Role of SREBPs in Liver Diseases: A Mini-review

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Abstract

Sterol regulator element binding proteins (SREBPs) are a family of transcription factors involved in the biogenesis of cholesterol, fatty acids and triglycerides. They also regulate physiological functions of many organs, such as thyroid, brain, heart, pancreas and hormone synthesis. Besides the physiological effects, SREBPs participate in some pathological processes, diabetes, endoplasmic reticulum stress, atherosclerosis and chronic kidney disease associated with SREBP expression changes. In the liver, SREBPs are involved in the pathogenesis of nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, hepatitis and hepatic cancer. There are several SREBP inhibitors that have potential for treating obesity, diabetes and cancer. This review assesses the recent findings about the roles of SREBPs in the physiology of organs’ function and pathogenesis of liver diseases.

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Introduction

The sterol regulator element binding proteins (SREBPs) are a family of transcription factors. These proteins are synthesized as 110-amino acid inactive precursors; then, they are inserted into the endoplasmic reticulum (ER) membrane.1 In the ER, SREBPs interact with a sterol sensor, the SREBP-cleavage activating protein (Scap).2 The SREBP/Scap complex moves to the Golgi apparatus, where the mature or nuclear forms of SREBP are generated by two proteases, the site 1 protease and the site 2 protease, and an anchoring protein. The insulin-induced gene (Insig)-1/2 also contributes.3 Then, the nuclear SREBPs translocate to the nucleus and bind to the target gene promoters, such as those of lipid metabolism-related genes.4 The expressions of these transcriptional genes regulated by feed-forward and feedback mechanisms (i.e. increased cholesterol in the cells) inhibit the proteolytic activation of SREBPs and decrease expression of SREBP target genes.5

Keywords: SREBP; Liver; Lipid.

Abbreviations: AMPK, AMP-activated protein kinase; ER, endoplasmic reticulum; FAS, fatty acid synthase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HNF-4α, hepatocyte nuclear factor-4 alpha; Insig, insulin-induced gene; LDL, low-density lipoprotein; LXR, liver X receptor; NALFD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NIFPLA2, patatin-like phospholipase3; S1-p, sphingosine-1-phosphate; Scap, SREBP-cleavage activating protein; SIRT1, silent information regulator 1; SREBP, sterol regulator element binding proteins; TH, thyroid hormone; VLDL, very low-density lipoprotein.

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The SREBP family consists of three members: SREBP-1a; SREBP-1c, from the SREBP-1 protein coding gene; and, SREBP-2, from the SREBP-2 protein coding gene.6,7 SREBP-1c is mainly expressed in the liver, white adipose tissue, adrenal gland, skeletal muscle and brain of mice and humans;8 but SREBP-1a is expressed in cell lines, spleen and intestinal tissues.8

Physiological function and regulation of SREBPs

The SREBP family plays a key role in lipid homeostasis (cholesterol and triglyceride). Moreover, SREBPs are also involved in the normal functions of some organs. One of these organs is the thyroid. Thyroid hormones (THs) change the SREBP-2 gene promoter; then, the low-density lipoprotein (LDL) receptor expression decreases and plasma cholesterol level increases.9,10 SREBPs are also known as regulators of the Na/I pump, iodide oxidation and iodination of thyroglobulin in TH synthesis.11 Another study by Rauer et al.12 showed 25-hydroxycorticosterol, as a SREBP-1c inhibitor, decreased the mRNA levels of thyroid peroxidase by 50%. Rochira and colleagues13 have also revealed that in HepG2 cells, 3,5,3'-triiodo-l-thyronine regulates SREBP-1 expression in a dose-/time-dependent manner. Their results also indicated that the AKT/P3K signaling pathway may be involved in this process. The 3,5-diiodo-l-thyronine, unlike 3,5,3'-triiodo-l-thyronine, blocks SREBP-1c activation in HepG2 cells, activates β-oxidation and reduces lipogenic factor expression via nongenomic mechanisms.14 In this way, the findings show that THs can effect SREBP expression, while, on the other hand, SREBP-1 can affect the thyroid gland and decrease thyroid peroxidase levels. Dehydroepiandrosterone is one of the adrenal hormones; the reduction of which is associated with poor sexual function. Dehydroepiandrosterone stimulates intracellular activity of the cyclic adenosine 3',5'-monophosphate and cyclic adenosine 3',5'-monophosphate-dependent protein kinase A that leads to down-regulation of SREBP-1 and PPARα, and inactivation of carnitine-palmitoyltransferase, therefore decreasing fat deposition.15 Androgens and progesterone also stimulate SREBP-1c and 2 expressions in normal cell lines, increase mRNA and protein levels of fatty acid synthase (FAS), acetyl-CoA-carboxylase, acetyl-CoA-synthase and HMG-CoA-reductase.16

In this context, another organ affected by SREBPs is the pancreas, and its hormone, insulin. In insulin signaling, it has been demonstrated that SREBP-1c binding to the Irs-1 promoter region suppresses Irs-1 gene transcription that leads to insulin resistance in the skeletal muscle.17,18 Insulin resistance is also associated with increased AMP-activated protein kinase (AMPK)α phosphorylation, FAS, CHREBP and SREBP-1 mRNA expression.19 Activation of both PKc/akt and PKcβ pathways lead to SREBP-1c expression increase.20

Review Article
Indeed, the activated liver X receptor (LXR)\textsubscript{a/-}\textsubscript{C/EBP}\textsubscript{b} complex binds to the SREBP-1c promoter in sites that are required for insulin induction,\textsuperscript{21} and LXR\textsubscript{a} loss leads to decrement of SREBP-1c, FAS and lipogenic factors and improvement of insulin sensitivity in LXR\textsubscript{a/-}deficient-ob/ob mice.\textsuperscript{22} But, Eberlé et al.\textsuperscript{1,21} did not find any effect of SREBP-1c stimulation, and determined that these effects were exclusive to SREBP-1a and SREBP-2. In another attempt, Cagen et al.\textsuperscript{21} have shown that insulin activates LXR, specificity protein 1 and nuclear factor-Y that are required for the full action of SREBP-1c. Taken together, the role of SREBPs in control of insulin signaling and secretion is important and inhibition of SREBP pathways may be a potential treatment in the future, possibly for obesity with type 2 diabetes.\textsuperscript{3,24}

Brain is the most cholesterol-rich organ, and mostly de novo pathways synthesize cholesterol. Studies have shown SREBP-2 expression in the normal hippocampus, cortex and striatum.\textsuperscript{25} It has also been shown that neuronal injury induced by kainite results in a down-regulation of SREBP-2 expression in lesion areas of the brain.\textsuperscript{26} Other documents have reported that SREBP-2 expression is decreased in streptozotocin-induced mice and in Alzheimer's disease.\textsuperscript{27} Reduction of the cholesterol sensor Scap in the brains of mice causes impaired synaptic transmission and altered cognitive function.\textsuperscript{28,29}

24 S-hydroxycholesterol is an important metabolic product of cholesterol in the brain.\textsuperscript{30} Wang et al.\textsuperscript{30} showed that under cholesterol excess 24S-hydroxycholesterol is increased, acting as a sensor and reducing cholesterol synthesis enzymes through SREBP-2 down-regulation. Brain acyl-CoA hydrolase is responsible for hydrolyzing the long-chain acyl-CoA among neurons; it has been demonstrated that SREBP-2 binds to the sterol regulatory element motif, activating brain acyl-CoA hydrolase enzyme and thereby the conversion of long-chain acyl-CoAs to fatty acids and CoA-SH.\textsuperscript{31} In total, these research findings have provided insights into the interaction between SREBP-2 and cholesterol metabolisms in neurons.

In healthy people, lipid storage is minimal in the heart, but Marfella et al.\textsuperscript{32} reported a significant correlation between in vivo SREBP-1c levels and increase of cardiac triglyceride accumulation among metabolic syndrome patients, which is associated with ejection fraction lowering and cardiac dysfunction. In addition, SREBP-1c gene silencing reduces triglyceride sand very low-density lipoprotein (VLDL) content in bovine hepatocytes\textsuperscript{33} (Fig. 1).

### Interaction between SREBPs and other transcription factors

The LXRs, LXR\textsubscript{a} and LXR\textsubscript{b}, are ligand-activated transcription factors and members of the DNA-binding transcription factors. Their functions are related to retinoid X receptors.\textsuperscript{34} The LXRs play an important role in cholesterol homeostasis and hepatic lipogenesis.\textsuperscript{35} LXR\textsubscript{a} allows for SREBP-1c induction.\textsuperscript{11} Studies have shown that activation of LXR\textsubscript{a} increases SREBP1c expression, which leads to hepatic lipogenesis and hypertriglyceridemia.\textsuperscript{36} In addition, insulin stimulates SREBP-1c expression through the nuclear receptor of LXR.\textsuperscript{37} The hepatocyte nuclear factor-4 alpha (HNF-4\textsubscript{a}) is another nuclear receptor protein involved in hepatic lipid homeostasis through regulation of VLDL and apolipoprotein B function.\textsuperscript{37} In this context, Misawa et al.\textsuperscript{36,37} reported that overexpression of HNF-4 in HEK293 cells augmented the expression of SREBP-responsive genes and that it seemedlikeHNF-4 potentiates the SREBP functions and stimulates the expression of SREBPs-responsive genes in the enterohepatic cells. Another study showed activation of SREBP2 blocking HNF-4\textsubscript{a} expression in the mouse liver.\textsuperscript{40} (Fig. 2)

### SREBPs in liver disease

#### Role of SREBPs in nonalcoholic fatty liver

SREBPs are involved in some metabolic disorders, including obesity, type 2 diabetes, dyslipidemia, atherosclerosis, etc.\textsuperscript{41,42} Nonalcoholic fatty liver disease (NAFLD), the most common liver disease, is simple hepatic steatosis, and nonalcoholic steatohepatitis (NASH) is a developed form of NAFLD that is associated with hepatic inflammation and fibrosis. NASH could lead to cirrhosis and hepatocarcinoma.\textsuperscript{35} Genetic background, obesity and insulin resistance are considered contributing factors to the pathophysiology of NASH.\textsuperscript{43} Studies on single nucleotide polymorphisms (i.e. rs2297508) and SREBP-1 gene variations have shown a positive relation with increased risk of NAFLD development.\textsuperscript{37} Other documents have confirmed that patatin-like phospholipase3 (PNPLA3) plays a key role in NASH development as well,\textsuperscript{44,45} and that PNPLA3 gene polymorphisms are strongly associated with severity of NAFLD.\textsuperscript{46} SREBP-1c binds to the PNPLA3 gene and activates its expression; then, PNPLA3 stimulates lipid accumulation, as shown in mouse hepatocytes.\textsuperscript{46,47}

The stimulatory effects of insulin on lipogenesis in the liver and the adipose tissue are well known, but the cellular mechanisms remain unclear. To our knowledge, insulin effects on hepatic lipogenesis are partly mediated by SREBP-1c, from SREBP-1c gene expression until entry to the cell nucleus.\textsuperscript{18} Indeed, insulin stimulates SREBP-1c gene expression, enhancing SCAP/SREBP complex export to the Golgi and proteolytic processing on the nascent SREBP-1c by reducing levels of Insig-1/2.\textsuperscript{49} Furthermore, we know that AMPK, an energy sensor for cellular energy of homeostasis, inhibits cleavage and transcriptional activation of SREBP via phosphorylation. In this regard, Li and colleagues\textsuperscript{41} reported that metformin stimulated AMPK activity; it also suppressed SREBP-1c cleavage and nuclear translocation via Ser372 phosphorylation, leading to liver steatosis attenuation in diet-induced insulin-resistant LDL receptor-deficient mice. On the other hand, there are many documents that provided evidence of SREBP-1c inducing lipogenic enzymes and causing lipid deposition associated with insulin resistance.\textsuperscript{50} Sun et al.\textsuperscript{51} found that early insulin therapy in type 2 diabetic rats leads to down-regulation of SREBP1 in hepatic tissue and fat shifting from liver to the adipose tissue.

Ding and colleagues\textsuperscript{52} have reported that curcumin inhibits SREBP expression, and improves serum lipid levels and insulin sensitivity in high-fat diet-induced obese mice. The current findings may consider two opposite roles for insulin in relation to SREBP1 that dependant on the tissue types, obese or nonobese, etc.\textsuperscript{6} In rats, injection of leptin leads to fat deposition with up-regulation of SREBP-1 though the JAK2-STAT3/PI3K signaling pathway.\textsuperscript{53}

Obesity is another feature of NAFLD pathogenesis. Western diets and modern diets are factors causing obesity and fatty liver diseases. High-fat diet, especially with different fat sources, usually induces obesity and lipid accumulation in the hepatocytes and adipocytes.\textsuperscript{54} In this context, Ronis et al.\textsuperscript{55} reported that olive oil increased SREBP1c expression greater than corn oil or echium oil in overfed male rats. Another study showed that docosahexaenoic acid/eicosapentaenoic acid at
a 1:2 ratio decreased serum triglycerides, total cholesterol, and LDL-cholesterol levels, lowered SREBP-1C and FAS mRNA expression and alleviated liver damage in mice. It seems that this process is probably mediated by both activation of AMPK and inhibition of mechanistic target of rapamycin complex 1.56,57 Moreover, it has been reported that dietary consumption of fish oil as a source of n-3 polyunsaturated fatty acids, down-regulates SREBP1c mRNA expression but probably does not influence SREBP-2 expression.58 Obesity can also cause insulin resistance, increased leptin levels and, importantly, stimulation of SREBP1c expression.59

Today, fructose has markedly increased in our diet and overconsumption of fructose has also been shown to stimulate SREBP1c expression and lead to hepatic lipid accumulation.60 In contrast, some foods such as soy supplements and probiotic foods are considered to decrease insulin secretion, and to suppress SREBP1c expression and enzymes involving lipid synthesis61 (Fig. 3).

**Role of SREBPs in ER stress**

ER, a critical membranous organelle, plays a key role in lipid synthesis, nascent protein folding and Ca\(^{2+}\) ion storage.62 In special circumstances, such as pharmacological stimuli, oxidative stress, viral infections and dietary demands, ER homeostasis can disrupt and create an ER stress phenomenon63 that causes abnormalities in insulin action, inflammatory responses, lipoprotein B100 degradation and hepatic lipogenesis.64 Three ER transmembrane sensors, inositol-requiring protein 1, protein kinase-like ER kinase and activating transcription factor 6, are activated by the glucose-regulated protein 78 required for folding of proteins in the ER. Tunicamycin, cow milk casein or oxidative stress induce acute ER stress,65,66 while overfeeding of fatty acids, cholesterol and fructose, due to the produced obesity and insulin resistance, induce chronic ER stress that is not fully restored.67 Many studies have shown that ER stress and glucose-regulated protein 78 activation up-regulate SREBPs directly and indirectly.68

Recently, it has been reported that elevated uric acid levels are associated with ER stress induction and hepatic lipid accumulation via SREBP-1c activation.69 One of the \(\omega-3\) polyunsaturated fatty acid derivatives and resolving D1, alleviated tunicamycin-induced ER stress and decreased SREBP1c via inhibition of c-Jun N-terminal kinase expression in hepatocytes.70,71 In contrast, AMPK activation down-regulates SREBP 1c expression and alleviates ER stress response through suppression of mechanistic target of rapamycin complex 1 signaling.

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**Fig. 1. Schematic diagram of the physiologic function of SREBP in several organs.**

**Fig. 2. Diagram of the interaction between SREBP and transcription factors.**
in the ER stress-induced hepatocytes. In the study by Sun et al., early insulin therapy reduced c-Jun N-terminal kinase and IRS-1 expression; it also improved ER stress and steatosis in the rat liver. Several pharmacologic agents, including rosiglitazone, naltrexone and tauroursodeoxycholic acid, also attenuated ER stress liver injury and down-regulated both SREBP1 and SREBP2 expression. (Fig. 4).

Role of SREBPs in hepatitis disease

Hepatitis C virus (HCV)-2 infection markedly leads to chronic hepatitis, liver cirrhosis and possibly hepatocellular carcinoma. Liver steatosis is frequently found in the patients who are infected with HCV, but the molecular mechanisms of HCV-associated steatosis are not clear. Since SREBPs are the key transcriptional factors in lipogenic gene expression, they are likely important in the HCV-induced liver steatosis. Some studies have shown that HCV nonstructural protein 2, HCV nonstructural 4B protein and HCV-3a core protein increase SREBPs expression. These results suggest activation of the PI3K and Akt-2 pathway, enhancement of HCV entry, replication and translation of HCV, increased SREBP-1 activity and steatosis.

Contrary to these studies, McPherson et al. have reported that among HCV patients, there was no significant difference in the hepatic expression of SREBP-1c or FAS mRNA compared with normal subjects. Moreover, a negative relationship was found between hepatic SREBP-1c mRNA expression and grade of steatosis. These findings state that SREBP-1c may play transient and not a prominent role in HCV-related steatosis. In other research, Kim et al. found that curcumin decreases HCV gene expression via suppression of the Akt-SREBP-1 pathway. Another study indicated that, among patients with HCV infection, although SREBP-2 expression was unchanged, HMG-CoA reductase, HMG-CoA synthase and SREBP-1c expression was up-regulated. Subtilisinexin isozyme-1/sphingosine 1-phosphate is recognized as a novel regulator of the HCV lifecycle. In hepatoma cells, subtilisinexin isozyme-1/sphingosine 1-phosphate-specific protein-based inhibitor blocked HCV from establishing infection and reduced lipid droplets; it could be considered as a therapeutic target against HCV infection and liver steatosis, though more evidence is required to support this hypothesis. These studies indicate that more evidence is also required to clarify the role of SREBP-1 in patients with HCV. Silent information regulator 1 (SIRT1) is another regulator of hepatic lipid metabolism. In 2013, Sun and colleagues found that HCV replication in Huh-7.5 cells decreased SIRT1, up-regulated SREBP-1c, FAS, ACC and SREBP-2, and increased lipid profile. Recently, it has been reported that retinoid-interferon-induced mortality reduces HCV-infected Huh7 cells and that activation of retinoid-interferon-induced mortality 19 attenuates intracellular lipid droplets through a decrease of SREBP-1c (Fig. 4).

SREBP inhibitor agents

Nowadays, research on SREBP inhibitory agents is being conducted. Inhibitors of SREBP processing can be helpful in reducing the risk of atherosclerosis, metabolic syndrome and obesity. There are several SREBP inhibitors, such as 24-HC, 25-HC, 27-HC, etc. But since LXR up-regulates SREBP expression, it’s important that inhibitors of SREBP do not activate LXR expression. Botulin, as a specific inhibitor of SREBP, suppresses SREBP maturation and decreases cholesterol and fatty acid synthesis. In this context, Quan and colleagues reported that betulinic acid reduced hepatic steatosis and levels of SREBP1 in HepG2 cells and in livers of mice that were fed a high-fat diet. They also showed that this function is mediated by the Ca(+2)-calmodulin dependent protein kinase-AMPK-SREBP1 signaling pathway.

Another agent is fatostatin, that interacts with Scap, blocks ER-Golgi translocation of SREBP and decreases blood glucose and liver steatosis in obese ob/ob mice. Fatostatin also has antitumor properties and inhibits cell growth. Other natural compounds, including and rographolide and anhydroicaritin,
ameliorate obesity, insulin resistance, liver steatosis and hyperlipemia via suppression of SREBP activation.\(^{39}\) Emodin from the *Rheum palmatum* herb has anti-inflammatory and anticancer effects, and attenuates obesity but decreases insulin sensitivity through regulation of the SREBP pathway.\(^{39}\)

However, it has been revealed that antipsychotic drugs, such as clozapine, olanzapine and haloperidol, increase lipogenesis gene expression via SREBP activation; although, there are some differences in rates of SREBP activation among these drugs.\(^{90}\)

### Role of SREBPs in cancer

Cholesterol and lipid are requirements for new membrane building and for maintaining active signaling in developing cancer cells;\(^{31}\) therefore, lipid metabolism-related transcriptional genes and their enzymes change in carcinoma cells. Hepatocellular carcinoma (HCC) is one of the most common liver malignancies in the world.\(^{84}\) Many research studies have demonstrated that SREBP up-regulation, and FAS and LDL receptor overexpression occur in prostate, breast and glioblastoma.\(^{92,93}\) Previously, Li et al.\(^{94}\) demonstrated that overexpression of SREBP-1 is associated with large tumor size, high histological grade and advanced tumor-node-metastasis stage in HCC patients, and that SREBP-1 down-regulation suppressed cell proliferation and apoptosis in both HepG2 and MHCC97L cells.\(^{94}\)

One of the effects of SREBP-2 in cell proliferation is mediated by regulation of farnesylidiphosphate synthase gene transcription.\(^{95}\) It has also been shown that tocotrienol (a minor form of vitamin E) reduced SREBP-2 activity and improved cell viability in prostate cancer cells.\(^{96}\) Obesity, fatty liver and hepatitis have potential roles in pathogenesis of HCC.\(^{97}\) In this regard, Zhang et al.\(^{98}\) have indicated that miR-449 inhibits SIRT1, and decreases SREBP1c expression and that of downstream target genes, including fatty acid synthase and 3-hydroxy-3-methylglutaryl CoA reductase. Also, miR-449 can repress DNA synthesis and proliferation, both in HepG2 and HuH7 cells.\(^{99}\)

Overexpression of NSSAQP37 protein, a HCC oncogenic screen and hepatitis C virus nonstructural protein 5A-associated binding protein, decreased intracellular triglyceride and total cholesterol contents, down-regulated SREBP1c and SREBP2 expression and inhibited cancer cell proliferation in human hepatoma cells.\(^{99}\) Moreover, SREBP pathway blocking by L-Scap-/- and L-gp78-/- mice led to reduced SREBP1c, SREBP1a and SREBP2 expression and to decrease in related enzymes, such as fatty acid synthase, ACC, LDLR and HMGCs, improving HCC tumor progression.\(^{100}\)

In human NFADL-associated HCC, SREBP-1 up-regulated HDAC8 and suppression of the histone deacetylase HDAC8, and decreased insulin resistance and NFADL-associated HCC.\(^{101}\)

Among SREBP inhibitor agents, it has been shown that fatostatin, andrographolides and silibinin have anticancer effects. Li et al.\(^{87}\) and other researchers have reported that fatostatin blocks cell proliferation through lipid-independent and Scap-independent mechanisms, causing G2-M cell-cycle arrest and inducing apoptosis. Silibinin also has been shown to induce apoptosis in prostatic cancer cells.\(^{102}\) (Fig. 4)

### Conclusions

SREBPs (SREBP1c, SREBP1a and SREBP2) are found in several organs and participate in physiologic and pathologic functions of the body. SREBPs are involved in lipid and glucose homeostasis as well as hormones synthesis. SREBPs also have a key role in the pathogenesis of NASH, obesity and cancers. Moreover, they cause lipid-regulated cellular disorders in hepatocytes that can lead to steatosis and liver injury. Several SREBP inhibitors, including natural and synthetic agents, have potential treatment effects in obesity, hepatic steatosis and even tumor cells.

### Conflict of interest

The authors have no conflict of interests related to this publication.

### Author contributions

Designed and wrote the manuscript (AM), searched references for the manuscript (ZH).

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Moslehi A. et al: SREBP liver

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