

Review Article

Therapeutic strategies targeting SREBP transcription factors: an update to 2024

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ABSTRACT

In addition to regulating lipid biosynthesis and uptake, sterol regulatory element binding protein (SREBP) is involved in mediating biological signaling networks. SREBP is a key transcription factor in the regulation of physiologic and pathologic lipid metabolism processes. "SREBP" was used as a keyword in searches on the Web of Science, Elsevier, Science Direct, and CNKI databases for relevant literature from 2021 to October 2024; the search results were analyzed. SREBP is first synthesized as an inactive precursor, then cleaved to release active NH₂-terminal domains. Mature SREBP enters the nucleus and promotes transcription of downstream genes by binding to the promoter elements of target genes. The classical pathway of SREBP precursor activation refers to transporter cleavage that is dependent on SCAP in response to signals from intracellular sterol depletion. However, in the case of endoplasmic reticulum stress, SREBP is activated via caspase-2 and independent of feedback inhibition by steroids or excess lipid uptake. Furthermore, the mechanism of action underlying SREBP in different diseases, as well as synthetic and natural compounds that inhibit SREBP activity, are summarized to provide new insights into SREBP as a therapeutic target for diseases.

Keywords: SREBPs, metabolism regulation, related diseases, therapeutic strategies

1. INTRODUCTION

Since the discovery of sterol regulatory element binding protein (SREBP), there are now > 6000 studies related to SREBP, which highlight the critical role of SREBP in regulating lipid metabolism and maintaining cellular and systemic homeostasis. In this review sufficient evidence was gathered to summarize the physiologic SREBP processes, the regulated signaling pathways, the diseases caused, and the compounds that inhibit SREBP activity. These studies are interrelated and provide a reference value for further exploration of metabolic networks and targeted inhibition of SREBP for disease prevention and treatment.

2. SREBP MECHANISM OF ACTION AND KEY MOLECULES

2.1 Classic activation pathway

Identified in the early 1990s by Spiegelman, Brown, and Goldstein, SREBP was isolated from nuclear extracts

obtained from cultured human HeLa cells. SREBPs are encoded by sterol regulatory element binding transcription factors (SREBF-1 and -2) in mammals and belong to a family of transcription factors characterized by a basic-helix-loop-helix leucine zipper (bHLH-LZ) structure that has a crucial role in regulating cholesterol and fatty acid synthesis [1, 2].

SREBP is initially produced as a 125 kDa inactive precursor that is anchored to the endoplasmic reticulum (ER) membrane in a hairpin configuration, where the NH₂- and COOH-terminal segments are oriented toward the cytosol and divided by a short hydrophilic sequence extending into the ER lumen [3]. This precursor then interacts with the SREBP cleavage-activating protein (SCAP). SCAP is a polyhedral membrane binding protein that consists of eight transmembrane helices divided by seven loops. SCAP contains a C-terminal WD40 domain that interacts with SREBP [4, 5]. When sterol levels are sufficient, 25-HC is positioned between the S4-S6 segments of SCAP and TMs 3/4 in insulin-induced gene-2 (INSIG-2), which is located in the luminal leaflet of the

membrane and forms the INSIG-SCAP-SREBP complex [6, 7]. Formation of the INSIG-SCAP-SREBP complex causes the separation of loops 1 and 7 in SCAP, resulting in a conformational alteration in cytosolic loop 6 that obscures the MELADL sequence, which hinders integration of the SREBP/SCAP complex into COPII vesicles. Conversely, when there is a reduction in sterol levels, SCAP dissociates from INSIGs and adopts a closed conformation in which loop 1 is associated with loop 7. The MELADL sequence present in loop 6 binds COPII proteins (sec23-sec24), facilitating the movement of the SREBP-SCAP complex toward the Golgi apparatus. Accordingly, INSIGs will be degraded by recruiting an E3 ubiquitin ligase, such as TRC8 and GP78. Then, SREBP travels to the Golgi, where SREBP undergoes sequential hydrolysis by site-1 protease (S1P), followed by site-2 protease (S2P). Two proteases located in the membrane are involved in the hydrolysis process; S1P (a serine protease related to subtilisin) cleaves the loop of SREBP within the ER lumen, while S2P (a zinc metallopeptidase) cuts the first transmembrane segment. This action results in the release of the NH₂-terminal domains, which migrate to the nucleus and modulate the transcription of target

genes by binding to the sterol regulatory elements (SREs) found in their promoter regions. Simultaneously, SCAP with the leftover SREBP C-terminal structural domain is transported in a retrograde direction to the ER, where the remaining SREBP undergoes degradation, allowing SCAP to initiate a new cycle of SREBP activation. **Figure 1** demonstrates the SREBP activation process in response to cellular sterol concentrations.

2.2 Multiple controls during transit

An evaluation of the mechanisms associated with SREBP transport indicated that signaling through epidermal growth factor receptor (EGFR) enhances N-glycosylation of SCAP by facilitating increased uptake of glucose. This glycosylation process helps stabilize SCAP and diminishes the interaction with INSIG-1, leading to translocation of SCAP/SREBP to the Golgi and subsequently resulting in activation of SREBP [8]. Moreover, cancer cells tend to favor glutamine as a substrate for fatty acid synthesis, a phenomenon referred to as glutaminolysis, which involves reconfiguration of glutamine metabolism. At this point, the ammonia that is generated from glutamine facilitates SREBP activation by

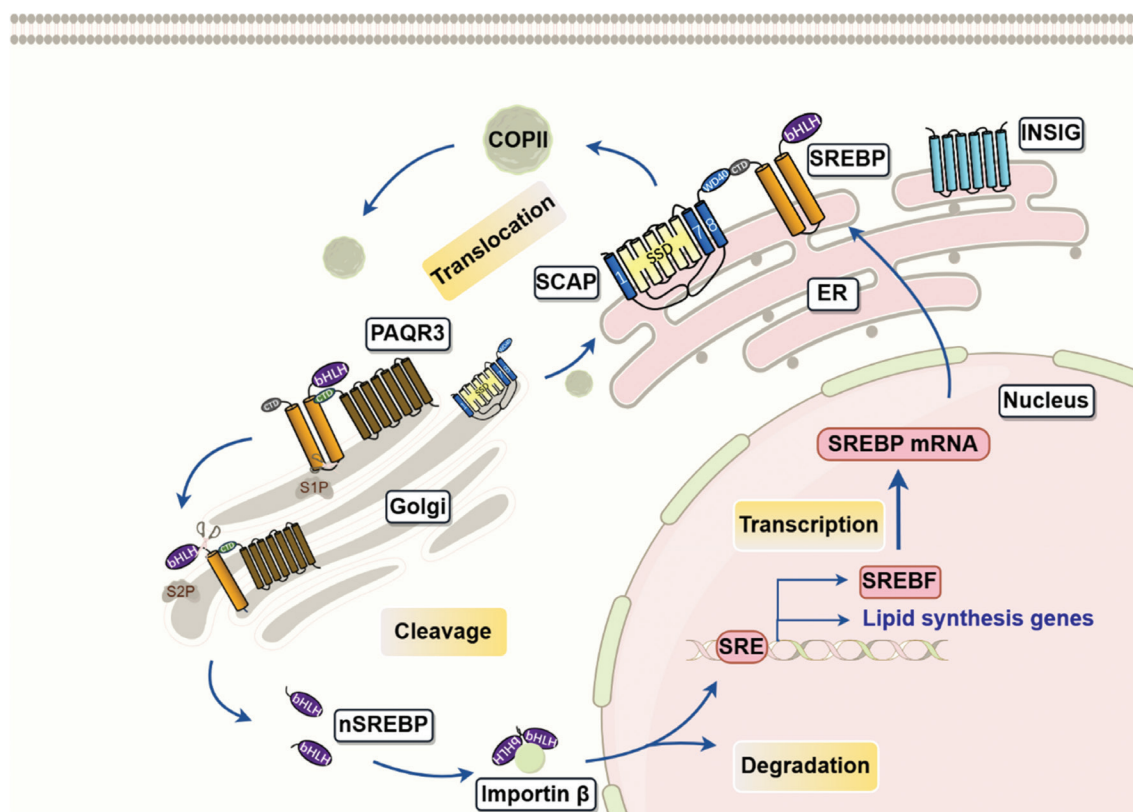


Figure 1 | SREBP activation process in response to sterol concentration.

In response to low intracellular sterol concentrations, the SCAP-SREBP complex separates from INSIG and is transported to the Golgi by fusion with COPII. PAQR3 anchors SREBP to the Golgi, where SREBP is progressively hydrolyzed by S1P and S2P, resulting in the release of the N-terminal structural domain of SREBP, while SCAP is recycled back to the ER. The activated form of SREBP, which enters the nucleus as a dimer, attaches to the SRE promoter sequence, triggering the transcription SREBP and downstream lipid synthesis-related genes and is eventually degraded.

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competing with 25-HC for the SCAP binding site, which is independent of the SCAP protein and N-glycosylation levels. SREBP induces conformational changes in the transmembrane structural domains, which dissociates from INSIG. These data also suggest that SCAP may be a key sensor linking glutamine, glucose, and lipid metabolism [9]. Furthermore, SCAP interacts with cell death-inducing DFF45-like effector B (Cideb) and binds sec12 to activate GTP kinase sar1, which allows SCAP/SREBP to converge into COPII vesicles after enrichment at the ER exit [10]. In addition, KLF2 binds to the promoter region of SCAP and promotes the SREBP1 maturation process by facilitating SCAP expression, which activates SREBP1 downstream targets to regulate adipogenesis [11]. Brahma-related gene 1 (BRG1) forms an interaction with Sp1 and directly binds to the SCAP promoter to stimulate SCAP transcription [12].

To date, INSIG-1 and -2, ER-resident six transmembrane proteins, block the transport of all three SREBP isoforms [13]. In addition, there are significant functional differences between INSIG isoforms. INSIG-1 is significantly upregulated in response to insulin, while INSIG-2a, a splice variant of INSIG-2 predominantly found in the liver, is suppressed by insulin [14]. To clarify the mechanism underlying the insulin-mediated reduction of INSIG-2a, it was shown that insulin activates CREBZF (a bZIP transcription factor belonging to the CREB/ATF family), which dimerizes with ATF4 to inhibit the expression of INSIG-2a [15]. Furthermore, fatty acid translocase (FAT/CD36), which is activated by insulin, is required for SREBP1 transport to the Golgi apparatus. Because CD36 creates a complex with INSIG-2, CD36 has a role in the dissociation of INSIG-2 from the SCAP-SREBP1 complex [16].

The Golgi-anchoring proteins for SREBP–SCAP, including progesterin, adipoQ receptor 3 (PAQR3) [17], and SREBP regulating gene (SPRING), have been identified [18, 19]. When the cholesterol level is low, PAQR3 competes with INSIG for SCAP interactions, then tethers the SCAP-SREBP-2 complex to the Golgi via distinct structural motifs, thus enhancing SREBP processing. SPRING, a membrane protein that is glycosylated and located in the Golgi, has a direct interaction with SCAP. However, when SPRING is absent, disruption of SREBP signaling is attributed to a reduction in SCAP levels and improper localization within the Golgi apparatus, which is unrelated to the sterol environment. This finding indicates the potential significance of retrograde transport to the ER in maintaining cholesterol homeostasis.

2.3 Interaction with other transcription factors

Examination of the SREBP-1c promoter revealed the presence of other transcription factor binding sites in the vicinity of the SRE motif, including the liver X receptor (LXR) response element. The SREBP1c promoter contains SREs that can be used for loop activation and is a key target for nutrient regulation [20, 21]. LXR, a member of the nuclear hormone receptor superfamily, forms a

heterodimer with retinoid X receptors (RXRs) to upregulate the expression of SREBP-1c [22]. It has been hypothesized [23] that LXR allows synthesis of a small amount of SREBP-1c by participating in the basal transcription of SREBP1c precursors. When dietary intake results in an elevation of the insulin, insulin will stimulate SREBP-1c processing, then the activated SREBP1c will enhance the effect of LXR on SREBP-1c through a feedback mechanism. Furthermore, Tian et al. reported that LXR α binds to CCAAT/enhancer-binding protein β (C/EBP β) in a complex, which interacts with the SREBP-1c promoter but has no significant influence on the SREBP-1a and -2 transcription levels [24]. BHLHE40 is part of the LXR-C/EBP β complex and is stimulated by insulin through an mTORC1-dependent pathway. However, BHLHE40 alone cannot fully account for insulin-induced transcription of SREBP-1c [25]. Moreover, clusterin downregulates SREBP-1c expression by directly affecting SREBP1c promoter activity or by inhibiting LXR and specificity protein 1 functions [26].

2.4 Alternative SREBP activation pathways

The canonical SREBP activation pathway, is regulated by the sterol concentration. Notably, this pathway only applies to SREBP-2 and -1a, while the mechanism underlying SREBP-1c activation is influenced by insulin caused by the nutritional environment and ER stress caused by various stresses [23]. Kim et al. concluded that diets abundant in glucose result in SREBP activation that depends on insulin and mediated by the SCAP pathway. But diets high in saturated fatty acids and fructose can induce ER stress with an elevated INSIG2 level. In contrast, ER stress activates SREBP through the Casp2/PIDDosome mechanism within the ER [27, 28]. See the section on regulation of SREBP activity for details.

3. DOWNSTREAM REGULATION OF SREBPS

SREBPs have a crucial role in establishing the energy and lipid supply, as well as shaping the immune and inflammatory environments surrounding tumor cells, functioning as a protective shield that facilitates the malignant growth of these cells. SREBP-1c and -2 are the main isoforms found in various tissues. In contrast, SREBP-1a is predominantly expressed in some tissues and cell types [29].

3.1 Regulatory scope of SREBP

SREBP-1c regulates fatty acid and glucose/insulin metabolism, interacting with various enzymes, including acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and components of the pentose phosphate pathway, such as glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (PGDH). SREBP-2 is closely linked to the synthesis of cholesterol, including HMG CoA reductase (HMGCR) and farnesyl diphosphate synthase (FDPS). SREBP-1a regulates genes related to the synthesis of free fatty acids (FFAs) and cholesterol.

Notably, SREBP-1a negatively influences the 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB) promoter, an enzyme that has a crucial role in the synthesis and breakdown of fructose 2,6-bisphosphate during gluconeogenesis [30].

In addition to regulating glycolytic and lipogenic genes, SREBP-1c is also capable of influencing genes that have roles in numerous hepatic cellular functions, including cell growth, programmed cell death, inflammation, targeting of intracellular membranes, cellular respiration, and RNA processing [23]. SREBP-1c induces transcription of miR-216a, inhibits cystathionine lyase expression, reduces hepatic H₂S levels, and facilitates sulfide-dependent activation of unc-51-like autophagy-activated kinase 1 (ULK1). Consequently, this series of events results in a reduction of autophagy and degradation of lipid droplets in intrahepatocyte fat accumulation [31]. It has been noted that SREBP-1c influences adipocyte aging by enhancing the DNA repair mechanism mediated by PARP1, a process that is independent of the canonical function of lipid synthesis [32, 33]. SREBP-1a is a minor transcript in the hamster intestine, the gene expression of which is not altered by changes in dietary cholesterol flux. However, with significant changes in cholesterol flux in the intestine, SREBP-2 assumes the role of SREBP-1 and regulates cholesterol and fatty acid synthesis in the intestine [34]. Adipose-specific overexpression of SREBP-1a, which has a much lower abundance than SREBP-1c in adipose tissues, significantly increases adipogenic gene expression and fatty acid synthesis in WAT and BAT, which leads to adipose tissue hypertrophy. However, adipose tissue overexpression is not associated with SREBP-1c overexpression, suggesting that SREBP-1a and -1c have different roles in adipocyte lipid metabolism *in vivo* [35]. Normal islets express SREBP-1a and -1c, which provide important lipids for β cell activity but may also impair β cell function and growth. When SREBP-1a is specifically overexpressed in β cells, insulin secretion is impaired and glucose tolerance is moderately impaired [36]. In brain cancer cells, where extracellular cholesterol is depleted and *ab initio* synthesis is insufficient to maintain cholesterol homeostasis, SREBP-1 upregulates the expression of key autophagy and lysosome-related genes, which can trigger lipophagy, promote the hydrolytic release of lipid droplet-stored cholesteryl esters to maintain cholesterol homeostasis, and promote tumor growth and survival [37]. Pathologic increases in SREBP-1c or genetic overexpression in the liver cause fatty liver [38]. Conversely, pharmacologic inhibition or genetic inactivation of SREBP-1c protects against the development of fatty liver [39]. The complete removal of the SREBP-2 gene results in total embryonic lethality, indicating that SREBP-2 is also vital during the early phases of development [40]. SREBP-1c is a key regulator of nutritional status (fasting/feeding) and metabolic disease (obesity/T2D). SREBP-1c is repressed during fasting and strongly activated during high carbohydrate diets. A more

detailed discussion of the related diseases can be found in Sections 4 (Regulation of Srebp Activity) and 5 (Role of Srebps in Diseases).

SREBP-1a has a higher level of expression in macrophages compared to SREBP-1c. SREBP-1a is involved in enhancing IL-1 β production during the inflammatory phase. In contrast, SREBP-1a stimulates gene activation triggered by TLR4 and modifies lipid metabolism in macrophages, which encompasses the synthesis of anti-inflammatory fatty acids [41]. However, SREBP-1c amplifies hyperactivation of the NF- κ B inflammatory pathway induced by non-esterified fatty acids through an increase in reactive oxygen species (ROS) production independent of TLR4, which consequently leads to additional hepatic inflammatory injury in cows with fatty liver [42].

In summary, SREBP and SREBP target genes have a crucial role in cellular metabolism and disease development and are potential targets for pharmacologic or gene therapy.

3.2 SREBP-specific regulation of target genes

It is evident that nuclear SREBP-1 and -2 are selective for cholesterol-producing and adipogenic genes, and this process has attracted the interest of researchers. Studies have shown that SREBP mainly recognizes SRE and E-box sequences, then binds to the promoter or enhancer regions of target genes to regulate the expression of lipid metabolism-related genes. Specifically, both SREBP-1a and -2 strongly and efficiently activate cholesterol-producing genes containing classical SREs in the promoter but not SREBP-1c. Second, SREBP-1a and -1c bind to the E-box, unlike SREBP-2. Third, the liposynthesis gene promoters containing SRE (SRE-like) sequences are strongly activated by SREBP-1a and modestly and equally activated by SREBP-1c and -2 [43].

In addition, the transcriptional activity of SREBP is regulated by a variety of co-activators and co-repressors, which regulate the expression of genes related to lipid metabolism by affecting binding to DNA, transcription initiation, or epigenetic modifications. It has been reported that PPAR γ co-activator-1 β (PGC-1 β) [44], CREB-regulated transcription co-activator 2 (CRTC2) [45], and ARC-mediator co-activator complex (ARC105 [also referred to as MED15]) [46] directly bind to SREBP and synergistically promote the expression of lipid synthesis genes. In contrast, fibroblast growth factor 21 (FGF21) inhibits SREBP-1c, which reduces hepatic lipogenesis [47]. Moreover, SREBP-1a has 24 more amino acid residues in the N-terminal trans-activating structural domain than SREBP-1c, which leads to acetylation by p300/CBP and enhances its stability and transcriptional activity [48].

In addition, SREBP DNA binding is affected by histone modifications. Nuclear receptor co-activator protein 1 (NCoR1) inhibits the transcriptional activity of SREBP-1c by recruiting histone deacetylase 3 (HDAC3) [49]. SIRT1 reduces SREBP-1c stability and promotes degradation through deacetylation [50].

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4. REGULATION OF SREBP ACTIVITY

4.1 Insulin-mediated PI3K/AKT/mTOR signaling pathway

The liver has a crucial role in energy metabolism. It is understood that following adequate food consumption, blood glucose and insulin levels rise, which activates insulin signaling. This process then stimulates specific kinases, such as PI3K, along with several downstream kinases, including Akt, aPKC, and mTORC, and phosphatases, like PPI and PP2, thereby accelerating glucose utilization. Recent studies have reported a potential mechanism of action by which preferential glycogenesis in hepatocytes lags lipogenesis. Chen et al. reported that among the metabolic intermediates of gluconeogenesis with the assistance of solute carrier family 35 member F5 (SLC35F5), uridine diphosphate glucose (UDPG) enters into Golgi and binds to the S1P enzyme, necessitating the Asn438 site for this binding. This interaction causes a change in the conformation of S1P, which subsequently results in degradation of S1P through the ubiquitin-proteasome pathway. As a result, cleavage of SREBPs mediated by S1P is hindered, leading to inhibition of lipogenesis [51].

Subsequently, in agreement with reported findings, insulin signaling promotes lipogenesis via SREBP activation mediated by the PI3K/Akt/mTORC1 pathway in hepatocytes. Notably, this signaling is frequently over-activated in cancer [52, 53]. The mTOR signaling pathway is crucial for regulation of lipid biosynthesis that is necessary for cell growth and division. mTORC2 is functionally more efficient, phosphorylating AKT to produce positive feedback on mTOR. Functionally, mTORC2 further activates mTOR by phosphorylating AKT. mTORC1 is also able to continue phosphorylating a variety of downstream substrates to enhance lipid synthesis through regulation of SREBP. First, under insulin stimulation, mTORC1 directly regulates the transcriptional level of SREBP and can also mediate the downstream effector ribosomal S6 kinase-1 (S6K1) to promote processing of SREBP-1c, although the target of S6K1 action on SREBP is not known [54]. In other studies, S6K1 has also been shown to be involved in the transcriptional activation of SREBP, possibly by directly phosphorylating serine residues of LXR [55]. E4 promoter-binding protein 4 (E4BP4) has also been proven to be a downstream regulator of mTOR signaling. Additionally, E4BP4 is a transcription factor with leucine zipper motifs and has a role in regulation of circadian rhythms and immune responses [56, 57]. Research indicates that E4BP4 functions as a direct transcriptional target of SREBP-1c and enhances the stability of mature SREBP-1c through acetylation [58]. Also, in an investigation determining whether SREBP activity is associated with a circadian drive, it was shown that the circadian clock may influence SREBP-1 promoter-specific activity in the nucleus in contrast to the regulation of SREBP-1 activity by nutrients, which primarily relies on the management of subcellular positioning.

Perhaps, there is a possibility of linking lipid metabolism to circadian rhythms between SREBPs and E4BP4 [57, 59]. Furthermore, unlike gluconeogenesis during fasting or ER stress, CREB-regulated transcription co-activator 2 (CRCT2), a transcriptional co-activator, is phosphorylated by mTORC1 and segregates from SEC31, thereby facilitating COPII vesicle translocation of SREBP1 from the ER to the Golgi [45]. Cho et al. showed that mTORC1 further phosphorylates the splicing factor, serine/arginine-rich splicing factor 1 (SRSF1), by activating the downstream SRPK2, thereby enhancing binding to FAM120A. FAM120A, as a key transcriptional co-factor, directly interacts with SREBP1 at the active promoter to link newly transcribed adipogenic genes from RNA polymerase II to the RNA splicing machinery containing SRSF1 and U170K, thus promoting fatty acid synthesis [60]. As reported, lipin-1, which acts as a negative regulator of SREBP activity, is inactivated by mTORC1 phosphorylation. Upon inactivation of mTORC1, lipin-1 moves into the nucleus, where lipin-1 suppresses SREBP activity by facilitating the creation of a repressive complex that hinders SREBP-mediated transcription. However, how mTORC1/lipin1 regulates SREBP nuclear protein levels remains unclear [61]. Primarily, it has not been established which mechanism holds the greatest significance in specific circumstances. It can be assumed that the preeminence of any pathway is influenced by the type of cells and the surrounding environment.

With further study, the insulin-mediated mTORC1-independent and -dependent pathways are gradually being resolved. First, insulin signaling can be inhibited by AKT phosphorylated GSK-3 β to inhibit kinase activity to attenuate Thr426 and/or Ser 430 phosphorylation in SREBP1, therefore blocking degradation of SREBP by the FBXW7-mediated ubiquitin-proteasome system [62]. Second, in mice that had a liver-specific knockout of Tsc1, it has been observed that insulin facilitates SREBP-SCAP complex export into the Golgi through the Akt-mediated suppression of INSIG2a mRNA. Importantly, this process is not dependent on mTORC1 signaling [15, 63]. Furthermore, the protein, folliculin (FLCN), has been shown to provide substrate specificity for mTORC1. Removal of FLCN obstructs the mTORC1-mediated phosphorylation of the transcription factor E3/B (TFE3/B) family, while not influencing the phosphorylation of typical substrates (S6K1 and 4E-BP1) driven by mTORC1. In the nucleus, unphosphorylated TFE3 stimulates INSIG2 expression, which blocks the protein hydrolytic processing of SREBP-1c and enhances the binding of TFE3 to chromatin near SREBP-1c, which leads to repression of adipogenic genes. Importantly, this mechanism functions independently of lipin-1 phosphorylation and LXR signaling [64]. In studies involving mTOR that do not differentiate between inhibitory mechanisms of action, opposite results have been reported. This finding suggests that as an important hub for cellular sensing of nutrients, mTOR has more abundant and unknown downstream substrates and branched chains. In conclusion, using

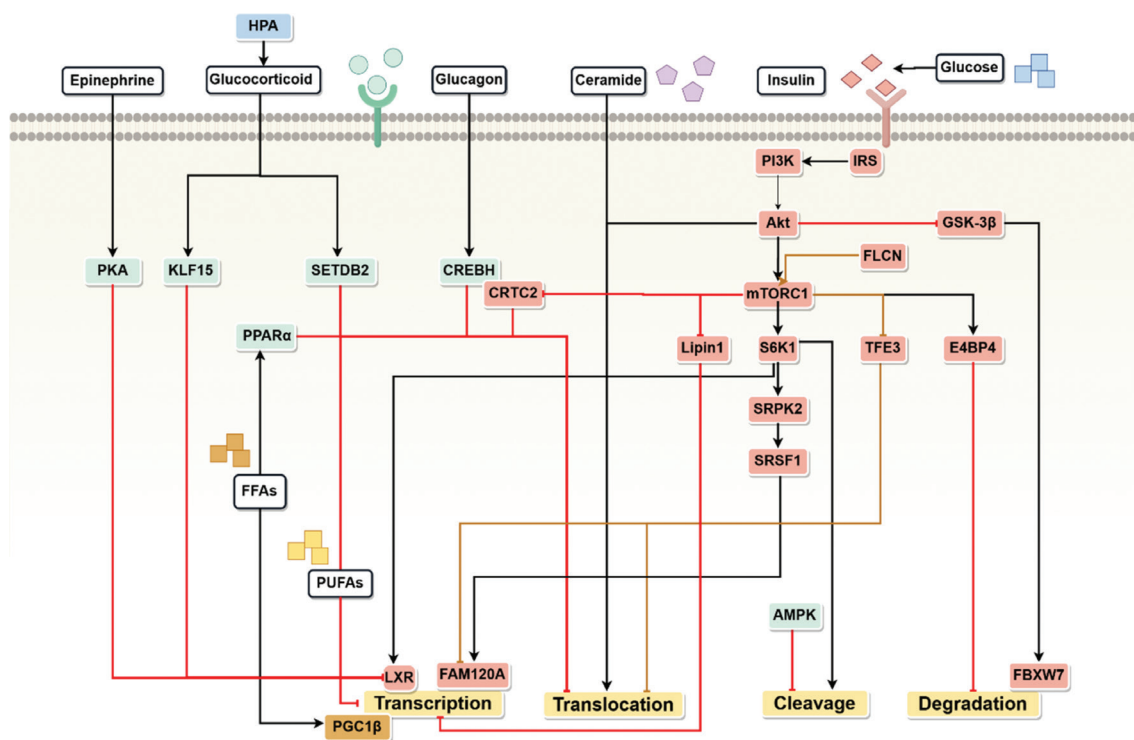


Figure 2 | The main signaling pathways regulating SREBP.

An elevated blood glucose concentration increases the release of insulin, which activates SREBP and lipid synthesis through the PI3K-AKT-mTOR signaling pathway and many of the PI3K-AKT-mTOR signaling pathway branches. Other nutrients, such as free fatty acids (FFAs) and polyunsaturated fatty acids (PUFAs), modulate SREBP activity at different levels. When energy is depleted, AMPK, cAMP-protein kinase A (PKA), and the hypothalamic-pituitary-adrenal (HPA) axis usually inhibit SREBP expression. Black arrows and red T-bars indicate stimulatory and inhibitory effects, respectively, and brown lines represent substrate-selective FLCN signaling pathways.

selective inhibitors to study the PI3K/AKT/mTOR/SREBP signaling pathway and its branches can help subsequent drug development by targeting key molecules and elucidation of the mechanism underlying drug action. **Figure 2** summarizes insulin-mediated PI3K/AKT/mTOR signaling axis regulation of SREBP activity.

4.2 ER stress-mediated SREBP activation

ER stress is any stress that results in a disruption of ER homeostasis. Different types of stress, including viral infections, oxidative pressure, low oxygen levels, and inflammation, can disrupt ER function. This disruption primarily results in the buildup of unfolded or misfolded proteins within the lumen of the ER, consequently initiating the unfolded protein response (UPR) to re-establish the dynamic balance of the ER. The UPR is carried out by three transmembrane proteins (PKR-like eukaryotic initiation factor 2 α -kinase [PERK], activating transcription factor 6 [ATF6], and inositol-requiring enzyme 1 [IRE1]). These proteins initiate three distinct signaling pathways that alleviate ER stress by diminishing protein translation, enhancing the folding capacity of the ER, and ensuring the degradation of misfolded proteins [65].

Several possible mechanisms can lead to activation of SREBP resulting from ER stress. In 2004 Lee and colleagues demonstrated that phosphorylation of EIF2 α mediated by PERK induces INSIG1 degradation under ER stress conditions, which facilitates the movement of SREBP from the ER to the Golgi apparatus, where SREBP is activated by protein hydrolysis [66]. Bobrovnikova-Marjon et al. reported that inhibition of protein translation via PERK dependency results in a reduction of INSIG-1 levels in mammary epithelial cells, which consequently causes the translocation and processing of SREBP-1 within the Golgi apparatus [67]. Importantly, Kim et al. identified the SCAP-independent Casp2-S1P-SREBP activation pathway. Upon excessive fructose intake, the liver undergoes ER stress to activate IRE1 and induces PIDDosome subunit caspase-2, RIP-associated ICH1/CED3-homologous protein with a death domain (RAIDD), p53-induced protein with a death domain (PIDD), and expression of INSIG2, a SCAP-dependent SREBP-activated repressor. Formation of the ternary complex PIDDosome activates caspase-2 and maintains IRE1 activation [27]. Caspase 2, once activated, co-localizes with S1P and cleaves S1P, resulting in a soluble variant that moves to the ER to trigger SCAP-independent activation of SREBP-1/2 within the ER [28]. In contrast to the standard SCAP-dependent mechanism,

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the Casp2-S1P-SREBP pathway remains unaffected by feedback inhibition caused by sterols or an excess of lipid absorption. Moreover, several other caspases have been reported to potentially activate SREBPs, including caspase-1, -4, -11, and -12. Caspase-1 is an effector protein of inflammatory vesicles that cleaves SREBP-1 and -2, generating truncated forms (e.g., p40-SREBP-1) that promote lipid accumulation and inflammatory responses. Caspase-1-dependent SREBP activation promotes atherosclerosis in macrophages [68]. Caspase-4 (human) and -11 (mouse) are intracellular receptors for bacterial lipopolysaccharide that promote lipid overload and cellular pyroptosis by cleaving SREBP-1/2 [69]. In addition, caspase-12 exacerbates diabetes-induced NAFLD by enhancing SREBP-1c activity during ER stress [70].

In addition, it was shown that the SREBP system also allows lipid species in the ER membrane to provide biosynthesis feedback. In the one-carbon cycle, SREBPs control a gene that synthesizes S-adenosylmethionine (an important methyl donor). Methylation is essential for phosphatidylcholine (PC) synthesis. When PC synthesis is blocked in the liver, the phospholipid composition of the ER membrane is altered, which directly triggers cleavage of SREBP-1. Notably, this alteration is not dependent on the classical SCAP-INSIG activation process [71].

4.3 Other nutrient-mediated responses to SREBP activity

Current evidence does not support the role of amino acids in activating SREBP-1c within the mammalian liver. Nevertheless, it is theoretically possible for amino acids to stimulate mTORC1 via a complex mechanism [72, 73], suggesting that amino acids might enhance insulin signaling.

Fatty acids are proven significant modulators of SREBP-1c, with various types exhibiting distinct impacts. Initially, the influence of saturated fatty acids on the regulation of SREBP-1c in mammals is not fully understood. Studies have indicated that acute intake of a diet rich in saturated fat increases SREBP-1c expression and target genes. It was shown that the increased expression of PGC1 β acts as a co-activator of SREBP-1c, thereby stimulating lipogenesis in the liver [74]. Moreover, palmitic acid activates SREBP-1c by promoting ceramide production via ER stress. The production of ceramide triggered by ceramide synthase 6 (CerS6) is the most effective activator of ER stress. Specifically, ceramide promotes the cleavage process of SREBP-1 by downregulating INSIG-1 levels. However, the mechanism underlying ceramide-induced ER stress is unclear [75]. In contrast, it has been demonstrated that PUFAs can impede the function of SREBP-1c at various stages. Augmented intake of ω -3 polyunsaturated fatty acids (PUFAs), including α -linolenic acid (ALA) and docosahexaenoic acid (DHA), has been shown to reduce the nuclear levels of SREBP-1 by diminishing the transcriptional activity of SREBP-1c, which enhances the breakdown of SREBP-1 via proteasomal mechanisms and decreases the levels of SREBP-1c mRNA [76]. Eicosapentaenoic acid (EPA) has been

previously shown to inhibit SREBP activity irrespective of PPAR- α [77]. Recent findings indicated that EPA triggers the phosphorylation of serine 106 in INSIG-2 via protein kinase A (PKA) activation, which is inducible by adenylylate cyclase. The phosphorylated form of INSIG-2 leads to inhibition of SREBP-1 protein hydrolysis, consequently obstructing fatty acid synthesis in human fibroblasts and rat hepatocytes. Notably, phosphorylated INSIG-2 does not interfere with SREBP-2 processing. Furthermore, because INSIG-1 does not contain the serine 106 site, EPA exerts no impact on INSIG-1 [78]. DHA has been proven to inhibit SREBP-1 transcription and cell proliferation by suppressing the Akt signaling pathway in MCF-7 cells [79]. In addition, PUFA has also been shown to create a complex with UBXD8, which results in detachment of UBXD8 from INSIG-1 and enhances stability of INSIG-1 by preventing degradation [80]. **Figure 2** summarizes the regulation of SREBP by other nutrients.

4.4 Regulation of SREBP by different energy regulators during fasting

The body transitions its metabolism from utilizing carbohydrates to relying on fats and ketones for energy during this fasting. This process also leads to suppression of hepatic *de novo* lipogenesis (DNL) while initiating gluconeogenesis. At this time, signals related to energy depletion inhibit SREBP-1 and adipogenesis. AMPK, a well-conserved sensor of cellular energy levels, directly phosphorylates the SREBP-1c Ser372 site. This action prevents protein hydrolytic cleavage and nuclear translocation, thereby inhibiting hepatic adipogenesis [81]. Wang and colleagues demonstrated that fasting and glucagon stimulate the transcription factor, cAMP-responsive element-binding protein H (CREBH). The complex formed by CREBH and CRTC2 attaches to the evolutionarily preserved CRE-BP-binding element found in the enhancer region of INSIG-2a, leading to an increase in mRNA and protein levels [82, 83]. Additionally, the transcription factor, PPAR α serves as another inducer of INSIG-2a. During periods of fasting, fatty acids activate PPAR α , which subsequently promotes the expression of INSIG-2a through the PPAR response element present in the INSIG-2a promoter [84]. The accumulation of INSIG-2a hinders SREBP activation, and thus adipogenesis is inhibited. Additionally, the cAMP-dependent protein kinase (PKA) pathway connects external signals of starvation, including glucagon and epinephrine, to adaptive mechanisms in response to an energy deficit. PKA modulates the sensitivity to glucagon by phosphorylating and impairing the DNA-binding function of nuclear SREBP-1, which affects the upstream LXR and downregulates expression of the SREBP1c gene involved in lipid metabolism, consequently hampering adipogenesis [85, 86].

Likewise, the hypothalamic-pituitary-adrenal (HPA) axis promotes glucocorticoid (GR) secretion during fasting. Glucocorticoids directly influence SETDB2 gene expression. Specifically, SETDB2 affects the motif chromatin loops of Lcn2 and INSIG-2 by means of dynamic

enhancer-promoter interactions, which results in a rise in INSIG2 protein levels and subsequently inhibits adipogenesis. This interaction occurs independent of the H3K9 methyltransferase function of SETDB2 and is further amplified as GR levels increase [87]. Unlike the GR-SETDB2 signaling pathway, HPA axis regulation of GR secretion also induces upregulation of Kruppel-like factor15 (KLF15). KLF15 downregulates SREBP-1 mRNA levels by interacting with RIP140-LXR at the SREBP-1 promoter site. Consequently, adipogenesis is inhibited during both early fasting stages and normoglycemic conditions before hypoglycemia and PKA activation. Overexpression of KLF15 notably improves hypertriglyceridemia while leaving LXR-mediated cholesterol metabolism unaffected *in vivo* [88, 89]. These studies suggest that signaling pathways regulated by the HPA axis are vital for regulating hepatic lipid metabolism in the context of fasting. **Figure 2** summarizes the regulation of SREBP by different signaling pathways during fasting.

4.5 Other regulatory factors

Mechanical signals from the extracellular matrix (ECM) influence lipid metabolism via lipin-1 and SREBP. A decrease in actomyosin contractility results in suppression of lipin-1, leading to the accumulation of SCAP/SREBP in the Golgi apparatus and ultimately promoting lipid synthesis and storage. This process occurs independent of YAP/TAZ, mTOR, and AMPK, while also being regulated through feedback by sterols [90]. Kondo et al. observed that an extracellular acidic pH activates SREBP-2, which acts as a transcriptional regulator that enhances cholesterol biosynthesis. This finding differs from cellular responses observed during hypoxia and nutrient deprivation [91]. It has been reported that the ethanol metabolite, acetaldehyde, may be responsible for inducing transcriptional activity of the SREBP regulatory promoter. Because this effect has only been reported in cell lines expressing alcohol dehydrogenase, the inhibitory effect of 4-methylpyrazole on ethanol oxidation blocks this process [71].

4.6 Feedback regulation of SREBPs in lipid metabolic homeostasis

SREBPs serve as master transcriptional regulators of lipid metabolism, the activity of which is tightly controlled by intricate feedback mechanisms to maintain metabolic equilibrium. These regulatory circuits ensure that lipid biosynthesis is dynamically adjusted according to cellular demands, while preventing excessive accumulation. Furthermore, crosstalk between SREBP signaling and nuclear receptors, such as LXRs, establish a sophisticated network that fine-tunes cholesterol and fatty acid metabolism.

4.6.1 Positive feedback: auto-amplification of SREBP activity. SREBPs enhance SREBP expression through a self-reinforcing transcriptional loop, constituting a canonical positive feedback mechanism. Both SREBF-1

and SREBF-2 possess SREs in the promoter regions, which enable active nuclear SREBPs (nSREBPs) to bind and upregulate nSREBP transcription [92]. This auto-amplification loop allows rapid escalation of SREBP levels under conditions of heightened lipid demand, such as insulin stimulation or sterol depletion. Consequently, downstream lipogenic genes, including FASN, ACC (fatty acid synthesis), HMGCR, and LDLR (cholesterol synthesis), are robustly activated, which drives lipid production [93].

4.6.2 Negative feedback: sterol-mediated suppression of SREBP processing. To prevent unchecked lipid accumulation, SREBP activity is counterbalanced by sterol-dependent inhibitory mechanisms, predominantly mediated by INSIG-1. Elevated cellular sterols (e.g., cholesterol) induce INSIG-1 expression via SREBP-1 [94]. INSIG-1 then binds to SCAP, sequestering the SCAP-SREBP complex in the ER and preventing Golgi translocation and proteolytic activation [95]. Moreover, oxysterols (e.g., 25-hydroxycholesterol) potentiate INSIG-SCAP interactions, further stabilizing ER retention and suppressing SREBP maturation [96]. This negative feedback loop ensures prompt attenuation of lipogenesis when sterol levels are sufficient.

4.6.3 Feedforward regulation by LXR: coordinated lipid homeostasis. Beyond intrinsic feedback loops, SREBP activity is modulated through feedforward regulation by LXRs, which sense cholesterol metabolites [e.g., 24(S),25-epoxycholesterol]. Upon activation, LXRs orchestrate a dual transcriptional program: (1) cholesterol efflux promotion involves direct upregulation of ABCA1 and ABCG1 enhances reverse cholesterol transport [97]; and (2) fatty acid synthesis stimulation involves LXR-induced SREBF1c transcription augments fatty acid biosynthesis [98].

This feedforward design enables cells to simultaneously eliminate excess cholesterol and generate fatty acids for esterification into inert lipid droplets, thereby mitigating lipotoxicity [99]. However, chronic activation of the LXR-SREBP-1c axis, as seen in obesity or insulin resistance, may exacerbate hepatic lipid deposition, contributing to pathologies like non-alcoholic fatty liver disease (NAFLD) [100].

5. ROLE OF SREBPS IN DISEASES

5.1 Metabolic diseases

Metabolic syndrome is defined as factors that increase the risk of developing cardiovascular disease and type 2 diabetes, mainly hypertension, atherosclerotic dyslipidemia, abdominal obesity, and hyperglycemia [101]. These symptoms reflect selective hepatic insulin resistance (IR); the liver resists gluconeogenesis by insulin signaling but is still sensitive to insulin stimulation of SREBP-1c to promote adipogenic effects. Thus, when insulin levels are elevated, the hormone over-activates SREBP-1c, which causes excessive hepatic lipogenesis, accumulation, and lesions [102]. In 2004 researchers

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reported that SREBPs directly repress IRS-2 transcription and inhibit hepatic insulin signaling. The IRS-2 promoter is activated by forkhead proteins via the IRE. Nuclear SREBPs effectively displace and interfere with the binding of these transcription factors, thereby inhibiting the downstream PI3K/Akt pathway and subsequently leading to reduced glycogen synthesis. These data suggest the existence of a molecular mechanism for the physiologic transition from glycogen synthesis to lipogenesis and for hepatic insulin resistance associated with hepatic steatosis [103]. SREBP-1c has a crucial role in coordinating the regulation of lipid and carbohydrate metabolism mediated by insulin. Moreover, insulin physiologically suppresses the gluconeogenesis process via the phosphorylation of forkhead box O1 (FOXO1) induced by Akt [104]. However, under insulin resistance, signaling by insulin receptor substrate 2 and Akt is not sufficient to phosphorylate FOXO1. Unphosphorylated FOXO1 enters the nucleus, at which point transcription of gluconeogenic genes is still facilitated under high insulin conditions. Similarly, when IR is present, forkhead box A2 (FOXA2) induces the expression of microsomal triglyceride transporter protein (MTTP) by binding to PPAR γ co-activator beta (PGC-1 β), which in turn increases apoB-containing VLDL secretion [44]. Simultaneously, the removal of triglyceride-rich lipoproteins becomes ineffective, resulting in elevated triglyceride levels. Additionally, as hepatic lipase modifies LDL and HDL particles, smaller and denser forms of LDL and HDL are created, which contributes to dyslipidemia associated with atherosclerosis [105]. To regulate cholesterol homeostasis and ER stress responses, cAMP-responsive element-binding protein 3 like 3 (CREB3L3), which is exclusively expressed in liver and intestinal cells, can competitively inhibit SREBPs expression by physically sharing the cleavage mechanism necessary for nuclear transactivation and promoting the formation of the SREBP-INSIG1-SCAP complex to suppress the transport of SREBPs. Therefore, CREB3L3 becomes an important target for anti-atherosclerosis [106].

5.2 Non-alcoholic fatty liver disease (NAFLD)

NAFLD encompasses various liver disorders, starting with liver steatosis, which is marked by an overabundance of lipids in the liver and progressing to non-alcoholic steatohepatitis (NASH), which is noted for liver inflammation and fibrosis [107]. In the end, NASH may advance to permanent liver injury, which can include conditions like cirrhosis and hepatocellular carcinoma (HCC) [108]. Initiation of NAFLD is thought to involve DNL accompanied by abnormal accumulation of FFAs. According to the findings of Donnelly et al., 59% of hepatic triglycerides (TG) in individuals with NAFLD originate from NEFA, 26.1% result from DNL, and 14.9% come from dietary sources. Additionally, the liver demonstrates a capacity to inter-utilize fat and fatty acids obtained from the diet [109]. Among other things, under insulin-resistant conditions, SREBP1c promotes DNL in the liver when

stimulated by insulin. This finding indicates that the PIDDosome and SCAP pathways regulate nutritionally induced ER stress in the liver in opposing ways, which as a crucial role in managing the non-linear progression from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) [27]. In addition, high lipid conditions induce upregulation of microRNA-21 expression, which in turn deregulates the inhibition of Srebp1c by HBP1 and p53 and promotes the development of DNL and cancer, which explains the existence of a potential link between NAFLD and HCC [110]. To date, the relationship between the pathogenic pathways of NAFLD and multiple metabolic pathways, genetics, and microbiome, and other relevant factors is not fully understood. There is only one FDA-approved drug therapy for NASH [111]. Adjustments in lifestyle, such as engaging in weight reduction, physical activity, and altering dietary habits, continue to be the primary approach to managing NAFLD [112]. Therefore, understanding the molecular mechanisms underlying aberrant lipid accumulation, fibrosis, and fatal HCC transformation may provide the potential to develop targeted therapeutic strategies for specific patient populations.

5.3 Type 2 diabetes (T2D)

The pathophysiology associated with T2D involves insulin resistance and an initial increase in insulin levels, which is subsequently accompanied by a progressive reduction in the pancreatic β -cell capacity to synthesize insulin. A combination of β -cell dysfunction and insulin resistance contributes to the intricate nature of T2D [113]. After the seminar experts confirmed that the pathophysiology of T2D is formed by defects in 11 signaling pathways connected with β -cell dysfunction, including abnormalities in hepatic nutrient metabolism and lipolysis [114]. Accordingly, a decrease in SREBP activity, which regulates lipid synthesis, alleviates the T2D process. For instance, hydroxysteroid 17- β dehydrogenase 6 (HSD17B6) has been identified as a molecule that can prevent SREBP maturation by interacting with the SREBP/SCAP/INSIG complex. As a result of this mechanism, the enhancement in glucose tolerance and a deceleration in the progression of obesity-related T2D was shown in a murine model. These discoveries position HSD17B6 as a promising candidate for therapeutic intervention in the treatment of T2D [115]. Additionally, activation of diacylglycerol (DAG) induces various protein kinase C (PKC) isoforms in the liver, which facilitates insulin resistance and plays a role in the progression of T2D. Mayer et al. identified PKD3 expressed in hepatocytes as an effector of DAG and PKC. The findings indicated that PKD3 suppresses the activity of downstream insulin effectors, such as the AKT and mTOR signaling pathways. In contrast, in the absence of PKD3, enhanced insulin signaling promotes SREBP-mediated adipogenesis. This finding implies that identifying crucial molecules that regulate PKD3 activity may help decrease hepatic lipid levels or enhance hepatic insulin sensitivity [116].

5.4 Osteoporosis

Osteoporosis develops due to impaired bone formation and/or excessive bone resorption. It has been shown that increased expression of SREBP-2 early in osteoclast formation and interference with cholesterol synthesis induces the expression of NFATc1 and matrix metalloproteinases, therefore inducing breast cancer-induced osteolysis [117]. This finding suggests that SREBP is potentially a new target for osteoporosis treatment. SREBP-2 inhibitor screening from natural product libraries revealed that anhydrocaritin inhibits osteoclast formation and ameliorates bone loss in an STZ-induced diabetic mouse model by decreasing the levels of SREBP2 and target genes in RANKL-induced osteoclasts [118]. Similarly, carnosic acid (CA) reduces nuclear localization of mature SREBP-2 to inhibit cholesterol synthesis. Additionally, CA directly interacts with $ERR\alpha$, promoting ubiquitination and subsequent degradation via the proteasome, which inhibits formation of osteoclasts induced by RANKL and helps mitigate bone loss associated with ovariectomy (OVX) [119].

5.5 Cancers

Rapid tumor growth requires reorganization of fat metabolism and it was found that SREBPs are markedly upregulated in various cancers [120].

5.5.1 Breast cancer. Breast cancer is a condition characterized by the uncontrolled growth of epithelial cells in the breast due to various carcinogenic influences. Although the precise cause of breast cancer remains unidentified, researchers have recognized numerous risk factors that are linked to breast cancer development. *In vitro* experiments indicated that SREBP-1 inhibition reduces the migration and invasion capabilities of breast cancer cells, including MDAMB-231 and MCF-7 [121]. There is a positive correlation between the p54(nrb) and SREBP-1a levels with the conserved Y267 residue being essential for the interaction with nuclear SREBP-1a. This finding implies that p54(NRB) has a crucial role in regulating the nuclear form of SREBP-1a [122]. Additionally, CtBP associates with ZEB1 to transcriptionally suppress SREBP-2 expression while activating TGF- β signaling, thereby maintaining intracellular cholesterol homeostasis in breast cancer [123].

5.5.2 Colorectal cancer. Colorectal cancer (CRC), a prevalent malignant tumor affecting the gastrointestinal tract in the colon, is primarily linked to a diet that is low in fiber and high in fats. The level of SREBP-1 expression in CRC tissues was shown to be markedly elevated compared to non-cancerous and normal tissues. This increase in SREBP-1 expression contributes to resistance against 5-FU by modulating the cleavage of PARP1 that is dependent on caspase-7 in CRC [124]. The excessive expression of SREBP-1 facilitates the angiogenesis and invasion of CRC cells by enhancing MMP-7 expression associated with phosphorylation of NF- κ B p65, which

could be linked to changes in cellular metabolism, such as mitochondrial respiration, glycolysis, and fatty acid oxidation [125]. In addition, a long non-coding RNA, ZFAS1, associates with polyadenylate-binding protein 2, which helps stabilize and elevate the levels of SREBP-1, along with downstream targets (FASN and SCD1), thereby facilitating lipid accumulation in CRC [126].

5.5.3 HCC. HCC is a type of primary liver cancer characterized by a significant mortality rate. This condition is linked to factors, such as genetic susceptibility, epigenetic changes, chronic infections with hepatitis B and C viruses, smoking habits, obesity, and the presence of diabetes mellitus. The level of SREBP-1 expression in HCC tissues have been shown to be significantly elevated compared to adjacent non-cancerous tissues [127]. Various pathways are capable of modulating SREBP-1 to influence lipogenesis in HCC, including apoptosis-antagonizing transcription factors (AATFs) [128] and acyl-CoA synthetases [129]. It has been reported that Zinc fingers and homeoboxes 2 (ZHX2) enhance the transcription of miRNA-24-3p, leading to the degradation of SREBP-1c, which suppresses advancement of HCC [130]. The neddylation process mediated by UBC12 extends the stability of SREBP-1 by reducing ubiquitination, thereby promoting HCC aggressiveness. This effect can be inhibited by the NEDD8-activating enzyme E1 inhibitor, MLN4924 [131]. Research indicates that in the mevalonate pathway, p53 blocks the activation of SREBP-2 by inducing the expression of ATP-binding cassette transporter A1 (ABCA1), thus inhibiting liver cancer [132].

5.5.4 Prostate cancer. Prostate cancer (PCa) is a type of epithelial cancer that arises from the prostate gland. Staining of clinical samples reveals elevated levels of SREBP-1 when compared to non-cancerous prostate tissue [133]. SREBP-1c has been demonstrated to specifically suppress the trans-activation of AR by interacting with the natural AR target promoter, potentially linked to the recruitment of histone deacetylase 1 [134]. Moreover, the regulatory region of SREBP-1 is engaged by AR and mTOR, which promotes the cleavage of SREBP-1 and subsequent translocation into the nucleus, potentially influenced by changes in metabolic signaling networks [135]. The transcription of miRNA-21 exerts control over the insulin receptor substrate 1/SREBP-1 signaling pathway, thereby enhancing the proliferation of PCa cells and contributing to tumorigenesis [136]. Additionally, miRNA-185 and miRNA-342 are capable of obstructing SREBP-1/2 activity along with target genes (FASN and HMGCR), effectively diminishing the tumorigenic potential of PCa [137, 138]. In conclusion, targeting the SREBP-regulated lipogenesis pathway presents a promising approach for therapeutic interventions in PCa.

5.5.5 Other cancers. Apatinib modulates GPX4 expression via a pathway regulated by SREBP-1a, establishing a crucial binding site (located at -1655 to -1645 bp

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relative to the transcription start site) that inhibits GPX4 transcription and contributes to anti-gastric cancer effects [139]. Glioblastoma (GBM), classified as a malignant glioma, encompasses tumors of neuroepithelial origin collectively labeled as gliomas. Xenograft studies have demonstrated that inhibiting SCAP N-glycosylation mitigates the growth of EGFRvIII-driven glioblastomas. Consequently, SCAP serves as a crucial glucose-responsive protein that connects oncogenic signaling with SREBP-dependent lipogenesis via fuel availability. The EGFR-activating mutation (EGFRvIII) leads to the cleavage and nuclear translocation of SREBP-1, which consequently regulates lipid metabolism within GBM [8, 140].

6. PHARMACOLOGIC REGULATION OF SREBPS

6.1 Synthetic inhibitors

6.1.1 Fatostatin and derivatives. Fatostatin (compound 1; Table 1), a diarylthiazole analogue, has been reported to be the first synthetic SREBP inhibitor [141]. Shao et al. demonstrated that fatostatin uniquely binds to SCAP at a location distinct from the sterol-binding domain, which subsequently prevents activation of SREBP by obstructing transport from the ER to the Golgi apparatus. Additionally, this inhibitory effect is independent of the INSIG protein [182]. In cultured cells and mouse liver, fatostatin primarily inhibits SREBP-1 activation, while the influence on SREBP-2 requires additional investigation. However, some studies have shown that fatostatin inhibits microtubule protein polymerization to disrupt mitotic spindle assembly and activates spindle assembly checkpoints to inhibit cellular mitosis [183] and that action is limited by low water solubility. Therefore, researchers have developed many fatostatin derivatives, such as the methanesulfonamide derivative of fatostatin (FGH10019 [compound 2]; Table 1) [142] with higher inhibitory activity. Fatostatin derivatives containing trifluoromethanesulfonamide (compounds 3 and 4; Table 1) have good oral bioavailability and amide substituted compounds (compound 5; Table 1) can reduce SREBP2 activity in HepG2 cells [143]. These compounds can lead to the death of cancer cells by reducing cholesterol and fatty acid synthesis and lowering the rate of cell division.

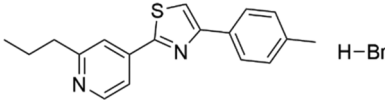
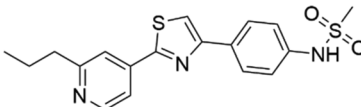
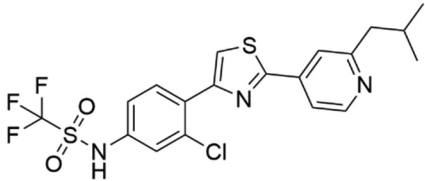
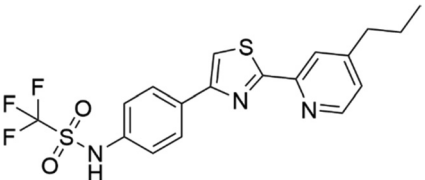
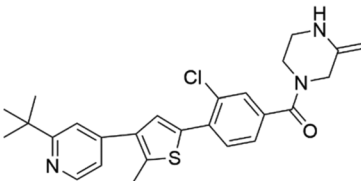
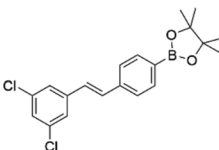
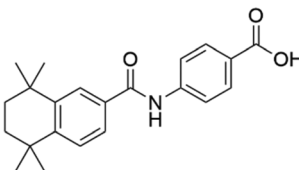
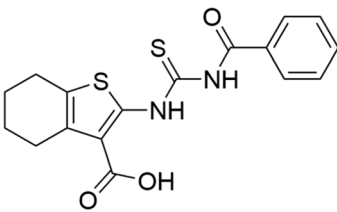
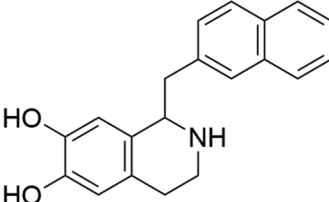
6.1.2 Other synthetic SREBP inhibitors. Unlike fatostatin and fatostatin derivatives, a study from Wang et al. showed that BF175 (compound 6; Table 1), pinacol borate substituted stilbene analogues and inhibited the aberrant expression of SREBP1, thereby preventing the proliferation of human endometrial cancer (EC) cells [184]. Specifically, BF175 inhibits the interaction between MED15-KIX of the multi-subunit co-factor complex and the SREBP1a-trans-activating structural domain, thereby inhibiting SREBP1 activity. Although the modified derivative of BF175 exhibits higher activity and stability than BF175, the underlying mechanisms warrant further investigation [144]. Avalon Flavivirus Therapeutics (HK) Ltd.

showed that the retinoic acid derivative, AM580 (compound 7; Table 1), reduced the mRNA levels of genes associated with fatty acid metabolism [145]. Mechanistically, the benzene ring present in AM580 engages with the Tyr335 residue of SREBP, thereby obstructing the SRE recognition site. This interaction inhibits the DNA-binding function of SREBP, ultimately leading to a reduction in lipid synthesis [185]. Furthermore, ZJ001 (compound 8; Table 1), which is a thiourea-based compound containing thiophene, not only decreased the transcription level of SREBP-1c within the liver but also lowered the mRNA quantities of SREBP-2 and HMGCR, while not impacting the level of SREBP-1a [146]. YS-51S (compound 9; Table 1), an isoquinoline alkaloid, contributes to suppress the transcription activation of liposome synthesis-related elements, including CD36 and SREBP-1c in fatty liver [147]. Research has revealed a group of 1,2-dithiazide derivatives that effectively prevent and address conditions linked to heightened LXR α or SREBP-1 activity. Notably, pretreatment with Oltipraz (compound 10; Table 1) blocked the increase in SREBP-1c gene expression that was triggered by the LXR agonists, T0901317, 22-hydroxycholesterol, and GW3965 [55]. In addition, other researchers have found UT-59 (compound 11; Table 1), which features a diaryl urea core scaffold with an ethyl ester modification at one end (right side) and a cyclobutyl-substituted oxadiazole ring at the opposite end (left side). Structurally, UT-59 does not resemble cholesterol, but UT-59 can still compete with cholesterol for cholesterol binding site on SCAP. This competition induces a conformational change in the SCAP protein, thereby promoting SCAP binding to INSIG, which helps retain the SCAP-SREBP complex in the ER and inhibits SREBP activation along with the lipid synthesis response [148]. Finally, we have also assembled studies of several site 1/2 protease inhibitors that block SREBP1 processing. PF-429242 (compound 12; Table 1) is a potent and competitive S1P inhibitor that inhibits renal cell carcinoma cell growth *in vitro* and *in vivo* [149]. 3,4-dichloroisocoumarin (compound 13; Table 1) is a potent serine-protease inhibitor and has been used in studies as an inhibitor of S1P. In addition, 1,10-phenanthroline (compound 14; Table 1) and nelfinavir (compound 15; Table 1) were also shown to inhibit S2P activity [150]. In summary, synthetic small molecule compounds mainly limit the activity of SREBP by inhibiting transcription and competing for endogenous repressor binding sites, thereby alleviating diseases caused by adipose overproduction. These synthetic compounds are characterized by high purity, a controllable structure, and target-specificity, which can accelerate the research process for them to become drug candidates and are important lead compounds for targeting SREBP inhibition.

6.2 Candidates from natural products

6.2.1 Flavonoids. Flavonoids have antioxidant, anti-inflammatory, and immunomodulatory properties [186]. Xiao et al. reported that an FKBP38 agonist,

Table 1 | Structures of compounds targeting SREBP inhibition.

Origins	Category	Number	Name	Chemical Structure	Reference
Synthetic inhibitors	Fatostatin and derivatives	1	Fatostatin		[141]
		2	FGH10019		[142]
		3	N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide		[143]
		4	1, 1,1-trifluoro-N-(4-(2-(4-propylpyridin-2-yl)thiazol-4-yl)phenyl)methanesulfonamide		
		5	(4-(4-(2-(tert-butyl)pyridin-4-yl)-5-methylthiophen-2-yl)-3-chlorophenyl) (3-methylenepiperazin-1-yl) methanone		
Other synthetic SREBP inhibitors		6	BF175		[144]
		7	AM580		[145]
		8	ZJ001		[146]
		9	YS-51S		[147]

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Table 1 | Continued

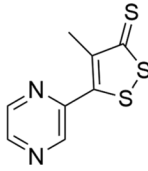
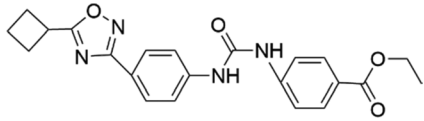
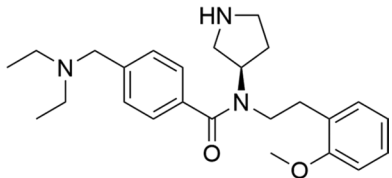
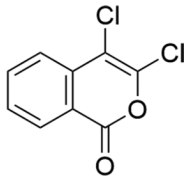
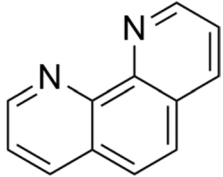
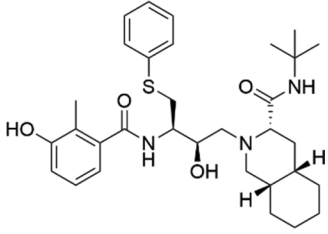
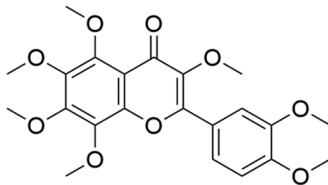
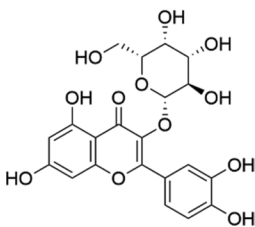
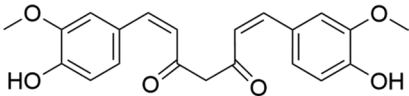
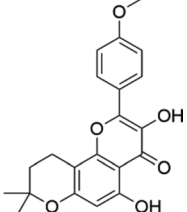
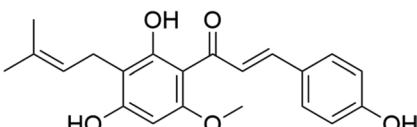
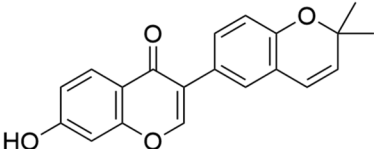
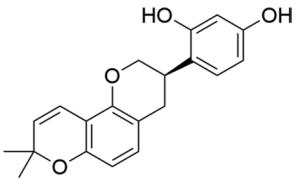
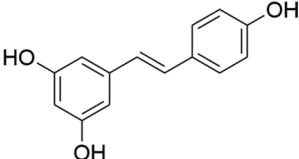
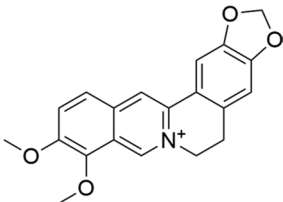
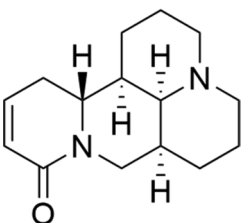
Origins	Category	Number	Name	Chemical Structure	Reference
		10	Oltipraz		[55]
		11	UT-59		[148]
		12	PF429242		[149]
		13	3,4-Dichloroisocoumarin		[150]
		14	1,10-Phenanthroline		
		15	Nelfinavir		
Candidates from natural products	Flavonoids	16	3,5,6,7,8,3',4'-Heptamethoxyflavone (HMF)		[151]
		17	Hyperoside		[152]

Table 1 | Continued

Origins	Category	Number	Name	Chemical Structure	Reference
		18	Curcumin		[153]
		19	Anhydroicaritin (AHI)		[118]
		20	Xanthohumol (XN)		[154]
		21	Corylin		[155]
		22	Photoglycyrrhizidine		[156]
		23	Resveratrol (3,5,4'-trihydroxystilbene)		[157]
	Alkaloids	24	Berberine (BBR)		[158]
		25	Sophocarpine		[159]

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Table 1 | Continued

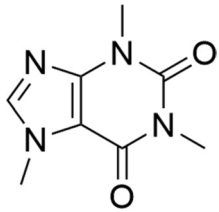
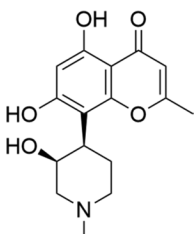
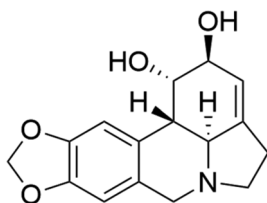
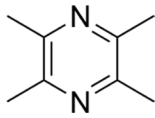
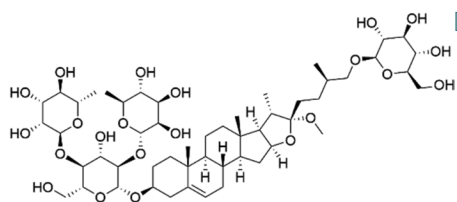
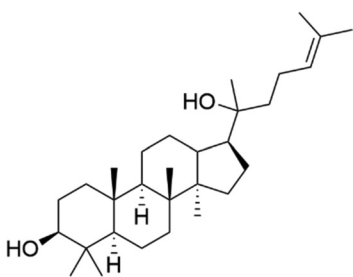
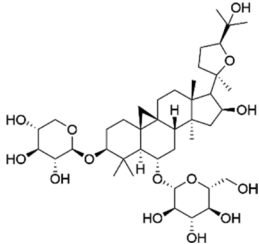
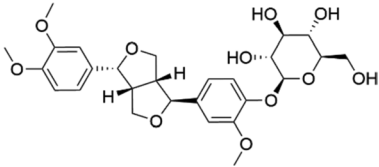
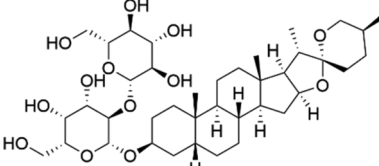
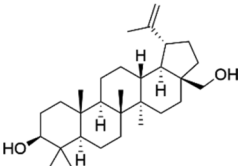
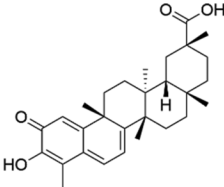
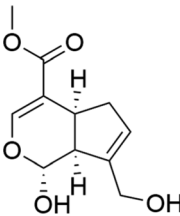
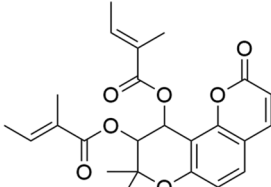
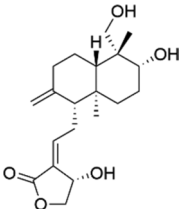
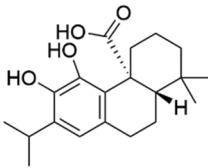
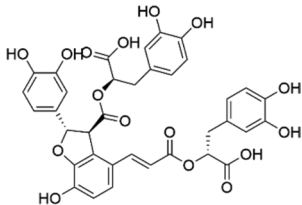
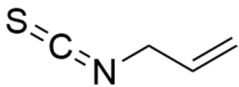
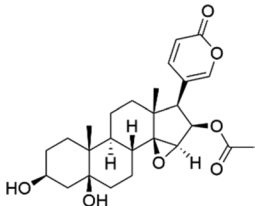
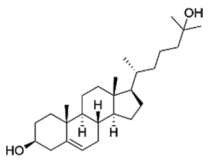
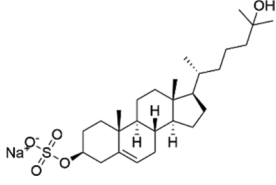
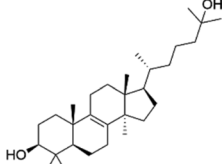
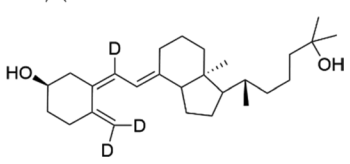
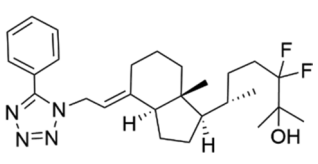
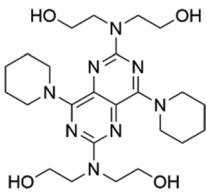
Origins	Category	Number	Name	Chemical Structure	Reference
		26	Caffeine		[160]
		27	Rohitukine		[161]
		28	Lycorine		[162]
		29	Tetramethylpyrazine (TMP)		[163]
		30	Methylprotodioscin (MPD)		[164]
	Saponin	31	Ginsenoside Re		[165]
		32	Astragaloside IV		[166]

Table 1 | Continued

Origins	Category	Number	Name	Chemical Structure	Reference
		33	Phillyrin		[167]
		34	Timosaponin AIII (TA3)		[168]
	Terpenoids	35	Betulin		[169]
		36	Celastrol		[170]
		37	Genipin		[171]
		38	Praeruptorin B		[172]
		39	Andrographolide		[173]
		40	Carnosic acid (CA)		[119]

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Table 1 | Continued

Origins	Category	Number	Name	Chemical Structure	Reference
	Other natural products	41	Salvianolic acid (SA)		[174]
		42	Allyl isothiocyanate (AITC)		[175]
		43	Cinobufotalin (CBF)		[176]
Sterols and derivatives		44	25-hydroxycholesterol (25HC)		[177]
		45	3-sulfate-25-hydroxycholesterol (25HC3S)		
		46	25-hydroxy lanosterol (25-HL)		[178]
		47	25-hydroxyvitamin D3 [25(OH)D3]		[179]
		48	KK052		[180]
		49	Dipyridamole		[181]

3,5,6,7,8,3',4'-heptamethoxyflavone [HMF] (compound 16; [Table 1](#)), reduced lipid levels and effectively ameliorated hyperlipidemia and insulin resistance in high-fat diet (HFD)-fed mice through inhibition of the mTOR/P70S6K/SREBPs pathway. HMF is a polymethoxyflavone isolated from citrus peels and possesses a wide range of biological activities, including anti-tumor, anti-inflammatory, and neuroprotective properties. HMF was suitable for the protein pocket of FKBP38 and established a hydrogen bond with FKBP38 at Gln97, which kept the structure stable. Then, FKBP38 binds to mTOR, and inhibits mTOR activity and the extent of dephosphorylation of p-mTOR, p-P70S6K, and p-SREBP1, which has no apparent effect on the phosphorylation of Akt, AMPK, and GSK-3 β . Moreover, downregulation of SREBP and SREBP target genes was observed. Overall, HMF has significant effects in improving obesity, insulin resistance, hepatic fat accumulation, and hyperlipidemia without significant side effects, suggesting that HMF is a promising and safe drug target for reducing lipid levels [151]. Hyperoside, which is also referred to as quercetin-3-O-galactoside (compound 17; [Table 1](#)), is a flavonol glycoside found in numerous herbal medicines, such as *Crataegus pinnatifida* Bge., *Artemisia capillaris* Thunb., and *Andrographis paniculata* (Burm.f.) Nees, and has anti-inflammatory, hepato-protective, and antioxidant protective effects. In rats fed a HFD, administration of hypericin inhibited ACC and SREBP1, and significantly reduced hepatic lipogenesis. Moreover, hypericin increases FXR activity in the liver, which promotes β -oxidation of FFAs to reduce DNL and is expected to be used for the treatment of NAFLD in rats [152]. Curcumin (compound 18; [Table 1](#)), the main active ingredient in *Curcuma Longa* L., has a long history of use as an Ayurvedic remedy and is widely recognized as a favored spice in Asian cooking. Curcumin is also a lead compound that may serve as a preventive measure against obesity and insulin resistance. Curcumin inhibits SRE promoter activity in a dose-dependent manner and significantly decreases mRNA expression of SREBP target genes linked to the synthesis of fatty acids and triglycerides, ultimately leading to a reduction in cholesterol and fatty acid biosynthesis [153]. Anhydroicaritin [AHI] (compound 19; [Table 1](#)) is an isopentenyl flavonoid extracted from *Epimedium brevicornu* Maxim. with strong pharmacologic activities, such as anti-tumor, bone protection, anti-virus, anti-inflammatory, and blood lipid regulation. In a study of osteoporosis caused by diabetes mellitus, AHI was shown to prevent the interaction between the SCAP/SREBPs complex and Sec23/Sec24 through modulation of the LKB1/AMPK/mTOR pathway. This action subsequently inhibits the processing of SREBPs, obstructs SREBP maturation, and decreases the expression of genes associated with cholesterol and fatty acid biosynthesis. Consequently, the lipid-lowering properties of AHI may be leveraged to prevent and manage metabolic disorders [118]. Xanthohumol [XN] (compound 20; [Table 1](#)), the most abundant isopentenyl

flavonoid in *Humulus lupulus* Linn., has been investigated for use in cancer therapy due to the antioxidant and anti-inflammatory properties. XN inhibits insulin-induced SREBP maturation in a manner distinct from sterols. Specifically, XN binding to Sec23/24 impedes SCAP/SREBP engaging in COPII vesicles and disrupts SREBP processing. Administration of XN inhibits the expression of SREBP-1 target genes in the liver *in vivo*, while hepatic SREBP-1 maturation is reduced, therefore ameliorating obesity and fatty liver in HFD mice [154]. In the livers of NAFLD patients and obese mice, HSP90 β is highly expressed and depletion of HSP90 β significantly reduces neutral lipid and cholesterol levels. Zheng et al. screened a flavonoid compound from a natural product library that selectively inhibits HSP90 β protein levels. Corylin (compound 21; [Table 1](#)), a natural flavonoid from the fruits of *Psoralea corylifolia* L., has been shown to have anti-inflammatory, anti-cancer, and anti-atherosclerotic effects. Corylin was shown to partially inhibit Akt activity at the Thr308 site and specifically promote ubiquitination and proteasomal degradation of mature SREBP via the Akt-GSK3 β -FBW7 pathway. In addition, corylin treatment also significantly improves obesity-induced fatty liver, T2D, and atherosclerosis in animal studies. This finding suggests that inhibition of HSP90 β may be a potential target for the treatment of lipid disorders and corylin may be an important compound for the treatment of lipid metabolism homeostasis-related diseases [155]. Photoglycyrrhizidine (compound 22; [Table 1](#)), the main component of isoflavanes in *Glycyrrhiza glabra* L. extracts, AMPK activation, leading to an increase in fatty acid oxidation, suppression of adipogenic gene expression in adipose tissue and the liver, and a reduction in obesity and hyperlipidemia among individuals with obesity [156]. Resveratrol [3,5,4'-trihydroxystilbene] (compound 23; [Table 1](#)), also an AMPK activator, has been reported to induce phosphorylation of acetyl-coA carboxylase at Ser79 and decrease expression of fatty acid synthase. Therefore, resveratrol has the ability to prevent the negative effects of excessive calorie intake and regulate the health and longevity of living organisms [157].

6.2.2 Alkaloids. Berberine [BBR] (compound 24; [Table 1](#)) is an isoquinoline alkaloid with a range of pharmacologic effects in modern and traditional medicine and has been used over-the-counter as a treatment for hepatitis, stomatitis, diarrhea, and dysentery. In studies on the prevention and treatment of NAFLD, BBR has been shown to reduce hepatic TG synthesis through activation of the AMPK-SREBP1c-SCD1 pathway [158] and ameliorate NAFLD by accelerating fatty acid β -oxidation, regulating intestinal flora, decreasing insulin resistance, and mitigating inflammatory responses [187]. In addition, BBR inhibits the growth of colon cancer xenograft tumors by downregulating adipogenesis-related genes and suppressing the growth and lipogenesis of colon cancer xenografts [188]. Sophocarpine [159] and caffeine [160]

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also activate the AMPK signaling pathway and significantly downregulate the mRNA expression of SREBP-1c. Sophocarpine (compound 25; [Table 1](#)), one of the major alkaloids extracted from *Sophora flavescens* Ait. Sophocarpine has a variety of pharmacologic effects, including antiviral, anti-tumor, and anti-inflammatory effects, as well as attenuating hepatocellular steatosis through activation of the AMPK signaling pathway. Caffeine (compound 26; [Table 1](#)), a central nervous system stimulant found in a variety of plants, decreases hepatic lipid accumulation influencing the AMPK-SREBP signaling pathway, which leads to a reduction in the level of SREBP mRNA expression and the associated target genes, while also enhancing the expression of CD36, a gene involved in lipid uptake and metabolism. Moreover, rohitukine (compound 27; [Table 1](#)), isolated from *Dysoxylum binaciferum* Hook., has significant anticancer effects. Rohitukine downregulates the mRNA expression of PPAR- γ and SREBP-1c to reduce hepatic lipogenesis. Rohitukine elevates LXR expression while reducing the levels of SREBP-2 and the associated targets, contributing to enhancement of dyslipidemia [161].

Second, some alkaloids have been reported to hinder SREBP processing. Lycorine (compound 28; [Table 1](#)) is a natural product extracted from Lycorisaceae herbs that possesses a wide range of pharmacologic functions, such as anti-tumor, anti-angiogenic, anti-viral, anti-bacterial, and anti-inflammatory functions. Lycorine has been shown to be a potent inhibitor of SCAP, inhibiting SREBP processing by promoting lysosomal translocation of SCAP without inducing ER stress or activation of LXR. Lycorine functions by facilitating the breakdown of SCAP via the lysosomal degradation (SMALD) pathway, which is independent of autophagy and mediated by SQSTM1. In animal studies, lycorine improves conditions, such as hyperlipidemia, hepatic steatosis, and insulin resistance resulting from a HFD in murine models [162]. Tetramethylpyrazine [TMP] (compound 29; [Table 1](#)), which is extracted from *Ligusticum chuanxiong* Hort., has been shown to have anti-atherosclerotic effects and is associated with amelioration of dyslipidemia. TMP downregulates the expression of PAQR3, disrupts the Golgi localization of the SCAP/SREBP complex, and inhibits of SREBP activation and cholesterol biosynthesis. PAQR3, SCAP, and SREBP-1c protein levels were shown to be decreased and lipid metabolism disorders and atherosclerosis in TMP-treated mice in an atherosclerosis model improved [163].

6.2.3 Saponin. Saponins has demonstrated hypolipidemic, anti-inflammatory, and anti-atherosclerotic effects in modern research and clinical applications, and has shown positive effects on lipid metabolism disorders. Methyl protodioscin [MPD] compound 30; [Table 1](#)), which is isolated from *Dioscorea nipponica* Makino, inhibits SREBP transcription by decreasing the level of microRNA 33a/b, thereby suppressing cholesterol and TG synthesis [164]. Ginsenoside Re (compound 31; [Table 1](#)),

a protopanaxatriol-type saponin isolated from *Panax ginseng* C. A. Mey., possesses anti-diabetic and hypolipidemic properties. Studies have shown that stimulation of AMPK leads to inhibition of SREBP-1c expression and the target genes, resulting in a decrease in TG levels and a reduction in fat accumulation in human HepG2 cell and the livers of mice on a HFD [165]. Similarly, astragaloside IV (compound 32; [Table 1](#)), extracted from *Astragalus membranaceus* (Fisch.) Bge., reduces lipid accumulation and insulin resistance in HepG2 cells through modulation of AMPK-dependent phosphorylation at the Ser372 residue of SREBP-1c [166]. In addition, phillyrin (compound 33; [Table 1](#)), extracted from *Forsythia suspensa* (Thunb.) Vahl, is frequently utilized as a crucial component in the food, beverage, and cosmetics sectors. Phillyrin has been reported to inhibit SREBP-1c and the downstream lipid synthesis genes by phosphorylating the Thr172 residue of AMPK α via liver kinase B1 (LKB1), thereby reducing lipid accumulation in HepG2 cells. This finding suggests that phillyrin may play an important role as an AMPK activator in the prevention and treatment of obesity [167].

Unlike the above inhibition of SREBP at the transcriptional level, Lin et al. showed that timosaponin AIII [TA3] (compound 34; [Table 1](#)), isolated from *Anemarrhena asphodeloides* Bunge., inhibits SREBP maturation by blocking SREBP processing through activation of hepatic A1R. TA3 has various pharmacologic activities, such as anti-cancer, anti-neuronal disorders, anti-inflammation, and anticoagulation, but TA3 also has a degree of hepatotoxicity [168]. Physiologically, hepatic A1R expression is weak. However, TA3 activates hepatic A1R. Activated A1R enhances the breakdown of SCAP proteins within the lysosome and decreases retention in the Golgi apparatus via the creation of the SCAP-sequestosome1 (SQSTM1) complex. TA3 improves MAFL and MASH in an A1R-dependent manner *in vivo* [189].

6.2.4 Terpenoids. Betulin (compound 35; [Table 1](#)), isolated from *Betula platyphylla* Sukaczew, belongs to lupine-type pentacyclic triterpenoids and has been shown to be a SREBP inhibitor. betulin largely reverses SIRT1 inhibition by alcohol and inhibits SREBP-1 activity through activation of the SIRT1-LKB1-AMPK signaling pathway to attenuate alcoholic liver injury in human hepatic stellate cells (LX-2) [169]. Using small molecule probe technology, Tang et al. reported that betulin directly binds SCAP covalently and inhibits the cleavage and activation of SREBP-1, explaining the mechanism of action in reducing the size of atherosclerotic plaques [190]. Subsequently, in a study involving HCC patients with a poor response to sorafenib, Cao and co-workers. showed that tumor cells had high levels of SREBP-1 and this was associated with poorer survival. In contrast, administration of betulin inhibits SREBP-1 to limit cellular glycolytic activity, impedes the metastatic potential of HCC cells, and enhances the anti-tumor effect of sorafenib in HCC [191]. These results suggest that betulin is a small-molecule drug with great potential for

development. Celastrol (compound 36; [Table 1](#)), primarily from *Tripterygium wilfordii* Hook. f., is used for the treatment of cancer and some inflammatory diseases. Recent studies have shown that celastrol reduces lipid synthesis by inhibiting hepatic SREBP-1c expression via SIRT and also improves the antioxidant and anti-inflammatory status of NAFLD by inhibiting nuclear factor kappa B (NFkB) activity as well as pro-inflammatory cytokine mRNA levels [\[170\]](#). Genipin (compound 37; [Table 1](#)) is the product of hydrolysis of gardenia glycosides by β -glucosidase, belongs to cyclic enol ether terpenoids, and is also the active ingredient of *Gardenia jasminoides* J.Ellis. Genipin serves a role in pharmacologic action by mitigating hyperlipidemia and hepatic lipid build-up in mice subjected to a HFD. On a molecular scale, genipin obstructs the adipogenic influence of SREBP through upregulation of miR-142a-5p expression, which enhances the interaction with the 3'UTR segment of SREBP-1c [\[171\]](#). Moreover, praeruptorin B (compound 38; [Table 1](#)), one of the major coumarin components isolated from *Peucedanum praeruptorum* Dunn, has pharmacologic activities including vasodilator, anti-tumor, and anti-inflammatory activities. Praeruptorin B decreases expression of the SREBP protein through the regulation of the PI3K/Akt/mTOR signaling pathway and this action has been shown to be advantageous for enhancing conditions related to metabolic disorders, including obesity, hyperlipidemia, and insulin resistance [\[172\]](#). Andrographolide (compound 39; [Table 1](#)), derived from *Andrographis paniculata* (Burm.f.) Nees, functions as an inhibitor of SREBP to downregulate the expression of downstream target genes and reduce lipid accumulation *in vitro* and *in vivo* [\[173\]](#). A phenolic diterpenoid first discovered in *Salvia japonica* Thunb., carnosic acid (CA, compound 40; [Table 1](#)) has potent antioxidant and anti-ageing effects. Studies have reported that CA inhibits bone loss through dual targeting of SREBP-2 and estrogen receptor-related receptor alpha ($ERR\alpha$). Specifically, CA facilitates the breakdown of mature SREBP-2 in hepatocytes through the action of the 26S proteasome, which in turn reduces cholesterol synthesis. CA obstructs the association between $ERR\alpha$ and PGC1 β by directly attaching to the $ERR\alpha$ ligand-binding domain, resulting in a decrease in the transcriptional activity of $ERR\alpha$ and expression of the target genes. In conclusion, CA targets SREBP-2 and $ERR\alpha$, thereby preventing RANKL-induced formation of osteoclasts and mitigating bone loss caused by ovariectomy, suggesting the potential as a candidate for pharmacologic interventions in osteoporosis [\[119\]](#).

6.2.5 Other natural products. Salvianolic acid [SA] compound 41; [Table 1](#)) is the main component of the water-soluble extract of *Salvia miltiorrhiza* Bunge. SA has been reported to attenuate OVX-induced weight gain and reduce hepatic fat accumulation. Mechanistically, SA may improve hepatic lipid metabolism in OVX-rats by reducing phosphorylation of signal transducer and

activator of transcription (STAT)-3 and lowering SREBP1 expression [\[174\]](#). Allyl isothiocyanate [AITC] (compound 42; [Table 1](#)), contained in Brassicaceae herbs, has been reported to downregulate the expression of SREBPs and target genes in human Huh-7 cells by inhibiting SRE activity [\[175\]](#). Similarly, cinobufotalin [CBF] (compound 43; [Table 1](#)), extracted from the skin secretions of *Bufo bufo gargarizans* Cantor, selectively inhibits SREBP-1 expression and interacts with SREBP-1, preventing cinobufotalin from entering the SRE and thus inhibiting lipogenic enzyme expression [\[176\]](#).

These results suggest that natural compounds show strong potential in inhibiting SREBP to improve metabolic diseases with translational value for development into pharmaceutical and nutritional products. We should acknowledge the unique role of traditional Chinese medicine (TCM) in treating metabolic diseases, reducing side effects, and improving complications, and at the same time develop more natural products for the treatment of a wide range of metabolic diseases to meet clinical needs based on the extensive experience in the clinical use of TCM. In addition, natural products are mostly secondary metabolites, which have the barriers of high extraction costs and complex synthesis processes, which will need to be resolved in the future by continuous updating of technology. In summary, inhibitors of SREBP in natural products are being extensively investigated, but due to the diverse sources and structural complexity, the associated pharmacologic findings need to be carefully evaluated to identify and appropriately manage any adverse effects.

6.3 Sterols and derivatives

SREBP activation is regulated by intracellular cholesterol levels. When intracellular cholesterol levels are too high, steroidogenic acute regulatory protein (StAR) expression is upregulated and transports cholesterol to mitochondria [\[192\]](#). Cholesterol is converted into potent hydroxysteroids in mitochondria. For example, 25-hydroxycholesterol [25HC] (compound 44; [Table 1](#)) and 3-sulfate-25-hydroxycholesterol [25HC3S] (compound 45; [Table 1](#)). HC downregulates intracellular cholesterol levels by hindering the cleavage of SREBP-2 and promoting the degradation of HMGCR. LXR is also activated by oxysterols, such as 24,25-epoxycholesterol and 25-HC during this process, resulting in increased expression of nSREBP-1 [\[177\]](#), 24-HC, 25-HC, and 27-HC. Therefore, LXR cannot be used for clinical treatment. However, Jiang et al. reported that 25-hydroxy lanosterol [25-HL] (compound 46; [Table 1](#)), obtained from a sterol library using a SREBP responsive luciferase reporter, binds to INSIG protein and stimulates the interaction of INSIG with SCAP. Therefore, inhibiting the transport and activation of SREBP-1 ameliorates the NAFLD process. Importantly, with a stronger effect than lovastatin or obeticholic acid (OCA), 25-HL fails to activate LXR. Structural modeling investigations uncovered three significant clashes between 25-HL and the

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LXR ligand pocket, suggesting spatial incompatibilities between 25-HL and LXR [178]. Moreover, 25-hydroxyvitamin D3 [25(OH)D3] (compound 47; Table 1) is the main circulating form of vitamin D3 and it has been shown that 25(OH)D3 inhibits the transport and splicing of SREBP by directly binding to the C-terminus of SCAP [179]. In addition, KK052 (compound 48; Table 1), the first vitamin D-based inhibitor of SREBP, is directly linked to SCAP, which in turn induces ubiquitous degradation of SCAP and SREBP, but does not cause changes in calcium ion concentration *in vivo* [180].

6.4 Others

Dipyridamole (compound 49; Table 1), which is an FDA-approved anti-thrombotic phosphodiesterase (PDE) inhibitor, inhibits the movement of SREBPs from the ER to the Golgi apparatus, thereby hindering activation. In addition, a chemically altered version of dipyridamole does not influence PDE activity but shows effectiveness in inhibiting SREBP [181]. Similarly, 13 drugs that inhibit SREBP pathway activation from pancreatic cancer cells in lipid-deficient cultures were identified through a self-established high-throughput screening system for 4474 FDA-approved drugs [193]. Drug repurposing provides a more time-efficient and cost-effective way to identify new therapeutic interventions for many FDA-approved drugs that may have secondary targets, but did not elaborate further on the mechanism of action of these drugs.

In summary, the findings from these studies indicate that targeting SREBP and the associated signaling pathways may serve as a potential therapeutic approach for addressing metabolic disorders, such as hyperlipidemia, T2D, NAFLD, and atherosclerosis. In addition to the origin and structural differences, the main pathways of SREBP inhibitor action can be classified into downregulation of the transcriptional level of SREBP, hindering the process of SREBP cleavage activation and promoting SREBP degradation through post-translational modification of the protein. While SREBP primarily functions in lipid metabolism, it is important to consider the alterations in the related metabolic network and other critical roles during the study of the inhibitors to better predict the adverse effects that will occur in the clinical studies.

7. CONCLUSIONS

This review summarized the recent findings of SREBPs mainly in terms of physiologic activation processes, regulatory processes, related diseases, and publicly available small molecule inhibitors with therapeutic potential. It is known that sterols dominate in the regulation of SREBP activation but recent studies indicate that SREBP-2 activation primarily responds to intracellular sterol levels, while SREBP1 activation is mainly subjected to insulin signaling and may undergo a different hydrolytic cleavage process in response to ER stress. Upregulation of SREBP expression caused by PI3K/Akt/mTOR signaling

and ER stress is associated with numerous diseases, such as metabolic syndrome, NAFLD, T2D, osteoporosis, and several types of cancer. To this end, researchers have continuously searched for effective inhibitors of SREBP, but unfortunately no FDA-approved inhibitor has yet been developed due to the heterogeneity of the transcription factor structure and the lack of an active site, which are traditionally considered difficult to be drug-gable. Herein 48 representative small molecules from publicly available data were summarized, among which natural products show great potential with structural diversity and rich sources. It is important to note that while these compounds certainly have an inhibitory effect on SREBP activity, this does not always imply that the mechanistic action of the inhibitor targets SREBP or the SREBP-activated pathway unless it is demonstrated that there is a direct interaction between the inhibitor and target protein. This finding suggests that more specific results are needed in subsequent studies to demonstrate whether the effect of compounds on SREBP activity is a cause or effect. Additionally, transcription factor genes are often regulated by miRNAs. miR-7, activated by PPAR α , was shown to induce upregulation of SREBP-1 and -2 expression, acting as a bridge between sterol and fatty acid metabolic pathways in the liver [194]. The miRNAs, miR-33a and miR-33b, are found within the SREBP-2 and -1 gene introns, respectively. These two miRNAs are co-expressed alongside the SREBP factor and contribute to the elevation of lipid levels in cells by inhibiting ABCA1 [195]. SREBP-2 directly activates a poly-cistronic miRNA locus encoding two miRNAs. Specifically, miR-182 and -96 can downregulate the expression of Fbxw7 and INSIG-2, respectively, leading to changes in nuclear SREBP levels and the synthesis of endogenous lipids [196]. In conclusion, miRNAs have a significant role in various stages of lipid metabolism. It is important to recognize that SREBP serves as a crucial transcription factor in regulating lipid synthesis in the liver. Therefore, excessively strong and broad inhibition of the lipogenic pathway may prove to be counterproductive in the treatment of diseases. This effect may be due to the inhibition of lipid synthesis genes altering the permeability and fluidity of phospholipid membranes, resulting in ER stress and severe organ damage [197]. This finding suggests that modulation of appropriate SREBP activity has a crucial role in balancing disease treatment and maintenance of organism homeostasis.

We anticipate that this review will offer novel perspectives for future research on SREBP in regulating lipid synthesis in different diseases and as a therapeutic target for drug development.

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ABBREVIATIONS

25-hydroxy lanosterol (25-HL), 25-hydroxycholesterol (25HC), 25-hydroxyvitamin D3 (25(OH)D3), 3-sulfate-25-hydroxycholesterol (25HC3S), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB), 6-phosphogluconate dehydrogenase (PGDH), acetyl-CoA carboxylase (ACC), activating transcription factor 6 (ATF) acyl-CoA synthetase short-chain family member 2 (ACSS2), allyl isothiocyanate (AITC), anhydroicaritin (AHI), apoptosis-antagonizing transcription factors (AATF), astragalus polysaccharides (APs), ATP-binding cassette transporter A1 (ABCA1), basic-helix-loop-helix leucine zipper (bHLH-LZ), berberine (BBR), brahma-related gene 1 (BRG1), cAMP-responsive element-binding protein 3 like 3 (CREB3L3), cAMP-responsive element-binding protein H (CREBH), carnosic acid (CA), CCAAT/enhancer-binding protein β (C/EBP β), cell death-inducing DFF45-like effector B (Cideb), ceramide synthase 6 (CerS6), cinobufotalin (CBF), colorectal cancer (CRC), CREB/ATF bZIP transcription factor (CREBZF), CREB-regulated transcription coactivator 2 (CRTC2), *de novo* lipogenesis (DNL), diacylglycerol (DAG), docosahexaenoic acid (DHA), E4 promoter-binding protein 4 (E4BP4), eicosapentaenoic acid (EPA), endometrial cancer (EC), endoplasmic reticulum (ER), epidermal growth factor receptor (EGFR), estrogen receptor-related receptor alpha (ERR α), extracellular matrix (ECM), extracellular signal-regulated kinase (ERK), farnesyl diphosphate synthase (FDS), fatty acid synthase (FAS), fatty acid translocase (FAT/CD36), FGF21 (fibroblast growth factor 21), folliculin (FLCN), forkhead box A2 (FOXA2), forkhead box O1 (FOXO1), free fatty acids (FFAs), glioblastoma (GBM), glucocorticoid (GR), glucose-6-phosphate dehydrogenase (G6PD), hepatocellular carcinoma (HCC), hepatoma-derived growth factor (HDGF), heptamethoxyflavone (HMF), high-fat diet (HFD), HMG CoA reductase (HMGCR), hydroxysteroid 17- β dehydrogenase 6 (HSD17B6), hypothalamic-pituitary-adrenal (HPA), inositol-requiring enzyme 1 (IRE1), insulin resistance (IR), insulin-induced gene (INSIG), kruppel-like factor 6 (KLF6), kruppel-like factor15 (KLF15), liver kinase B1 (LKB1), liver X receptor (LXR), methyl protodioscin (MPD), microsomal triglyceride transporter protein (MTTP), mitotic protein monoclonal-2 (MPM-2), mouse embryonic fibroblasts (MEFs), mutant huntingtin (mHTT), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), NCoR1 (nuclear receptor co-activator protein 1), non-small cell lung cancer (NSCLC), nuclear factor- γ (NFY), ovariectomy (OVX), p53-induced protein with a death domain (PIDD), peroxisome proliferator-activated receptor alpha (PPAR α), phosphodiesterase (PDE), phosphoenolpyruvate carboxykinase 1 (PCK1), pituitary tumor-transforming gene-1 (PTTG1), PKR-like eukaryotic initiation factor 2 α -kinase (PERK), polyunsaturated fatty acids (PUFAs), PPAR γ co-activator beta (PGC-1 β), progesterin and adipoQ receptors 3 (PAQR3), prostate cancer (PCa), protein kinase A (PKA), protein kinase C (PKC), reactive oxygen species (ROS), retinoid X receptors (RXRs), RIP-associated ICH1/CED3-homologous protein with a death domain (RAIDD), R- α -lipoic acid (LA), s6 kinase-1 (S6K1), salvianolic acid (SA), SCAP-sequestosome1 (SQSTM1), serine/

arginine-rich splicing factor 1 (SRSF1), signal transducer and activator of transcription (STAT), site-1 protease (S1P), site-2 protease (S2P), solute carrier family 35 member F5 (SLC35F5), SQSTM1-mediated autophagy-independent lysosomal degradation (SMAILD), SREBP cleavage-activating protein (SCAP), SREBP regulating gene (SPRING), staphylococcal nuclease and tudor domain containing-1 (SND-1), steroidogenic acute regulatory protein (StAR), sterol regulatory element binding protein (SREBP), sterol regulatory elements (SREs), sterol-regulatory element-binding transcription factor (SREBF), tetramethylpyrazine (TMP), timosaponin AIII (TA3), traditional Chinese medicine (TCM), transcription factor E3/B (TFE3/B), triglycerides (TG), type 2 diabetes (T2D), unc-51-like autophagy-activated kinase 1 (ULK1), unfolded protein response (UPR), uridine diphosphate glucose (UDPG), xanthohumol (XN), zinc fingers and homeoboxes 2 (ZHX2), zucker diabetic fatty (ZDF), α -linolenic acid (ALA)

CONFLICTS OF INTEREST

There are no conflicts to declare concerning publication of this paper.

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