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Progress in the Study of Sterol Regulatory Element Binding Protein 1 Signal Pathway

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Abstract

Sterol Regulatory Element-Binding Protein 1 (SREBP1) is one of the important nuclear transcription factors in lipid metabolism. SREBP1 can regulate the biosynthesis of fatty acid, triglyceride and cholesterol. Anomalies of SREBP1 and its target genes can cause a series of metabolic diseases such as insulin resistance, diabetes and fatty liver disease. Therefore, it is very important to know the role of various factors in SREBP1 pathway. In this review, we summarize the feature of target genes regulated by SREBP1, emphatically introduce the role of insulin and other upstream factors in regulating SREBP1, which will contribute to a better idea for the guidance and treatment of various metabolism diseases.

Keywords: Insulin; Lipid Metabolism; Sterol Regulatory Element Binding Protein 1; Target Genes

Introduction

Sterol Regulatory Element-Binding Proteins (SREBPs) belongs to the basic helix-loop-helix-leucine zipper (bHLH-Zip) family of transcription factors, contains three subtypes: SREBP1a, SREBP1c and SREBP2 [1,2]. A series of animal studies utilizing transgenic and knockout mice for each SREBP gene and isoform demonstrated that SREBP1c primarily controls lipogenic gene expression, whereas SREBP2 regulates the transcription of genes related to cholesterol metabolism. Physiologically, SREBP1a strongly activates global lipid synthesis in rapidly growing cells, whereas SREBP1c has a role in the nutritional regulation of fatty acids and triglycerides in lipogenic organs such as the liver. Conversely, SREBP2 mediates sterol regulation in every tissue. This functional specificity is more apparent in vivo than in vitro, but when overexpressed, the isoforms exhibit functional overlap [3]. The study found that the excessive expression of SREBP1 would lead to the disorder of lipid metabolism, leading to the excessive accumulation of fat in non-adipose tissue, thus leading to metabolic diseases such as obesity, insulin resistance and fatty liver [4]. Although the downstream target gene of SREBP1 regulating lipid metabolism has been identified, the upstream regulatory factors and pathways regulating the SREBP1 pathway are still relatively vague and complex. Therefore, this paper reviews and elaborates its role in lipid metabolism regulation from the upstream and downstream signaling pathway of SREBP1.

Structure and Function of SREBP1

SREBP1a and SREBP1c are encoded by the SREBP1 gene (SREBF) located on chromosome 17. Human SREBP1 protein is composed of 1,147 amino acids, including the N-terminal transcriptional activity domain composed of 480 amino acids, the hydrophobic region composed of 80 amino acids and the C-terminal regulatory domain composed of 590 amino acids [1]. The resultant SREBP1 protein was bound to the Endoplasmic Reticulum (ER) and the nuclear membrane of the cell through the mesenchymal hydrophobic region, while both the N-terminal and C-terminal were oriented toward the cytoplasm side. SREBP1a and SREBP1c are generated from different transcription start sites, the first exon is different (exon 1a and exon 1c), and the rest are the same. SREBP1a preferentially promotes the synthesis of fatty acids, followed by cholesterol synthesis, and SREBP1c plays a key role in the formation of triglycerides and phospholipids [5].

Proteolytic Processing of SREBP1

Surprisingly, SREBPs are synthesized as membrane proteins that are inserted into the ER in a hairpin orientation with their N-termini and C-termini extending into the cytoplasm. Once

SREBPs exit the ER and enter the Golgi apparatus, they are subjected to two-step proteolytic processing by two cleavage enzymes, Membrane Bound Transcription Factor Peptidase, Site 1 (SIP, also known as MBTPS1) and Membrane Bound Transcription Factor Peptidase, Site 2 (SIP, also known as MBTPS2). This processing generates a soluble N-terminal-cleaved transcription factor of the basic helix-loop-helix leucine zipper family [1,6], which enables SREBPs to enter the nucleus as homodimers, bind to SRE sequences and stimulate the transcription of target genes [3]. In the ER membrane, SREBPs form heterodimeric complexes with another ER membrane protein, SREBP Cleavage-Activating Protein (SCAP) [1,6], which has eight transmembrane domains. The C terminal region of SCAP, which contains a WD40 repeat domain, projects into the cytoplasm and interacts with the C termini of SREBP1 and SREBP2. SCAP is essential for the transport of SREBPs from the ER to the Golgi. To accomplish this function, SCAP acts as an escort protein that allows SREBPs to enter ER transport vesicles that contain COPII vesicle coat proteins. In addition to the eight transmembrane helices, SCAP possesses two large ER luminal loops, designated Loop1 and Loop7. Loop1 binds to Loop7, which enables SCAP to bind COPII proteins such as SEC23 and SEC24 [7]. When an increasing level of cholesterol in the ER, however, Loop1 binds to cholesterol instead, thereby disrupting direct binding between the two loops and preventing the SREBP-SCAP complex from exiting the ER. Simultaneously, two additional ER-retention membrane proteins, Insulin-Induced Gene 1 (INSIG1) and INSIG2, interact with SCAP, causing the SREBP-SCAP complex to be retained on the ER membrane [8,9]. Activation of SREBP2 is assumed to be under the control of this cholesterol-dependent ER to Golgi transport system, whereas proteolysis of SREBP1 is not strongly sterol-regulated, but rather is inhibited by Polyunsaturated Fatty Acids (PUFAs) and induced by insulin or high-glucose conditions. Long-chain unsaturated fatty acids, including oleic acid, and some PUFAs are reported to hinder SREBP1 activation while having little or no effect on SREBP2 processing [10]. Ubiquitin Regulatory X Domain-Containing Protein 8 (UBXD8, also known as Fas Associated Factor Family Member 2, FAF2), an INSIG-binding protein, is a potential mediator of this inhibitory effect of unsaturated fatty acids [11]. UBXD8 interacts with the polyubiquitin chains attached to INSIG1 through GP78, in turn recruiting the Valosin Containing Protein (VCP, also known as p97) complex, which facilitates proteasomal degradation. Long-chain unsaturated fatty acids form a complex with UBXD8, thereby detaching UBXD8 from INSIG1, which stabilizes INSIG1 by preventing degradation [12]. As a result of increased levels of INSIG1, the SREBP1-SCAP complex is retained in the ER, and transactivation of SREBP1 target genes is reduced.

SREBPs are transported from the ER to the Golgi as a SREBP-SCAP complex and proteolytically processed for activation in two steps. The first step is cleavage of the ER luminal loop of SREBPs by S1P. Inactivation of S1P by serine protease inhibitors such as 4-(2-Aminoethyl) Benzenesulfonyl Fluoride Hydrochloride (AEBSF) decreases both the activity of SREBPs and the expression of SREBP target genes [13,14]. This first cleavage step generates a SREBP protein that is half of its original size. Next, the N-terminal region is cleaved off by S2P. After sheared by S1P and S2P, SREBP precursor release active amino end part, which enter into the nucleus and combine with the Sterol Regulatory Element (SRE) sequence. Finally, the expression of downstream genes was activated.

The Downstream Target Gene Regulated by SREBP1

Transcription factors need combined with a specific element when activate or prevent the target genes, namely the Transcription Factor Binding Sites (TFBS). TFBS are pieces of DNA that bind to transcription factors, ranging in length from a few to a dozen base pairs. Transcription factors often regulate several genes at the same time, and their binding sequences on different genes are not identical, but have certain similarities. The binding site of each transcription factor usually has a specific pattern, which is called the motif [15]. Traditional studies suggest that binding sites of transcription factor nSREBP1 should contain two motifs: SREs (5'-TCACNCCAC-3') and (or) E box (5'-CANNTG-3') [16,17].

Based on the known information of two TFBS motifs of SREBP1, the clearer SREBP1 target genes in the present study include: Acetyl-CoA Carboxylase (ACC) [18,19], Fatty Acid Synthase (FASN) [20], Low Density Lipoprotein Receptor (LDLR) [16], Thyroid Hormone Response Spot 14 (THRSP or S14) [21], Glucosekinase (GCK) [22] and Phosphoenolpyruvate Carboxykinase 1 (PCK1) [23] and other genes associated with fat synthesis and glucose metabolism. According to literature statistics, 79 target genes regulated by SREBP1 in liver tissue have been found till 2008 [24]. With the popularization of expression chips and the in-depth study of the nSREBP1 binding site, the target gene profile of nSREBP1 involved in regulation was also greatly amplified. Based on the latest ChIP-chip and ChIP-seq studies, hundreds of candidate genes regulated by nSREBP1 have been found in the whole genome [24-26].

By integrating ChIP-seq and differential expression data, SREBP1 regulated genes can be divided into three types of models. Target genes directly regulated by SREBP1: that is, there are different transcription genes adjacent to TFBS, such as FASN, Glycerol-3-Phosphate Acyltransferase, Mitochondrial (GPAM), Acetoacetyl-Co A Synthetase (AACS), Cytochrome P450 Family 51 (CYP51), Farnesyl Diphosphate Synthase (FDPS), Squalene Epoxidase (SQLE) [27-32], Cluster Of Differentiation 36 (CD36) [33], Insig-1 [29], Fatty Acid Binding Protein 3 (FABP3), ELOVL Fatty Acid Elongase 6 (ELOVL6), Stearoyl-CoA Desaturase 1 (SCD1), Acyl-CoA Synthetase Short Chain Family Member 2 (ACSS2), Isocitrate Dehydrogenase 1 (IDH1), Nuclear Receptor

Subfamily 1 Group H Member 3 (NR1H3), Peroxisome Proliferator Activated Receptor Gamma (PPARG), Lipin 1 (LPIN1) [34], Keratin 80 (KRT80) [35], Transforming Growth Factor Beta Receptor I (TGFBR1), Transforming Growth Factor Beta 1 (TGFB1) [36], 25-Hydroxy Vitamin D3 1α-Hydroxylase (CYP27B1), 25-Hydroxyvitamin D3 24-Hydroxylase (CYP24A1) [37], Tumor Protein P53 (TP53) [38], Low-Density Lipoprotein Receptor (LDLR), 3-Hydroxy-3-Methylglutaryl-CoA Reductase (HMGCR) [39]. Genes that are indirectly or remotely regulated by SREBP1: namely, there are no differential transcription genes adjacent to TFBS. It was speculated that these genes might be indirectly regulated under SREBP1 or high glucose conditions, such as 3-Hydroxy-3-Methylglutaryl CoA Synthase 1 (HMGCS1), Acetyl-CoA Carboxylase Alpha (ACACA), Farnesyl - Diphosphate Farnesyltransferase 1 (FDFT1), Malic Enzyme (Mel), Acyl-CoA Synthase Long Chain Family Member 1 (ACSL1), Diacylglycerol O-Acyltransferase 1 (DGAT1), SCAP [34] and so on. Although their expressions were very different, no corresponding TFBS were found in the adjacent regions of genes. This indirect regulation mechanism may be the regulation of target genes by SREBP1 through the interaction of other transcription factors (or co-activators) [40]. The target genes that SREBP1 may regulate: that is, there are differentially transcribed genes of TFBS that are close to suspicious (sequencing data analysis suggests that it may be false positive TFBS), such as, PCK1,GCK, ATP Citrate Lyase (ACLY) [41-44], Cytidylyltransferase-α (CCTα) [33] (Figure 1).

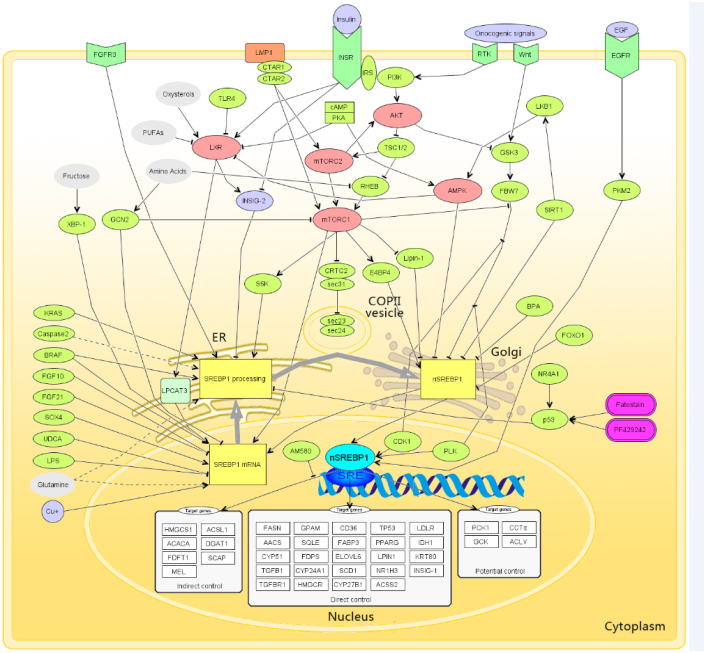

Figure 1: The upstream and downstream signal pathway of sterol regulatory element-binding protein 1.

Black solid arrows and T-bars denote direct stimulatory and inhibitory actions, respectively. Black dashed arrows indicate indirect effect.

Regulation of The Transcription Activity of SREBP1 by Upstream Factors

The expression and proteolytic processing of SREBP1 is very complex in vivo, and the regulation of SREBP1 is not only affected by the cholesterol level in cells, but also affected by the whole body's nutritional conditions and hormone levels [45], which are interrelated and interact with each other, forming a complex and delicate regulatory network. They regulate the activity of SREBP1 in both the transcriptional and post-transcriptional levels, thus playing a role in regulating the balance of lipid metabolism in the body.

Regulation of SREBP1 by Insulin

In general, Insulin signaling pathways begin with Insulin Receptor Substrate 1 (IRS-1) and/or tyrosine phosphorylation of IRS-2 [46]. After the IRS phosphorylation and then activate the downstream activation of Phosphoinositide 3-Kinase (PI3K), PI3K Catalytic Membrane Phosphatidylinositol 4, 5-Bisphosphate (PIP2) into Phosphatidylinositol-3, 4, 5-Triphosphate (PIP3) [47]. PIP3 can interact with AKT, and recruit AKT into the cell membrane and activate it [48]. AKT is a serine/threonine kinase that plays an important role in cell survival, apoptosis, cell size, angiogenesis, cell metabolism and migration [47,48]. Mammalian Target of Rapamycin (mTOR), a target molecule of rapamycin, is a serine/threonine kinase and an effector protein downstream of PI3K/AKT signaling pathway. mTOR is activated by phosphorylation and regulates the translation of specific subgroup mRNA by activating p70S6K [49]. p70S6K is the 40S subunit S6 protein kinase of ribosome, which regulates the synthesis of many translation elements by phosphorylating S6 protein [50,51]. Glycogen Synthase Kinase 3 (GSK3) is a serine/threonine protein kinase that plays an important role in glucose metabolism, protein synthesis, cell differentiation and proliferation. Insulin, growth factor and other signaling molecules can inhibit GSK3 through the PI3K/PKB pathway, and the activated AKT can induce the Ser9/21 phosphorylation of GSK3 and prevent its binding to the substrate [52] (Figure 1).

It is well known that insulin can effectively induce de novo synthesis of lipid and regulate the activity of lipogenic enzymes [53]. More and more evidence suggests that insulin regulates the activity of SREBP1 through multiple pathways, including transcription of SREBP1 mRNA, proteolytic processing of SREBP1, regulation of the stability abundance of mature nSREBP1 and transcription of SREBP1 from ER to Golgi.

Regulation of Insulin On the mRNA Level of SREBP1

As the target gene of itself, SREBP1 mRNA level can be induced by nSREBP1. In addition, SREBP1c mRNA levels in the liver of mice and rats decreased dramatically when insulin was exposed [54]. When insulin levels were inhibited under fasting conditions, the transcription of SREBP1c decreased in mouse liver [55]. In rat primary hepatocytes cultured in vitro, SREBP1c mRNA increased 40 times induced by insulin within 6 hours [50,56]. At the same time, SREBP1c mRNA levels were decreased when streptozotocin inhibited insulin secretion in rats [57]. These results indicate that insulin can effectively induce the transcription of SREBP1c.

The transcription regulation of insulin on SREBP1 was mainly through the PI3K/AKT-mTORC1 pathway. Studies have shown that insulin activation of mTOR inhibits the function of TSC Complex Subunit 1/2 (TSC1/2) through AKT-regulated phosphorylation [54], and TSC1/2 inhibits the expression level of Ras Homolog, MTORC1 Binding (RHEB), which phosphorylates and activates mTOR [58,59] (Figure 1).

When wortmannin, a PI3K inhibitor, is present, the insulin pathway that induces the increase of SREBP1c mRNA is blocked [54]. More importantly, the transcription of SREBP1 can also be blocked by low-concentration rapamycin, indicating that mTORC1 is required in the transcription of SREBP1 [54]. These studies showed that insulin increased the transcription of SREBP1c mRNA mainly through mTORC1 regulation.

Regulation of Insulin On SREBP1 Proteolytic Processing

In addition to regulating the SREBP1c mRNA level, insulin can also affect the proteolytic processing of SREBP1 in two different ways: (i) reduce the expression of INSIG2; (ii) promote the activation of p70S6K induced by mTORC1 [54].

The expression level of INSIGs is related to insulin in vivo. When fasting (low insulin), the transcription and translation of INSIG2 increased in mice, INSIG2 stuck SREBP on the endoplasmic reticulum membrane by binding with SCAP, and then the transport of SREBP1 was blocked, and the mature nSREBP1c could not be produced in the liver [60]. As the target gene of SREBP1, INSIG1 mRNA and protein levels also decreased after fasting, and when the mice were refed (with high insulin), INSIG2 transcription was inhibited, and INSIG2 rapid ubiquitination was mediated by gp78 [61], releasing SCAP/SREBP complex transport to Golgi. At the same time, the mature nSREBP1c activated the downstream INSIG1 gene, and the INSIG1 mRNA and protein levels were restored [60]. These results revealed that insulin could enhance the proteolytic process of SREBP1 by regulating the expression of INSIG2.

Recently, Owen et al [54] generated a transgenic rat with additional tabular SREBP1c through human APOE promoter expression module. This transgenic rat excluded the effect of insulin on SREBP1 transcription. Endogenous SREBP1c mRNA increased 14 times in transgenic rats without inhibitors. When rapamycin was added, the SREBP1c mRNA level was reduced by 85%. Interestingly, expression of endogenous SREBP1c mRNA was not affected by LYS6K2, an inhibition of S6K downstream of mTORC1 [54]. Similarly, insulin increased the transgenic nSREBP1c protein levels by 12 times within 6 hours. When LYS6K2 was added, nSREBP1c decreased by 74%, but only by 64% in the rapamycin treatment group. Considering that insulin does not affect mRNA level of SREBP1c, it is indicated that the proteolytic processing of LYS6K2 inhibiting SREBP1c does not occur at the transcription level [54]. In conclusion, insulin can enhance the proteolytic process of SREBP1 by activating S6K through PI3K/AKT-mTORC1 pathway, but it is not clear which pathway S6K increases this process (Figure 1).

Regulation of Insulin On Mature Karyotype nSREBP1

In addition to regulating mRNA level of SREBP1 and proteolytic processing, insulin also regulates the stability and abundance of nuclear SREBP1. Studies have confirmed that insulin signaling pathway has branches at AKT. One of them is the activation of mTORC1 to regulate the activity of SREBP1, while the other is to inhibit the degradation of nSREBP1 through the GSK3-FBW7 pathway. AKT can phosphorylate GSK3 on its ninth serine residue, and the phosphorylation of GSK3 inhibits the action of glycogen synthase [51]. When nSREBP1 is connected with DNA on the target gene, the recruited GSK3 can phosphorylate the 434th serine on nSREBP1 [62,63], and then the 426th threonine of nSREBP1 is also phosphorylated by GSK3 [63]. Finally, ubiquitin ligase SCF-FBW7 was also recruited, leading to ubiquitination degradation of nSREBP1 [62,63]. Other studies have confirmed that SCF-FWB7 can degrade nSREBP2, and inactivation of endogenous FBW7 makes karyotype nSREBP1 and 2 stable [64]. Therefore, insulin can inhibit GSK3 through the AKT pathway and prevent recruitment of FBW7 to stabilize the expression of nSREBP1 in vivo [65]. Interestingly, AKT-dependent accumulation of exogenous wild-type mSREBP could still be observed in the presence of rapamycin, indicating that mTORC1 function is dispensable for stabilization of mSREBP1 in response to AKT activation. Porstmann et al observed that AKT also regulates SREBP1 activity in a GSK3-independent, mTORC1-dependent manner. These results indicate that AKT-dependent activation of endogenous SREBP does not solely involve regulation of the stability of SREBP but suggest an additional, mTORC1-dependent pathway that contributes to SREBP activation [66].

Previously, we have mentioned that mTORC1, as a factor downstream of AKT, can control the expression of SREBP1c by regulating transcription and processing. Recently, however,

Peterson et al [67] demonstrated that mTORC1 can improve the abundance of nSREBP1 through Lipin-1. This aggregation of Lipin-1 in the nucleus inhibits the transcription of SREBP1. Although the mechanism by which mTORC1/Lipin-1 regulates nSREBP1 expression level is not clear, studies show that lamin A may be involved in the regulation of this process, and further mechanisms need to be further studied (Figure 1). In addition to S6K, E4 Promoter-Binding Protein 4 (E4BP4), a leucine-zipper transcription factor involved in clock and immune regulation, has been proposed as a downstream regulator of mTOR signaling via its activation of the AKT-mTORC1-SREBP1c pathway in hepatocytes through acetylation and concomitant stabilization of SREBP1c [68].

Regulation of Insulin On Translocation of SREBP1

A mechanism was discovered in mice that CREB Regulated Transcription Coactivator 2 (CRTC2) functions as a mediator of mTOR signaling to modulate COPII-dependent SREBP1 processing. CRTC2 competes with Sec23A, a subunit of the COPII complex, to interact with Sec31A, another COPII subunit, thus disrupting SREBP1 transport. During feeding, mTOR phosphorylates CRTC2 and attenuates its inhibitory effect on COPII-dependent SREBP1 maturation. As hepatic overexpression of an mTOR-defective CRTC2 mutant in obese mice improved the lipogenic program and insulin sensitivity, these results demonstrate how the transcriptional coactivator CRTC2 regulates mTOR-mediated lipid homeostasis in the fed state and in obesity [69].

In summary, insulin activates SREBP1 via AKT through two mechanisms at least: (i) the stability of nSREBP1 is enhanced by inhibiting GSK3; (ii) increase the expression of SREBP1 through activation of mTORC1. The effect of mTORC1 on SREBP1 can be divided into four stages: (i) mTORC1 can increase the expression of SREBP1c mRNA at the transcription level; (ii) mTORC1 can strengthen the proteolytic process of SREBP1 by activating S6K; (iii) mTORC1 can inhibit Lipin-1 and then increase the content of mature nSREBP1; (iv) mTORC1-mediated phosphorylation of CRTC2 facilitates translocation of SREBP1 from the ER to the Golgi by releasing inhibitory Sec31 for formation of the Sec23-Sec24 complex to maintain COPII vesicle function.

Regulation of SREBP1 by Liver X Receptor

Liver X Receptor (LXR) is another important steroidal regulatory transcription factor. It has two subtypes, LXRα and LXRβ. LXR and Retinoid X Receptor (RXR) form heterodimer, which regulate the transcription level of SREBP and the protease digestion process.

There are two Liver X Receptor Response Elements (LXREs) in the promoter region of SREBP1c gene, and LXR can improve the transcription level of SREBP1 [70]. However, other LXR target gene promoter regions, such as ATP-Binding Cassette Subfamily A1 (ABC1), Cholesteryl Ester Transfer Protein (CETP) and Cytochrome P450, Family 7, Subfamily A (CYP7A), only one LXRE was found [71-73], indicating that LXR and RXR had a strong excitatory effect on SREBP1c. In fact, even in the case of cholesterol overload in the body, LXR or RXR can significantly enhance the transcription of SREBP1c and induce the corresponding increase in fatty acid synthesis [60]. In contrast, polyunsaturated fatty acids decrease the level of SREBP1c mRNA and fat generation by inhibiting connection between the heterodimer LXRα/RXRα and LXREs in the SREBP1c promoter region [74] (Figure 1). Bo Wang et al showed that LXRs modulate membrane phospholipid composition through activation of Lysophosphatidylcholine Acyltransferase 3 (LPCAT3, also known as lysophospholipid acyltransferase 5), a phospholipid remodeling enzyme that catalyse the incorporation of polyunsaturated fatty acids at the sn-2 site of lysophospholipids. LXR activation increases LPCAT3 expression and the abundance of polyunsaturated phospholipids in cell membranes, thereby ameliorating ER stress induced by saturated free fatty acids in vitro or by hepatic lipid accumulation in vivo. Subsequent studies revealed that LPCAT3 activity is also involved in the effects of LXRs on SREBP1c-dependent lipogenesis in the liver. Incorporation of polyunsaturated fatty acids into phospholipids by LPCAT3 promotes SREBP1c processing and lipogenesis. Inhibition of LPCAT3 activity in obese mice reduces SREBP1c pathway activity, blunts lipogenesis and ameliorates the development of fatty liver [75].

Oxysterol is a natural activator of LXR, including 24, 25-epoxy cholesterol and 25-hydroxyl cholesterol [76]. 24-hydroxyl cholesterol, 25-hydroxyl cholesterol and 27-hydroxyl cholesterol are well-known inhibitors of the SREBP1 enzymatic process, but they are not used to treat hyperlipidemia clinically because they also activate LXR [76]. Recently, Zhang Y et al [77] shows that lack of LXRα expression in the liver, a kind of synthetic LXR agonists can induce resistance to atherosclerosis. The main reason may be the target genes LXR of SREBP1 mainly expressed in the liver, and knockout LXRα can significantly reduce SREBP1 expression in the liver, thereby reducing the synthesis of fatty acids (Figure 1).

Interestingly, although LXR can effectively activate the expression of SREBP1c and improve the expression of the precursor SREBP1c. LXR cannot increase the content of nSREBP1 and its target gene in vivo [78,79]. This suggests that the effect of LXR increasing SREBP1c mRNA levels is limited during proteolytic processing. Corresponding studies also confirmed that LXR can regulate the expression of INSIG2 mRNA and protein levels, and leave SREBP1c stuck on the ER (Figure 1).

On the other hand, studies have shown that insulin can significantly upregulate the expression of LXR [80]. The knockout of LXR gene significantly inhibited the expression of insulin-regulated enzymes related to fatty acids and cholesterol metabolism

in mice [81]. This suggests that the interaction between LXR and insulin plays an important role in regulating cholesterol and fatty acid metabolism (Figure 1). Further, the LXR pathway is subject to negative regulation by Toll-Like Receptors 4 (TLR4). This suggests that macrophage fatty acid synthesis is influenced by TLR signaling via temporal modulation of LXR activities [82].

Regulation of SREBP1 by cAMP/PKA

Glucagon, epinephrine and other substances can upregulate the expression of Cyclic Adenosine Monophosphate (cAMP), which can activate a series of extracellular signaling pathways and regulate the functions of various cells. cAMP dependent kinase, Protein Kinase A (PKA) associated with lipid metabolism in the body, under physiological conditions, enzymes involved in lipid metabolism in the liver such as FASN, SCD and Glycerol-3-Phosphate Transferase (GPAT) are regulated by the intracellular cAMP levels of negative feedback [83].

A recent study showed that PKA inhibited the expression of SREBP1c by regulating the vitality of LXR [84]. PKA can make LXR phosphorylation, which blocks the formation of LXR/RXR heterodimers, thus slightly weakening the connection between LXR and LXREs on the target gene SREBP1 and reducing the transcription of SREBP1. Lu et al [85] found that SREBP1a amino terminal 338 serine is also a site of PKA phosphorylation. The serine in the 314th position of SREBP1c is the same as that in the 338th position of SREBP1a, which is also phosphorylated by PKA. These findings suggest that the cAMP/PKA signaling pathway can phosphorylate SREBP1 to reduce its transactivation [85], leading to decreased expression of relevant target genes of SREBP1. As a highly conserved serine/threonine kinase, AMP Activated Protein Kinase (AMPK) regulates energy balance in vivo at both cellular and physiological levels [86-88]. PKA is a regulation of AMPK upstream factor. Studies have shown that the use of a PKA inhibitors H89 can reverse to raise the level of the expression of intracellular cAMP, thus increase the phosphorylation of AMPK by PKA activation [89], and AMPK can phosphorylate SREBP1c directly, and therefore can directly inhibit SREBP1c enzyme processing, prevent the karyotype nSREBP1c in their transfer to the nucleus, which affects lipid metabolism [90]. These results indicated that the nutrient level in vivo regulated the activity of LXR and AMPK through cAMP/PKA pathway to control the expression and fat generation of SREBP1 (Figure 1).

Regulation of SREBP1 by PUFAs

PUFAs can reduce the expression of SREBP1c through various mechanisms, including reducing the transcription of SREBP1c, reducing the proteolytic processing of SREBP1c and reducing the stability of mRNA [91,92]. PUFAs inhibited the mRNA levels of SREBP1a and 1c in the liver, but did not reduce the expression level of SREBP2 [91]. There is evidence that PUFAs downregulate the transcription activity of SREBP1 through LXR-dependent methods or an independent mechanism [91]. In liver, PUFAs inhibit the protein processing of SREBP1 mainly through their influence on the metabolism of sphincter lipids [10]. PUFAs in CHO cells inhibited SREBP1 proteolytic processing and increased sphingomyelinase activity [92,93], while nSREBP2 was also inhibited in cells after sphingomyelinase incubation [94]. Therefore, PUFAs inhibiting SREBP processing may cause the redistribution of cholesterol in the plasma membrane (Figure 1).

Regulation of SREBP1 by LMP1

Latent Membrane Protein 1 (LMP1) is an integral membrane protein containing two signaling domains: CTAR1 and CTAR2, and among the EBV-encoded gene products expressed in Nasopharyngeal Carcinoma (NPC), LMP1 is of particular interest, as it shows oncogenic properties in vitro and in vivo. Using siRNA targeting raptor or rictor, study shows that both the mTORC1 and Mammalian Target of Rapamycin Complex 2 (mTORC2) signaling pathways are involved in LMP1-mediated lipogenesis. Furthermore, inhibition of the mTOR pathway, through use of either mTOR inhibitor or siRNAs, significantly reduced LMP1-mediated SREBP1 activity and lipogenesis, indicating that LMP1 activation of the mTOR pathway is required for SREBP1-mediated lipogenesis. Luciferase promoter reporter assays and RT-qPCR analysis demonstrate that LMP1 upregulates SREBP1 at the transcriptional level, and western blotting analysis demonstrates that LMP1 promotes SREBP1 maturation and the expression of its downstream target FASN [95]. Dirk et al showed that mTORC2, via its downstream effector AKT, promotes SREBP1 expression and prevents SREBP1 degradation in cancer cells [33].

Regulation of SREBP1 by Amino Acids

The level of amino acids can also activate and regulate SREBP expression. Amino acids activate mTORC1 in the lysosome and regulate both protein synthesis and autophagy. The serine/threonine-protein kinase known as General Control Nonderepressive-2 (GCN2, also known as eIF-2α kinase GCN2), which functions as a sensor of amino acids deficiency and suppresses protein translation, decreases levels of SREBP1 and lipogenic enzymes in response to nutrient deprivation. As a result of this relationship, GCN2-deficient mice develop liver steatosis. Under conditions of fasting or amino acids deprivation, SREBP1c is suppressed either via GCN2 or the mTOR pathway. Amino acids sensors such as Sestrin-2 (which senses leucine), CASTOR1 and/or CASTOR2 (which sense arginine), and their regulators GATOR1 and GATOR2 have been linked with mTORC1, and are thus probably also linked with SREBPs and lipid metabolism [3].

Regulation of SREBP1 by Oncogenic Signals

As mentioned earlier, insulin signaling through PI3K-AKT-mTORC1-SREBP is the key anabolic pathway regulating

lipogenesis in response to changing nutritional status. This PI3K-AKT-mTORC1 signaling is also an established survival pathway that is constitutively activated in many types of cancer and has prominent roles in growth, malignant transformation, prevention of apoptosis, drug resistance and metastasis. Many oncogenic signaling molecules such as p53, PTEN, PI3K and KRAS converge on the PI3K-AKT-mTOR pathway, activating both protein and lipid biosynthesis to meet lipid demands for cell growth even in conditions of poor oxygenation and high acidity [3].

Mei Yi et al show that activation of SREBP1 is required for oncogenic PI3K (H1047R) and K-Ras (G12 V) stimulated de novo lipid synthesis and breast epithelial cell growth. SREBP1 protein is stabilized upon sequential phosphorylation by mitotic kinase CDK1 and PLK1 during mitosis, blocking binding between the ubiquitin ligase FBW7 and SREBP1 and attenuating SREBP1 degradation. Activation of EGFR signaling induces nuclear translocation of Pyruvate Kinase M2 (PKM2) [96,97], a key enzyme in Warburg effect. A latest study unveiled that nuclear PKM2 physically interacts with SREBP1 and stimulates lipid biosynthesis through stabilizing SREBP1 protein [98]. Fibroblast Growth Factor Receptor 3 (FGFR3) also stimulates SCD1 expression to accelerate tumor growth via activating SREBP1 in bladder cancers [99].

Nuclear Receptor Subfamily 4 Group A Member 1 (NR4A1, also known as NURR77, TR3 or NGFI-B), is an orphan nuclear receptor with diverse functions. It has been reported that NR4A1, as a transcriptional activator, is implicated in glucose and lipid metabolism. Qin et al show that overexpression of NR4A1 in 3T3-L1 cells resulted in reduced expression of SREBP1c and its downstream FAS. While knockout NR4A1 resulted in reduced p53 expression, therefore, NR4A1 might indirectly modulate the expression of SREBP1c via p53, then hinder excess fat accumulation in adipocytes [100]. On the other hand, Fatostatin is a non-sterol synthetic diarylthiazole derivative which inhibits SREBP1 maturation and its nuclear translocation. PF429242 is a reversible, competitive aminopyrrolidineamide inhibitor of S1P, which inhibits endogenous SREBP processing. Both fatostatin and PF429242 significantly reduced the expression of p53. And two sterol regulatory element sequences (50-ATCACCCCAC-30) with 100% homogeneity in p53 gene sequence at 1904-1911 and 2350-2358 base pairs in BLAST analysis suggesting a potential regulatory role of SREBP1 over p53 gene expression. Thus, they speculate that since the majority of p53 is mutated in tumor cells, the reduction in the level with SREBP1 inhibitors most likely reflects a reduction in the mutant form of p53.

Forkhead Box (FOX) proteins are a family of evolutionarily conserved transcriptional regulators defined by a common DNA-Binding Domain (DBD) termed the forkhead box or winged helix domain. There are 17 Fox gene subfamilies (FOXA-R), with at least 41 genes currently identified in humans. FOXO1 and SREBP1 are important in the lipogenesis and tumorigenesis of Endometrial Cancer (EC), and are all targets of insulin. Western blot analysis was performed and the results demonstrated that the protein level of SREBP1 in Ishikawa and AN3 CA transduced with lentiviruses containing FOXO1 overexpression vectors was lower than the control group. A previous study reported that FOXO1 is able to directly repress SREBP1 expression in hepatic lipogenesis. In addition, the present study supported the hypothesis that increased FOXO1 expression decreases the level of SREBP1 [101].

Talebi et al find that alterations in the expression of these enzymes by mutant BRAF inhibition was confirmed by RT-qPCR on an extended panel of therapy-sensitive $BRAF^{V600E}$ parental and isogenic cell lines that have acquired resistance to vemurafenib through diverse mechanisms. Their findings indicate that inhibition of oncogenic BRAF inhibits de novo lipogenesis and thereby enhances membrane poly-unsaturation. The selected lipogenic enzymes, the expression of which are downregulated upon oncogenic BRAF inhibition, are well established transcriptional targets of SREBP1. Taken together, oncogenic BRAF targeting inhibits the processing and activation of SREBP1 in therapy-sensitive, but not therapy-resistant, melanoma cells and this effect is, by and large, mediated by a posttranslational mechanism [102].

Regulation of SREBP1 by Other Pathways

A recent study found that glutamine also regulated SREBP1 gene expression and proteolytic processing, a finding that links amino acid metabolism to lipid metabolism. Glutamine appeared to be able to increase the mRNA levels of multiple SREBP1 target genes. Glutamine enhances the expression of the SREBP1 gene by strengthening the connection between the transcription factor Sp1 and the SREBP1a promoter. Glutamine is also able to increase the enzymatic processing of SREBP1 protein, which may be realized by stimulating the transport of SREBP-SCAP complex from the endoplasmic reticulum to Golgi [103] (Figure 1).

Ponugoti et al show that NAD^+- dependent SIRT1 (Sirtulin 1) can directly affect SREBP1c, to take off the acetylation to reduce its protein expression and the expression of target genes corresponding [104]. In addition, SIRT1 can also downregulate the expression of SREBP1c in the state of fasting in vivo [105]. However, these studies have focused on liver tissue, and recent studies have shown that SIRT1 also regulates the expression of SREBP1c in skeletal muscle cells. Interestingly, when the LXR response element in the SREBP1 promoter region was deleted, SIRT1 expression regulation of SREBP1c was completely eliminated, indicating that SIRT1 regulation of SREBP1c was through the deacetylation of LXR in muscle cells [106] (Figure 1).

SIRT1 does not only influence nuclear factors, there are also considerable interactions with upstream enzymes that regulate the activity of key cellular pathways. AMPK, for instance is an energy sensor in the cell and is activated upon increases in the

AMP/ATP ratio. Deacetylation of Liver Kinase β-1 (LKB1) by SIRT1 potentiates the activity of LKB1 targets such as AMPK. Subsequently, AMPK activity inhibited ACC and FAS and thus limits the generation of fatty acids. SIRT1 by virtue of its interaction with the LKB1 blocks the synthesis of lipids via the de novo synthesis pathway [107].

Bisphenol A (BPA), a representative endocrine disrupting compound, exists ubiquitously in the aquatic environment. Several studies on fish have validated the role of BPA in the lipid metabolism. Therefore, the present results implied that BPA could disturb the transcriptional regulation of target genes of ACACA, FASN and CPT1α via altering the SREBP1 binding to their SREs, subsequently affecting triglyceride synthesis [108].

X-Box Binding Protein-1 (XBP-1) is a major transcription regulator of the Unfolded Protein Response (UPR), mediating adaptation to ERS. Xian Yu et al showed that in the presence of high fructose (20 mmol/L), there was significant upregulation of XBP-1s (active form) and downregulation of XBP-1u (inactive form). To elucidate the underlying mechanisms, they investigated hepatic regulation of TG synthesis by activating XBP-1. XBP-1s overexpression increased cellular TG accumulation, which was accompanied by increased mRNA expression of SREBP1c and protein content of three key target enzymes associated with lipogenesis, ACC, FAS, and SCD1. Therefore, they explored the causal relationship between XBP-1s and lipid accumulation and found that high fructose-induced cellular lipid deposition in NAFLD was partially regulated by XBP-1s [109].

AM580, a retinoid derivative and RAR-α agonist, demonstrates potent and broad-spectrum antiviral activities in vitro and in vivo. Shuofeng Yuan et al find that AM580 blocks the interaction of SREBP1/2 proteins with the non-palindromic SREs in the promoter/enhancer regions of multiple lipogenic genes, which inhibits their transcription and thus reverses the virus-induced lipid hyper-biosynthesis [110].

Lipopolysaccharides (LPS) from the cell wall of gram-negative bacteria are also referred to as a bacterial endotoxin. Bacteria will release LPS during clinical disease such as ruminal acidosis, mammary and uterine infection as well as during heat stress. Wang et al find that LPS decreased the concentration of TG and the formation of lipid droplets in (dairy cow mammary epithelial cells) DCMECs, and decreased the transcriptional and nuclear translocation of lipogenic transcription factor SREBP1 in DCMECs. Moreover, their findings suggest that LPS affects the synthesis of dairy cow milk fat by down-regulating expression of SREBP1 and milk fat de novo synthesis of related enzyme genes [111].

Fibroblast Growth Factor 10 (FGF10), a member of FGF family, was primarily identified in mouse embryos in 1996, and it was found to regulate the development and maturity of multiple tissues and organs. Xu et al show that using two specific siRNAs, SREBP1 expression was significantly decreased 53% compared with control [112].

SRY-Box Transcription Factor 4 (SOX4), a transcription factor that regulates cell proliferation and differentiation, play an important role in hepatic triglyceride metabolism. SOX4 expression levels are markedly upregulated in livers of obese rodents and humans. Jiao et al find that cellular TG content and expression levels of SREBP1c were increased after SOX4 overexpression in a dose dependent manner. Knockdown of SREBP1c in Hep1-6 cells largely prevented the role of SOX4 overexpression on lipogenic enzyme expression and cellular TG contents [113].

Copper (Cu) is a vital trace element for all animals. It is co-factor of many enzymes and plays important roles in many physiological processes of animals. Studies have shown that dietary Cu deficiency reduced appetite and growth performance. In contrast, excessive Cu in diet can be toxic and cause growth retardation, oxidative stress and intestine damage. Chen et al show that compared to fish fed low-Cu diet, dietary Cu addition down-regulated mRNA levels of SREBP1. In the mid-intestine, compared to fish fed low-Cu diet, dietary Cu addition down-regulated mRNA expression of SREBP1. Thus, these observations indicated that Cu-evoked alterations in lipid metabolism, at least in part, was via the SREBP1 pathways [114].

Ursodeoxycholic Acid (UDCA) is a hydrophilic Bile Acid (BA) and has been administered occasionally as a hepatoprotective drug for cholestasis and chronic hepatitis. Early reports indicate that UDCA improves glucose metabolism; that is, administration of high-dose UDCA improves glycemic parameters, insulin sensitivity, and insulin resistance surrogate markers in patients with NASH. Recent reports indicate that UDCA modulates multiple molecular targets and has potent anti-inflammatory activities and improves glucose and lipid metabolism. Chen et al observed that the administration of UDCA decreased SREBP1c, CD36. These results suggested that UDCA attenuated HFFA-induced lipid accumulation, ROS production, mitochondrial dysfunction, and inflammation in AML12 cells [115].

Most caspases are activated during apoptosis, but hepatocytes with persistently elevated DNL and cholesterol synthesis are not apoptotic. Unlike other caspases, Casp2 was reported to enter the ER lumen and the Golgi apparatus. Casp2 does not trigger apoptosis and cannot activate SREBP1/2 directly. Prior to its secretion, Casp2-activated S1P cleaves SREBP1/2 at site 1, followed by the S2P-mediated cleavage step that results in final SREBP activation. Notably, SREBP1/2 activation by the Casp2-S1P pathway is SCAP-independent, and Casp2, S1P, and SREBP2 cohabitate the same juxta-nuclear compartment. This unique pathway of SREBP1/2 activation results in persistent upregulation

of DNL, which is needed for NAFLD initiation and accumulation of hepatocyte free cholesterol, which drives the transition from simple steatosis to NASH [116].

Conclusion

As an important nuclear transcription factor in vivo, SREBP1 not only plays an important regulatory role in cholesterol and fatty acid metabolism, but also is a key link point in related diseases such as metabolic syndrome, and its regulatory role in the body has been receiving more and more attention. Through the application of gene chip and sequencing technology, our understanding of the downstream target genes regulated by SREBP1 is relatively clear, and it is understood that the target genes regulated by SREBP1 can be divided into three types: direct regulation, indirect regulation and possible regulation [15]. On the other hand, we are not very familiar with the specific mechanism and role of each factor in regulating SREBP1. Currently, insulin is known to play an important role in the regulation of SREBP1, including the transcription of SREBP1 mRNA, the proteolytic processing of SREBP1, and the regulation of the stability abundance of mature nSREBP1. Therefore, in order to further understand the regulation mechanism of SREBP1 comprehensively, it is necessary to collect and sort out the latest research progress of SREBP1, and delineate more detailed and comprehensive signal pathways through the use of bioinformatics analysis method, so as to provide new targets for the prevention and treatment of SREBP1 related metabolic diseases, in the hope of opening up a new approach in treatment.

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