell lines [43,45,46]. Moreover a recent study showed that inhibition of SCD1 blocks prostate cancer progression in mice [47]. In contrast, Moore et al. observed that loss of SCD1 expression is often seen in prostate cancer [42]. Furthermore, inhibition of SCD1 does not seem to affect cell death in the human breast carcinoma MDA-MB-468 [43]. Hence, further investigations are needed to precisely clarify the role of SCD1 in tumorogenesis.

Evidences describe SCD1 as a potential target to prevent or treat obesity and the associated metabolic syndrome. Most of this was based on the observations made in mice. Mouse models of obesity which have a high level of SCD1 expression present a liver steatosis and insulin resistance [48,49]. In contrast, mice deficient in SCD1 are lean, resistant to diet-induced obesity and insulin sensitive [49,50]. Furthermore, two studies performed in human and another one in mouse showed that increased cellular SCD1 activity influences the general cellular fatty acid composition by promoting fatty acid synthesis and decreasing oxidation [51–53]. Hence, decreasing SCD1 expression might protect against obesity and insulin resistance. However, two other independent studies performed in humans have associated a low hepatic SCD1 activity with fatty liver and insulin resistance [54,55]. More data are needed in order to confirm the exact role of SCD1 in obesity and the associated metabolic syndrome.

4. The hormonal regulation of SCD1

4.1. Insulin

Insulin is a powerful activator of SCD1 transcription and has been shown, *in-vitro* and *in-vivo,* to induce SCD1 expression in many species including mice [33,56], bovine [30], chicken [22] and human [57]. Sequence analyses of SCD1 promoters display similar structures among chicken, mice and human revealing the presence of consensus binding sites for transcription factors known to mediate the insulin response. This includes binding sites for SREBP-1c, C/EBP-α, NF-1 and NF-Y. This also suggests a similar regulation between species [22,28,58]. The characterization of the insulin effect on SCD1 transcription has been mainly studied in adipose tissue and liver cells (Table 1).

The preadipocyte model 3T3-L1 has been extensively used to study the regulation of SCD1 expression. 3T3-L1 can be differentiated into adipocytes by 3-isobutyl-1-methylxanthine, dexamethasone and a strong dose of insulin [59]. Growth arrested preadipocytes are first characterized by a transient increase in C/EBP-β expression followed by the terminal differentiation where transcription factors such as C/EBP-α and SREBP-1c are expressed. Their activations then coordinate the expression of lipogenic genes including SCD1 to create and maintain the adipocyte phenotype [60]. In this system, Casimir and Ntambi showed that SCD1

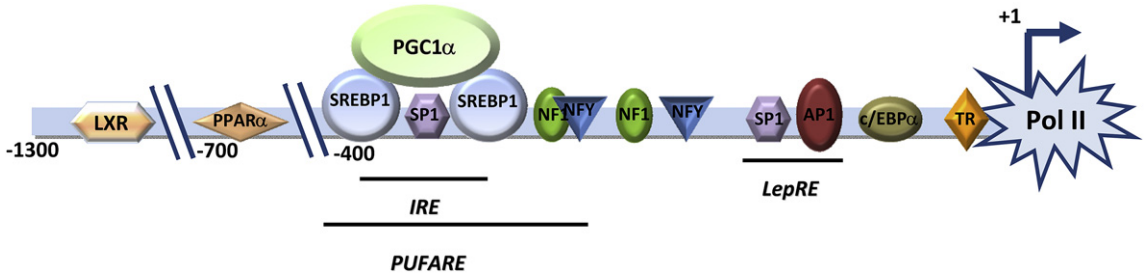

Fig. 1. Diagram of the SCD1 gene promoter. The diagram shows the different transcription factors and regions involved in the regulation of SCD1 gene transcription. It represents elements characterized in human, mouse or chicken promoters which are conserved between species. *LXR*: Liver X Receptor, *PPAR*: Peroxisome Proliferator-Activated Receptor, *SREBP*: Sterol Regulatory Element Binding Protein, *PGC-1α*: peroxisome proliferator-activated receptor co-activator-1α, NF-1/Y: Nuclear factor 1/Y, *AP-1*: Activator Protein-1; *C/EBP*: CAAT/enhance binding protein, *TR*: Triiodothyronine receptor, *Pol II*: RNA polymerase II; *IRE*: Insulin response element, *PUFARE*: Polyunsaturated Fatty Acid response element; *LepRE*: Leptin response element.