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Review

SCD (stearoyl-CoA desaturase (delta-9-desaturase))

Amir Mehdizadeh, Shabnam Fayezi, Masoud Darabi

Liver, Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, (AM, MD); Students Research Committee, Department of Anatomy, Cell Biology, Shahid Beheshti University of Medical Sciences School of Medicine, Tehran (SF), Iran; mehdizadeha@tbzmed.ac.ir; shfayezi@sbmu.ac.ir; darabim@tbzmed.ac.ir

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Abstract

Despite the presence of monounsaturated fatty acids (MUFA) in the usual diet, these fatty acids may also be synthesized de novo from saturated fatty acids (SFA) through enzymatic desaturase activity (Arregui et al., 2012). Stearoyl-CoA desaturase (SCD)1 and SCD5 isozymes have been identified in human. SCD1 or ?9 desaturase is predominantly expressed in adipose tissue, meibomian, harderian and preputial glands. This enzyme is highly induced in response to high carbohydrate diet (Mauvoisin Mounier, 2011). It has been proven that the elevated levels of SCD1 are associated with obesity, metabolic disorders and malignancies. Altogether, these findings propose SCD1 as a new therapeutic target.

Keywords

Stearoyl-CoA desaturase 1, monounsaturated fatty acids, saturated fatty acids

Identity

Other names: PRO1933, FADS5, MSTP0081, SCDOS, SCD1

HGNC (Hugo): SCD

Location: 10q24.31

Local order

Locus tag (NCBI), PRO1933. 5'- 100347015 - 100364831 -3'; strand: (-). The human SCD1 gene is centromeric to LINC00263 (long intergenic non-protein coding RNA 263) and telomeric to PKD2L1 (polycystic kidney disease 2-like 1).

DNA/RNA

Note

SCD1 gene encodes an enzyme that serves as a fatty acid synthesizing enzyme and mostly produces oleic acid from stearic acid. Transcripts with alternative polyadenlyation and sizes 3.9 and 5.2 kb has been detected for this gene.

Description

SCD1 gene is located on chromosome 10q24.31, spans approximately 24 kb and has 6 exons and is mostly expressed in white adipose tissue and the liver (Arregui et al., 2012). The exon 1 is only 324bp while the exon 6 encodes for around 2 kb 3'-untranslated region (Mauvoisin & Mounier, 2011).

Exon number	1	2	3	4	5	6
Base number	1..517	1050..1332	5352..5482	7413..7618	9518..9750	13720..1781

Schematic representation of the genomic organization of exons of the SCD1 gene (17817 bp).

Domain	Cytoplasmic	Transmembrane	Lumenal	Transmembrane	Cytoplasmic	Transmembrane	Lumenal	Transmembrane	Cytoplasmic
Position	1-71	72-93	94-102	103-119	120-216	217-235	236-250	251-273	274-359

A schematic representation of the domain structure of SCD1 protein (359 amino acids total), which consists of cytoplasmic, transmembrane, and lumenal domains.

Transcription

The critical region for promoter activity is located between nucleotides 496-609 upstream of the translation start site. CCAAT box is identified as an important cis-element binding site in this region (Zhang, Ge, Tran, Stenn, & Prouty, 2001). Different transcription factors such as SREBP-1c, LXR, PPAR-a, C/EBP-a, NF-1, NF-Y, AP-1, Sp1, TR and PGC1-a bind to SCD1 promoter controlling the expression level of SCD1 (Mauvoisin & Mounier, 2011).

Pseudogene

Pseudogene of this gene is located on chromosome 17 at 17p11.2. The SCD1 pseudogene has two premature in-frame stop codons and is transcriptionally inactive (Zhang, Ge, Parimoo, Stenn, & Prouty, 1999).

Protein

Note

SCD1 is an iron containing enzyme which catalyses the oxidation of palmitoyl-CoA and stearoyl-CoA in ?9 position to produce corresponding derivatives palmitoleoyl-CoA and oleoyl-CoA, respectively. Formation of cis double bond is mediated by electeron-transfer proteins sequentially NADH-cytochrome b5 reductase, cytochrome b5 and SCD. Electrons flow from NADPH source to cytochrome b5 reductase and to the cytochrome b5 as the direct electron donor to SCD1 and finally to O_2 which is reduced to H_2O. The rate-limiting step in this reaction is desaturase (Zhang et al., 1999).

Description

SCD1 contains four transmembrane domain which two NH_2 and COOH terminals are located in cytoplasmic side. The single cytoplasmic loop and COOH terminus collectively contain eight Histidine residues forming His box and bind to iron at the center of catalytic site of desaturase. Two ER luminal loops are relatively smaller than cytosolic loop which contain two of the three conserved His motifs. Purified SCD1 remains in 37kDa band on SDS-PAGE and His segments located in 119, 156 and 296 provide ligands for nonheme iron within the catalytic site of the SCD1 (Paton & Ntambi, 2009).

Expression

SCD1 promoter contains several transcription factor binding sites that are involved in positive or negative regulation of SCD1 gene. Sterol regulatory element-binding proteins (SREBP) are a group of transcriptional factors belonging to helix-loop-helix leucine zipper family and are responsible for regulating cholesterol, fatty acids and triglyceride synthesis enzymes (Miyazaki et al., 2004). SREBP-1a is the dominant isoform of SREBP in human cultured cells and induces SCD1 gene expression (Shimomura, Shimano, Horton, Goldstein, & Brown, 1997). Furthermore, Liver X Receptors (LXR) including LXR-? and LXR-? serve as positive inducers of SCD1 gene (Peter et al., 2008). Therefore, PPARa in combination with LXR causes elevation in the levels of SCD1 gene expression (Hebbachi, Knight, Wiggins, Patel, & Gibbons, 2008). The involvement of PPARa in transcriptional regulation of SCD1 has also been reported in human pancreatic cells. Specifically, MEK/ERK1/2- and EGFR-dependent pathways exerted inhibitory effect on the expression and activity of SCD1 in these cells, possibly via PPARa activation (Byagowi et al. 2015).

Localisation

SCD1 is anchored to reticulum endoplasmic membrane (Liu, Strable, & Ntambi, 2011).

Function

SCD1 is a rate-limiting enzyme which converts SFA to MUFA mainly oleate and palmitate causing high contents of MUFA in membrane phospholipids, triclycerides and cholesterol esters (Matsui et al., 2012).

Homology

Two SCD isoforms, SCD1 and SCD5 have been identified in human. SCD1 has a high degree of homology with SCD5 in human genome. Four SCD isoforms, SCD1 to SCD4 have also been identified in mouse. SCD1 shares about 85% amino acid identity with all 4 mouse SCD isoforms, as well as with rat SCD1 and SCD2. In contrast, SCD5 shares limited homology with the rodent SCDs and appears to be unique to primates (Wang et al., 2005). [supplied by OMIM, Mar 2008]. (Leung & Kim, 2013).

Mutations

SCD1 gene is located on 10q24.31 position and shows different sequence polymorphisms (SNPs). Among these polymorphisms, rs3071, rs1502593 and rs10883463 SNPs have a higher degree of mean allele frequency (MAF) and are more studied. These SNPs has been implicated in multiple aspects of lipid metabolism. Also, rare alleles of rs10883463, rs7849, rs2167444, and rs508384 are associated with decreased BMI and improved insulin sensitivity (Abdelmagid et al., 2013; Arregui et al., 2012; Gong et al., 2011).

Implicated in

Breast cancer

Over-expression of SCD1 is associated with enhanced growth rate of breast cancer cell lines and shorter overall survival and relapse-free survival (RFS) in breast cancer patients (Holder et al., 2013). Furthermore, it is demonstrated that high desaturation index has a negative correlation with the risk of breast cancer (Chajs et al., 1999). Down-regulation of SCD1 by specific siRNA also leads to reduction of proliferation rate, cell cycles' gene expression and phosphorylation state of ERK1/2 (Mauvoisin, Charfi, Lounis, Rassart, Mounier, 2013).

On the other hand, Mohammadzadeh et al. study revealed that inhibition of SCD1 by a selective inhibitor causes significant alteration in fatty acid composition of tissue cultured breast carcinoma in comparison to normal-appearing breast tissues and this has been attributed to the different level of SCD1 activity (Mohammadzadeh et al., 2014).

Hepatocellular carcinoma

Bansal et al. study indicated that SCD1 was significantly over-expressed in hepatocellular carcinoma (HCC) tissues in comparison to adjacent normal tissues and in HCC cell lines including HepG2, Hep3B and PLC/PLF/5.

Furthermore, the level of SCD1 was negatively associated with tumour differentiation grade. Treatment of liver cancer cell lines with different panel of chemotherapeutic agents also caused over expression of SCD1 in a time dependent manner and the consequent resistance to drug induced apoptosis. It is also demonstrated that inhibition of SCD1 by genetic manipulation or chemical inhibitors leads to elevated sensitivity to chemotherapeutic agents (Bansal et al., 2013).

Colorectal cancer

Recent studies have revealed that cell death is induced in colorectal cancer cells following SCD1 inhibition.

This effect is most possibly mediated through caspase 3 activity and PPAR-cleavage (Minville-Walz et al., 2010). Other studies have also reported that HTC116 colon cancer cell lines are susceptible to SCD1 depletion and subsequent decreased cell viability (Mason et al., 2012).

Esophageal cancer

Shuai Guo et al. study has shown SCD1 up-regulation in esophageal cancerous tissues in comparison to adjacent normal tissues. Furthermore, tissue lipid distribution analysis revealed that MUFA/PUFA ratio is elevated in cancerous microenvironment due to over activation of SCD1 (Guo, Wang, Zhou, Li, 2014).

Gastric cancer

Roongta et al. reported SCD1 inhibition causes tumour growth delay in a xenograft model in nude mice (Roongta et al., 2011).

Obesity

Obesity and type 2 diabetes are highly associated with abnormal lipid metabolism and intramyocellular accumulation of triglycerides. Hulver et al reported that SCD1 is up-regulated in skeletal myocytes of obese individuals. Overexpression and overactivity of SCD1 is linked to lower fatty acid ?-oxidation rate and elevation of triglyceride and MUFA synthesis in extremely obese population (Hulver et al., 2005).

Lipotoxicity and inflammation

Lipotoxicity is a common characteristic of diabetes and metabolic syndrome. It is defined by the elevation of intracellular fatty acid metabolites including diacylglycerol and ceramides leading to endoplasmic reticulum (ER) stress. This cellular stress triggers phosphorylation of insulin receptor substrates in serine/threonine residues and activation of the nuclear factor (NF)-?B pathway (Eizirik, Cardozo, Cnop, 2008). Such signalling pathways induce an acute inflammatory response with cytokines secretion and diminished down-stream events of insulin receptor signalling cascade resulting in low-grade inflammatory state (Peter et al., 2009). Among SFA, stearate and palmitate have a high lipotoxicity potential to induce inflammation, ER stress and insulin resistance (Staiger et al., 2006). SCD1 enzyme desaturases stearate and palmitate to less toxic monounsaturated forms oleate and palmitoleate (Peter et al., 2008). Overexpression of SCD1 is also associated with increased triglyceride storage and decreased palmitate-induced apoptosis, ceramide and diacylglycerol synthesis, as well as insulin resistance (Pinnamaneni, Southgate, Febbraio, Watt, 2006).

To be noted

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