Sterol regulatory element-binding proteins: Master regulators of lipid metabolic reprogramming in cancer and emerging therapeutic targets (Review)

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Abstract. Sterol regulatory element-binding proteins (SREBPs) are key regulatory factors of lipid synthesis. Tumor cells are highly dependent on SREBP-driven lipid synthesis for the biogenesis of their cell membranes and signaling molecules. The aberrant activation of SREBPs is a critical event that drives tumorigenesis and progression. SREBPs are a subset of membrane-bound proteins that function as basic helix-loop-helix leucine zipper (bHLH-Zip) transcription factors. They mainly maintain the homeostasis of lipid metabolism in the body by activating the genes related to the synthesis and uptake of cholesterol, fatty acids and triglycerides. In addition to their involvement in tumor lipid metabolic reprogramming, SREBPs play critical roles in obesity, atherosclerosis, diabetes mellitus and neurodegenerative diseases. The present review summarizes the regulatory mechanisms of SREBPs, their aberrant activation in tumors, their role in promoting the malignant progression of tumors, as well as the relevant targeted therapeutic strategies from different aspects. In conclusion, targeting SREBPs is a promising anticancer strategy, and future studies are needed to further elucidate their intricate regulatory networks to advance precision medicine.

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Contents

1. Introduction

Sterol regulatory element-binding proteins (SREBPs), first identified in 1993, are membrane-bound transcription factors (TFs) that serve as master regulators of lipid homeostasis. Structurally each SREBP precursor comprises two primary domains: An N-terminal domain that functions as a basic helix-loop-helix leucine zipper (bHLH-Zip) TF, and a C-terminal regulatory domain (1,2). In humans, there are two SREBP proteins: SREBP1 encoded by the SREBF1 gene and SREBP2 encoded by the SREBF2 gene. SREBP1 has two isoforms: SREBP1a and SREBP1c, which mainly regulate the expression of enzymes involved in fatty acid (FA) biosynthesis. SREBP2 belongs to the same family and regulates the expression of enzymes involved in cholesterol biosynthesis (3). SREBPs are localized to the endoplasmic reticulum (ER) as inactive precursors by forming a complex with SREBP cleavage-activating proteins (SCAPs) and insulin-induced gene proteins (INSIG) (4). SREBPs are activated by proteolytic cleavage, then translocate to the cell nucleus, and stimulate the expression of target genes. Upon cellular cholesterol depletion, SREBPs move from the ER to the Golgi apparatus, where the 1-site protease (S1P) cleaves and releases the amino-terminal fragment of SREBPs, which can be further cleaved by the 2-site metalloprotease (S2P) within its transmembrane helix. The processed form of mature SREBPs is released into the cytoplasm and translocates to the nucleus, where it regulates the expression of several genes governing cholesterol and

FA homeostasis (5). The SREBPs pathway is frequently and abnormally, continuously activated in cancer. The SREBPs pathway can protect tumor cells from nutrient deprivation by providing energy, lipids, and other essential factors. The SREBPs pathway is regulated through various mechanisms, including the PI3K/AKT pathway, insulin-related mTORC1 regulation, and microRNA (microRNA or miR)-mediated regulation (6-8). Moreover, the abnormal activation of SREBP pathways in cancer cells is closely associated with their enhanced survival and proliferative capabilities. Tumor cells often face a harsh microenvironment characterized by nutrient deprivation and hypoxia (9). Lipid metabolic reprogramming enables these cells to synthesize essential lipids, such as phospholipids for membrane biogenesis and signaling molecules for intercellular communication, thereby supporting their rapid growth and proliferation. Additionally, SREBPs can promote the synthesis of lipid droplets, which serve as energy reservoirs and protect tumor cells from lipotoxicity under stress conditions (10).

Even under oxygen-replete conditions, tumor cells tend to metabolize glucose to lactate via the glycolytic pathway rather than transporting it into mitochondria for efficient oxidative phosphorylation (OXPHOS), as most normal cells do. This effect, first observed by the German physiologist Otto Warburg in the 1920s, is named after him as the Warburg effect and is also known as aerobic glycolysis (11). Despite its inefficiency, the Warburg effect confers multiple advantages for the rapid growth and proliferation of cancer cells: including accelerated adenosine triphosphate (ATP) production, generation of biosynthetic precursors, maintenance of redox balance, adaptation to hypoxic microenvironments, and modulation of cellular signaling and epigenetics. The Warburg effect is a core hallmark and key component of tumor metabolic reprogramming. Tumor metabolic reprogramming refers to the metabolic adaptations of tumor cells in response to various stresses (12), involving the alterations in glucose, amino acid and lipid metabolism (13). Tumor metabolic reprogramming is a broader concept encompassing systematic alterations in tumor cells' energy acquisition, material synthesis and environmental adaptation. This reprogramming is jointly driven by oncogene activation, tumor suppressor inactivation and microenvironmental stress. By regulating the expression and activity of key metabolic enzymes and transporters, it enables tumor cells to maintain survival and proliferative advantages under nutrient deprivation and hypoxic conditions.

SREBPs particularly play a pivotal role in lipid metabolic reprogramming. To meet the demands of rapid proliferation, tumor cells have to synthesize abundant membrane components and signal transduction molecules, the biosynthesis of which is inseparable from the involvement of lipids. As core regulatory factors in the lipid synthesis pathway, SREBPs can activate a series of genes involved in the synthesis and uptake of cholesterol, FAs and triglycerides, thereby ensuring that tumor cells can maintain lipid metabolic homeostasis and sufficient lipid supply even under harsh microenvironmental conditions. Studies have demonstrated that the activity of SREBPs is significantly upregulated in multiple tumor types, and this alteration not only promotes the proliferation and survival of tumor cells but is also closely associated with the development of their invasiveness, metastasis and chemoresistance (14-16).

Given the fundamental role of SREBPs in cancer metabolism and progression, targeting SREBP pathways has emerged as a promising therapeutic strategy. Several approaches have been explored to inhibit SREBP activation or function, including small molecule inhibitors, RNA interference and CRISPR-Cas9 gene editing (17-19). These strategies aim to disrupt the lipid metabolic reprogramming in tumor cells, thereby depriving them of essential nutrients and inducing cell death. However, the clinical translation of these approaches faces challenges, such as off-target effects and the development of drug resistance. Therefore, a deeper understanding of the complex regulatory networks governing SREBP activity in cancer is crucial for the development of more effective and specific therapeutic interventions.

2. Elaborating regulatory network of SREBP activity

Canonical sterol-dependent regulatory pathway. The canonical sterol-dependent regulatory pathway is an exquisite and highly efficient negative feedback system. It ensures that cells synthesize lipids on demand, which not only meets the requirements for cell proliferation but also avoids toxic lipid accumulation. This pathway dynamically modulates the activity state of SREBPs by precisely sensing changes in intracellular cholesterol levels, thereby regulates the expression of genes related to the synthesis of cholesterol, FAs and other lipids.

SREBP-1a and SREBP-1c regulate the synthesis of FAs, while SREBP-2 regulates cholesterol metabolism. SREBPs combine with the SCAPs to form the SCAP/SREBP complex. This complex can bind to and is regulated by INSIG, affecting ER-to-Golgi translocation. SREBPs are sheared by S1P and S2P in a regular sequence on arrival at the Golgi apparatus, and are processed, matured and transported to the nucleus for action (20). Sterols (mainly cholesterol and oxysterols) maintain SREBPs in an inactive state via SCAP and INSIG proteins, which represents a core mechanism for the precise regulation of cellular lipid homeostasis. SCAP is an ER transmembrane protein whose sterol-sensing domain (SSD) is critical for detecting sterol levels. When sterols (such as 25-hydroxy cholesterol) are abundant, they bind to SCAP's SSD while also interacting with Insig proteins. This binding induces a conformational change in SCAP, significantly increasing its affinity for Insig (21). Upon binding to Insig, SCAP forms a SCAP-Insig complex that anchors SREBP to the ER. A critical hexapeptide sequence 'MELADL' resides on a specific cytoplasmic loop of the SCAP protein, serving as the 'exit tag' essential for SCAP's preparation to enter the intracellular transport machinery (COPII vesicles) for transport to the Golgi apparatus. The combination of SCAP and Insig masks the MELADL signal, preventing SCAP from being recognized by COPII vesicles. As a result, the SREBP/SCAP complex cannot exit the ER, preventing the SREBP precursor from undergoing subsequent proteolytic processing. Subsequently, it remains 'imprisoned' in an inactive form on the ER membrane (22). When cholesterol in the ER exceeds the threshold, sterols bind to Scap, triggering multiple conformational changes that prevent the Scap-SREBP complex from leaving the ER. Consequently, SREBP is no longer processed, cholesterol synthesis

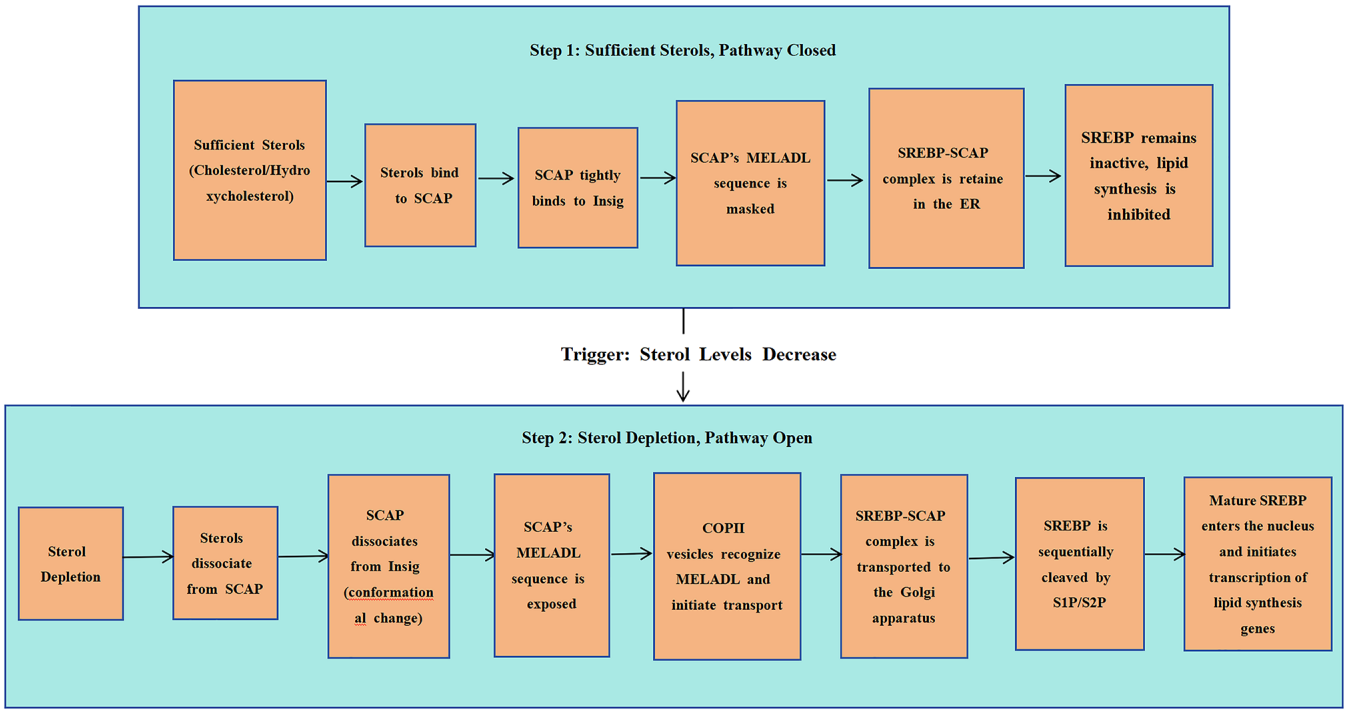

Figure 1. Canonical sterol-dependent regulatory pathway of SREBPs. SREBPs: Membrane-associated transcription factor precursors serve as the 'effect terminal' of the pathway. SCAP: The SREBP co-activator protein serves as the pathway's 'sterol sensor' and 'molecular escort.' Insig: An ER-resident protein that serves as an 'anchor protein' in the pathway. COPII: The vesicle coat responsible for transporting proteins from the ER to the Golgi apparatus, serving as the pathway's 'transport vehicle'. SREBP, sterol regulatory element-binding proteins; ER, endoplasmic reticulum; SCAP, SREBP cleavage-activating protein; Insig, insulin-induced gene protein.

and uptake are inhibited, and cholesterol homeostasis is restored (23). This intricate regulatory mechanism is crucial for normal cell proliferation and metabolic balance (Fig. 1).

Non-canonical activation pathway in tumors. In tumors, in addition to being regulated by canonical sterol levels, the SREBP pathway is hijacked by various oncogenic signals and tumor-specific microenvironments, and is constitutively activated through non-canonical mechanisms, thereby supplying the lipids required for the uncontrolled proliferation of tumors.

Oncogenic signal-driven: In tumor cells, the transduction of oncogenic signals activates SREBPs in a sterol-independent manner. The PI3K-AKT-mTORC1 pathway is one of the most potent driving signals, representing a significant upstream activator of SREBPs (24). Growth factors activate PI3K, which in turn activates Akt. Then, the activated Akt activates mTORC1 via mechanisms such as the inhibition of TSC2 (25). AKT, as a key kinase, plays multiple roles in regulating cell proliferation and metabolism, including the regulation of the SREBP pathway. AKT can phosphorylate Insig1/2, reducing their affinity for SCAP, thereby releasing SREBPs even under sterol-replete conditions. Xu *et al* (26) revealed that in human hepatocellular carcinoma (HCC), activated AKT can phosphorylate Ser90 of phosphoenolpyruvate carboxykinase 1 (PCK1), which is the rate-limiting enzyme in the gluconeogenic pathway. Phosphorylated PCK1 translocates to the ER and phosphorylates Ser207 of INSIG1 and Ser151 of INSIG2 using GTP as the phosphate donor. This phosphorylation modification impairs the sterol-binding capacity of INSIG1 and INSIG2, thereby disrupting the interaction between INSIG and SCAP. As a result, the SCAP-SREBP complex can be transported from the ER to the Golgi apparatus even under conditions of sufficient levels of intracellular sterols. In the Golgi apparatus, SREBP proteins (SREBP1 or SREBP2) are cleaved and activated, translocate into the nucleus, initiate the transcription of downstream lipid synthesis-related genes, and ultimately promote tumor cell proliferation and tumorigenesis. Therefore, activated AKT phosphorylates a series of downstream target proteins, that can influence the processing and activation of SREBPs.

AKT phosphorylates and inhibits TSC2, leading to the inactivation of the TSC complex. The TSC complex normally functions as a GTPase-activating protein (GAP) for Rheb; upon its inactivation, GTP bound to Rheb cannot be hydrolyzed, resulting in the substantial accumulation of Rheb-GTP, that directly binds to and potently activates mTORC1 (27,28). This represents the primary mechanism by which AKT regulates mTORC1. The mTORC1 is a crucial nutrient-sensing and cell proliferation regulatory complex that integrates multiple growth signals and nutritional status information. By phosphorylating downstream effector molecules such as S6K1 and 4E-BP1, it promotes protein synthesis and cell proliferation (29).

Activated mTORC1 drives cellular anabolism by phosphorylating key downstream substrates, activates SREBP TFs, upregulates the expression of genes related to FA and cholesterol synthesis, and thereby promotes lipid synthesis (30). Huang *et al* (6) confirmed through *in vivo* experiments in mammals that activated AKT2 can stimulate SREBP1 and its downstream lipid metabolic pathways, thereby promoting

hepatic steatosis and carcinogenesis. This indicates that SREBPs are essential for PI3K/Akt pathway-mediated regulation of cell proliferation (increased cell size). Inhibition of SREBPs impairs Akt activation-induced increase in cell size; notably, this inhibitory effect on Akt-driven cell enlargement is consistently observed upon SREBP suppression. In cancers such as melanoma, the PI3K-Akt-mTORC1-SREBP signaling axis can form a positive feedback loop. Activation of this pathway induces SREBP to promote cholesterol synthesis, which supports the integrity of lipid raft structures. This in turn further aggregates and enhances Akt signaling, amplifying oncogenic signals (31).

The PI3K-AKT-mTORC1 pathway is one of the most critical upstream signaling pathways regulating SREBPs. Sun *et al* (32) demonstrated that glutaminase 1 (GLS1) drives lipid accumulation and *de novo* FA synthesis in HCC. GLS1 mediates SREBP-1-driven lipid metabolism in HCC through the PI3K-AKT-mTORC1 signaling pathway, thereby promoting lipid metabolism in HCC. By activating SREBPs, it coordinates lipid synthesis and provides the material basis required for the proliferation of rapidly proliferating cells such as tumor cells, which has been confirmed in both basic research and disease mechanism studies. Mutations or aberrant activation of this pathway are highly prevalent in human cancers. This renders tumor cells no longer subject to the normal regulation of extracellular signals and nutrient status, continuously driving lipid synthesis via SREBPs to support their uncontrolled growth.

In addition to the PI3K-AKT-mTORC1 pathway, other oncogenic signaling pathways such as the RAS-RAF-MEK-ERK pathway may also be involved in the non-canonical activation of SREBPs (33). RAS gene mutations occur frequently in various tumors and activated RAS proteins can initiate the downstream RAF-MEK-ERK cascade. As the terminal kinase of this pathway, ERK can translocate into the nucleus and phosphorylate multiple TFs. Meanwhile, it may also promote SREBP activation by affecting their processing and translocation. Specifically, ERK directly phosphorylates specific sites of SREBPs (for example, Ser117 of SREBP-1a and Ser432/455 of SREBP-2) (34,35) enhancing their DNA-binding and transcriptional activities independently of SCAP-SREBP proteolytic activation. Additionally, the RAS-RAF-MEK-ERK pathway activates downstream TFs to promote SREBP gene expression. It cooperates synergistically with the PI3K/AKT/mTORC1 pathway to co-regulate SREBP activity, integrates cell proliferation and metabolic signals, thereby drives lipid metabolic reprogramming to meet the growth demands of tumor cells.

In various cancers such as lymphoma and breast cancer (BC), the overexpression of c-Myc is closely associated with a marked increase in lipid synthesis metabolism, serving as a key driver of tumor metabolic reprogramming (36,37). The c-Myc is a potent oncogenic TF that can upregulate all components of the SREBPs pathway at the source. Also, it regulates multiple rate-limiting enzymes in the cholesterol synthesis pathway, such as 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), thus enhancing cholesterol biosynthesis (38). Cholesterol is a crucial component of cell membranes and is essential for rapidly proliferating tumor cells. As validated in models such as prostate cancer (PC), the activation of c-Myc serves as a key factor driving cholesterol synthesis and tumor progression (39). Other studies on various cancer models such as B-cell lymphoma and HCC have shown that c-Myc not only directly promotes the transcription of key lipogenic enzymes [for example, ACLY, acetyl-CoA carboxylase (ACC), FA synthase (FASN) and SCD] (40) but also forms a synergistic amplification effect with SREBPs, the core TF of lipid metabolism (40,41). By inducing SREBP1 expression, c-Myc can activate the FA synthesis pathway, driving the incorporation of glucose and glutamine into FA chain elongation. This synergistic effect is further confirmed at the molecular level: Knocking down SREBP1 significantly attenuated c-Myc's upregulation of genes such as Acly, Acaca, Fasn and Scd1. Therefore, the synergistic interaction between c-Myc and SREBPs is considered a key driver of tumor metabolic reprogramming and rapid growth (42). In addition to promoting FA synthesis, c-Myc, as a TF, directly binds to the promoter region of the FA-binding protein 5 (FABP5) gene, inducing its expression (43). Following substantial cytoplasmic expression, FABP5 protein binds to intracellular long-chain FAs, enhance their cellular uptake, and transport them to specific organelles or signaling pathways. FABP5 can transport FAs to the mitochondria for β-oxidation, providing ATP energy for rapid proliferation of cancer cells (44). Furthermore, the FAs transported by FABP5 act as signaling molecules, leading to activation of nuclear receptor pathways such as PPARγ/PPARβ/δ, thereby upregulating the expression of a series of genes that promote cell proliferation, migration and survival (45).

Hypoxia and hypoxia-inducible factors (HIF): The tumor microenvironment (TME) has unique features such as hypoxia, low pH, nutrient deprivation, and the presence of numerous cytokines and growth factors. These factors can act synergistically to activate SREBPs through non-canonical pathways.

Hypoxia is one of the common features of the TME. It is a widespread characteristic of solid tumors caused by rapid proliferation of tumor cells exceeding the capacity of blood supply. The oxygen partial pressure often drops to 5-10 mmHg in solid tumors vs. 30-40 mmHg in normal tissue and some areas may be completely hypoxic (<2 mmHg) (46,47). Under hypoxic conditions, oxygen-sensitive signaling pathways within the cell are activated, with HIF playing a central role (48). HIF is a heterodimeric TF composed of an oxygen-sensitive α subunit (HIF-1α, HIF-2α) and a stable β subunit (HIF-1β). Under normoxic conditions, the HIF-α subunit is hydroxylated by prolyl hydroxylases (PHDs), which then allows recognition by the VHL protein and rapid degradation via the ubiquitin-proteasome pathway (49). Under hypoxic conditions, this hydroxylation process is inhibited, allowing HIF-α to remain stable and form a dimer with HIF-1β, translocate into the nucleus, and activate the transcription of downstream target genes (50). HIF can induce the expression of various genes to adapt to the hypoxic environment. Hypoxia and HIF signaling influence SREBPs activity and lipid metabolism through multiple direct and indirect mechanisms, forming a complex and context-dependent regulatory network (51). On one hand, HIF may promote SREBPs cleavage and maturation by affecting the expression or activity of proteins involved in SREBPs' processing. On the other hand, HIF works synergistically with SREBPs to co-activate the transcription of genes

related to lipid synthesis, thereby ensuring that tumor cells can maintain a balanced and sufficient supply of lipid metabolism under hypoxic conditions (52).

Hypoxic TME initially causes the stabilization and accumulation of HIF-α (HIF-1α, HIF-2α), then indirectly stabilizes SREBPs through intermediate steps such as regulating miRs (53), mediator proteins (54) and classic signaling pathways (55), thereby ensuring the lipid synthesis needs of tumor cells. Hypoxic conditions induce a significant increase in HIF-1α expression, which indirectly stabilizes SREBP-1c by downregulating the expression of miR-122-5p (Fig. 2). Research showed that in obese rat models, hypoxia training can induce upregulation of HIF-1α expression in the liver, which in turn sequentially downregulates the expression of C/EBPα and miR-122-5p, forming an important metabolic regulatory axis (53). Since miR-122-5p can inhibit the expression of SREBP-1c, its reduction alleviates this inhibition, leading to an increase in SREBP-1c mRNA and protein levels. Hence, HIF-1α indirectly maintains the stability of SREBP-1c, through the intermediary molecule miR-122-5p, ensuring its function as a key TF for FA synthesis in tumor cells (56,57). In summary, hypoxia remodels the miRNA expression profile of tumor cells via HIF-1α. These regulated miRNAs, through a complex network, employ a 'de-repression' mechanism to indirectly stabilize and activate SREBPs, thereby driving lipid synthesis and prolonging tumor cells' survival. Targeting specific oncogenic miRNAs (such as using miR-153 inhibitors) (58) or supplementing tumor suppressor miRNAs (such as using miR-185 mimics) (59) may be effective strategies to interfere with tumor lipid metabolism and to inhibit tumor growth. Hypoxia in the TME can also regulate SREBPs through mediator complex subunit 15 (MED15), a key mediator protein (60). Under hypoxic conditions, HIF-2α in tumor cells accumulates and becomes activated due to impaired degradation. As a TF, HIF-2α directly binds to the promoter region of the mediator protein MED15, initiating its transcriptional activation through activation of the promoter region and significantly upregulating its expression level. As a core subunit of the mediator complex, MED15 serves as a crucial bridge connecting upstream signals and downstream TF regulation, and its upregulation lays the molecular foundation for subsequent SREBPs regulation. MED15 can also act as a coactivator of SREBPs, regulating their stability and activity through direct interaction (54). It has been shown that MED15 promoted lipid deposition and tumor progression in clear cell renal cell carcinoma (ccRCC) by altering lipid synthesis pathways (61). MED15 directly interacts with SREBPs and RNA polymerase II to regulate the expression of SREBP-dependent key lipid biosynthetic enzymes. Additionally, MED15 can activate the PLK1/AKT pathway to further enhance the transcriptional activation of SREBPs. Depletion of HIF-2α or MED15 in ccRCC inhibits lipid droplet formation and tumor progression. Experiments have confirmed that knockdown of PLK1 abrogates the increase in SREBP1 and SREBP2 protein levels induced by MED15 overexpression. This dual regulatory mechanism not only ensures the stable existence of SREBPs but also continuously enhances their functional activity, forming an efficient regulatory network that drives lipid metabolic reprogramming in tumor cells. As shown in Fig. 3, under hypoxic conditions, HIF-α indirectly stabilizes SREBP by activating the PI3K/AKT pathway. Phosphorylated AKT inhibits glycogen synthase kinase-3 beta (GSK-3β), thereby reduce SREBP degradation, while simultaneously activating mTORC1 to promote SREBP maturation. Collaboratively, these actions maintain SREBP-mediated lipid synthesis.

Various cytokines and growth factors present in the TME, such as tumor necrosis factor-α (TNF-α), interleukin (IL-1β), insulin-like growth factor (IGF) and fibroblast growth factor (FGF), can also bind to their corresponding receptors on the cell surface, activating intracellular signal transduction pathways, and thereby affect the activity of SREBPs. These signaling pathways may crosstalk with classical or non-canonical SREBP activation pathways, forming a complex regulatory network that collectively regulates lipid metabolic reprogramming in tumor cells (Fig. 4). In the TME, the regulation of SREBPs by TNF-α exhibits a complex 'duality'; it can directly activate SREBPs through a sterol-independent mechanism to drive lipid synthesis and inflammatory gene expression (62,63). Correspondingly, its induced downstream metabolites (such as specific oxysterols) may induce feedback-inhibition of the SREBP pathway, forming a dynamic balance or pathological regulatory loop. Studies have found that in hepatocytes, TNF-α can downregulate AMP-activated protein kinase (AMPK) activity, relieving the inhibitory effect of AMPK on SREBP-1 and promoting SREBP-1 to activate downstream genes such as FASN, thereby accelerating lipid synthesis (64). Conversely, in human macrophages (62), TNF-α can induce the late-phase activation of SREBP-2, which binds to inflammation-related gene loci to promote inflammatory responses, a process independent of its classical function in cholesterol metabolism. Additionally, TNF-α can indirectly upregulate the transcriptional activity of SREBP family molecules by activating the NF-κB signaling pathway, exacerbating lipid metabolism disorders and the formation of an inflammatory TME (65). IL-1β is extensively secreted by monocytes, macrophages and other cells, serving as a key pro-inflammatory factor in the TME. It promotes the translocation of the SCAP-SREBP2 complex from the ER to the Golgi apparatus by increasing the mRNA ratio of SCAP/Insig-1, thereby activating SREBP2 and leading to the overexpression of the LDL receptor and cellular lipid deposition (66). IGF, a key growth factor that promotes tumor proliferation in the TME, can induce the phosphorylation of PCK1 at specific sites by stimulating the AKT signaling pathway. Phosphorylated PCK1 binds to Insig1/2 and phosphorylates them, which impairs their sterol-binding capacity. As a key protein inhibiting SREBP activation, the impaired function of Insig allows the SCAP-SREBP complex to be smoothly transported from the ER to the Golgi apparatus and being activated. Ultimately, this promotes SREBP1/2-mediated lipid synthesis and drives the progression of tumors such as HCC (26). Research has found that FGF21 is highly expressed in various tumors (67). It can activate the FGFR1-PI3K-AKT-mTOR pathway in $CD8^+$ T cells, maintaining sustained activation of mTORC1 and thereby upregulating the expression of genes encoding SREBP-1. Concurrently, FGF21 elevated nuclear levels of mature SREBP-1 protein, driving the expression of key cholesterol synthesis genes such as HMGCR. Tumor cells exploit this pathway to increase intracellular cholesterol levels in T cells, impairing their cytotoxic activity and enabling immune

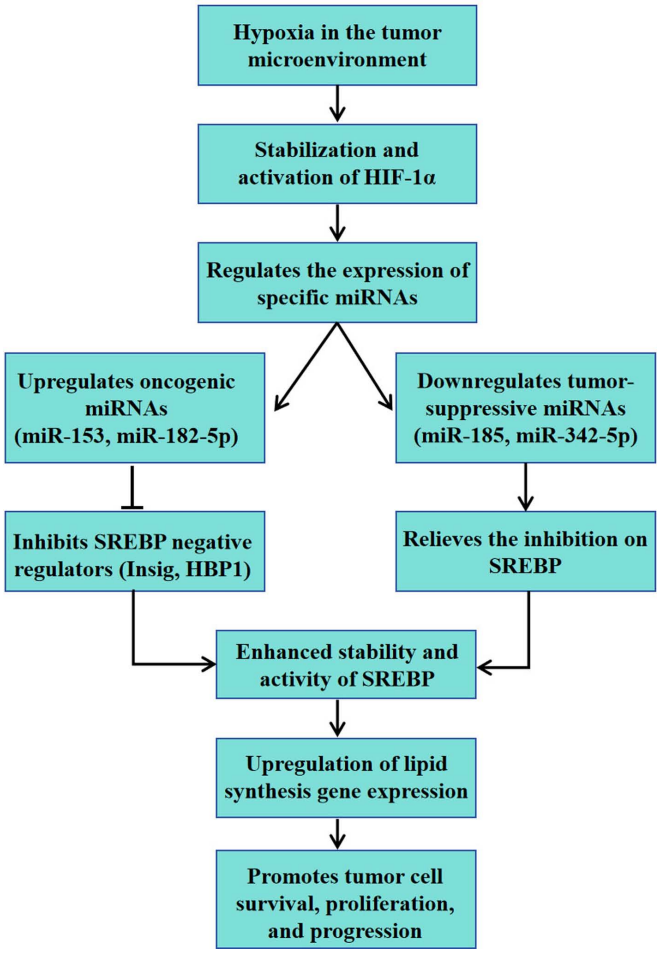

Figure 2. Hypoxia mainly alters the expression profile of specific miRNAs through its core regulator, HIF-1α. These miRNAs subsequently act as key mediators, directly or indirectly affecting the stability and transcriptional activity of SREBPs, ultimately driving lipid synthesis to meet the proliferation demands of tumor cells. The core regulatory pathway is summarized as shown in figure. miR or miRNA, microRNA; HIF, hypoxia-inducible factor; SREBP, sterol regulatory element-binding proteins; Insig, insulin-induced gene protein.

evasion. Knocking down SREBP-1 completely abolished FGF21-induced cholesterol synthesis and immunosuppressive effects (68).

Metabolite sensing. The core mechanism is that metabolites indirectly regulate the stability, processing, or transcriptional activity of SREBPs by altering intracellular signal transduction and post-translational modifications (PTMs) of proteins. The mechanisms by which metabolites such as succinate affect SREBP activity through non-canonical pathways have been recently confirmed, but these pathways are generally independent of the classical feedback regulation mediated by sterol levels (69).

In non-canonical activation pathways of tumors, succinate, a prototypical cancer-specific metabolite, often accumulates abnormally due to mutations or downregulation of succinate dehydrogenase (SDH) in tumor cells (70). Succinate, an intermediate metabolite of the tricarboxylic acid (TCA) cycle and a competitive inhibitor of HIF PHDs, promotes SREBPs transcriptional activation through the core non-canonical pathway which involves HIF-1α stabilization (71-73). In tumors (such as SDH-deficient tumors), excessive accumulation of succinate inhibits the degradation of HIF-1α, leading to its stabilization (71). The stabilized HIF-1α translocates into the nucleus and act as a TF to directly or indirectly regulate a range of genes, such as transcriptionally upregulating various growth factors (for example, IGF-2). These factors can activate receptor tyrosine kinases on the cell membrane through autocrine/paracrine mechanisms, thereby initiating downstream signaling pathways including PI3K/AKT/mTORC1 (26). These pathways serve as key upstream signals for SREBP activation, promoting the processing, maturation, and transcriptional activity of SREBPs. Yu *et al* (74) demonstrated that in PC cells, accumulated HIF-1α can directly bind to the promoter region of SREBP-1c, significantly increasing their mRNA and protein expression levels, thereby activating the transcriptional process of SREBP-1c and ultimately promoting *de novo* lipogenesis in tumor cells in order to meet the lipid demand for malignant tumor proliferation. Furthermore, succinate can also alter the activity of relevant regulatory proteins through PTMs, that indirectly affects the stability of SREBPs (75). On one hand, succinate can induce protein succinylation. For example, in tumor-associated macrophages (TAMs) (76), succinate induces succinylation of histone H3K122 and promotes succinylation of mitochondrial isocitrate dehydrogenase 2 (IDH2) while inhibiting its activity. This epigenetic modification and enzyme activity regulation indirectly influence the transcriptional environment of lipid metabolism-related genes, creating favorable conditions for maintaining SREBPs activity.

On the other hand, accumulated succinate promotes the phosphorylation of the E2 ubiquitin-conjugating enzyme (UBC12), which impairs its enzymatic activity and reduces cullins neddylation (70). UBC12 is capable of mediating the neddylation of SREBP-1; its impaired function reduces the ubiquitin-dependent degradation of SREBP-1, thereby maintaining the stability of SREBP proteins and ensuring their activity in regulating lipid synthesis (77). Wang *et al* (75) demonstrated that succinate can alter the activity of target proteins by promoting protein succinylation. For example, it significantly increased the level of protein succinylation in BEAS-2B cells and can specifically modify the K68 site of SOD2 while inhibiting its enzymatic activity. Given the fact that SREBPs stability often depends on the activity regulation of metabolism-related enzymes, it can be inferred that if succinate mediates the succinylation of lipid metabolism-related proteins in the SREBP pathway, it would indirectly affect the cleavage, activation, or degradation of SREBPs. Correspondingly, the aforementioned study ascertained that succinate induces protein succinylation through non-enzymatic or enzymatic pathways, providing a theoretical basis for further exploring the regulation of SREBP-related proteins by succinate. In addition, succinate indirectly regulated SREBPs by activating the signaling pathway mediated by the succinate receptor 1 (SUCNR1). After succinate secreted by tumor cells binds to SUCNR1 on the macrophages surface, it induces the polarization of macrophages into TAMs by activating the PI3K-HIF-1α signaling axis (78). HIF-1α is a key molecule regulating SREBP activity; it can enhance the transcriptional activity of SREBP-1 by upregulating the expression of lipid synthesis-related genes to adapt to the lipid demand of tumors under hypoxic conditions, providing a clear signaling cascade for the indirect regulation of SREBP

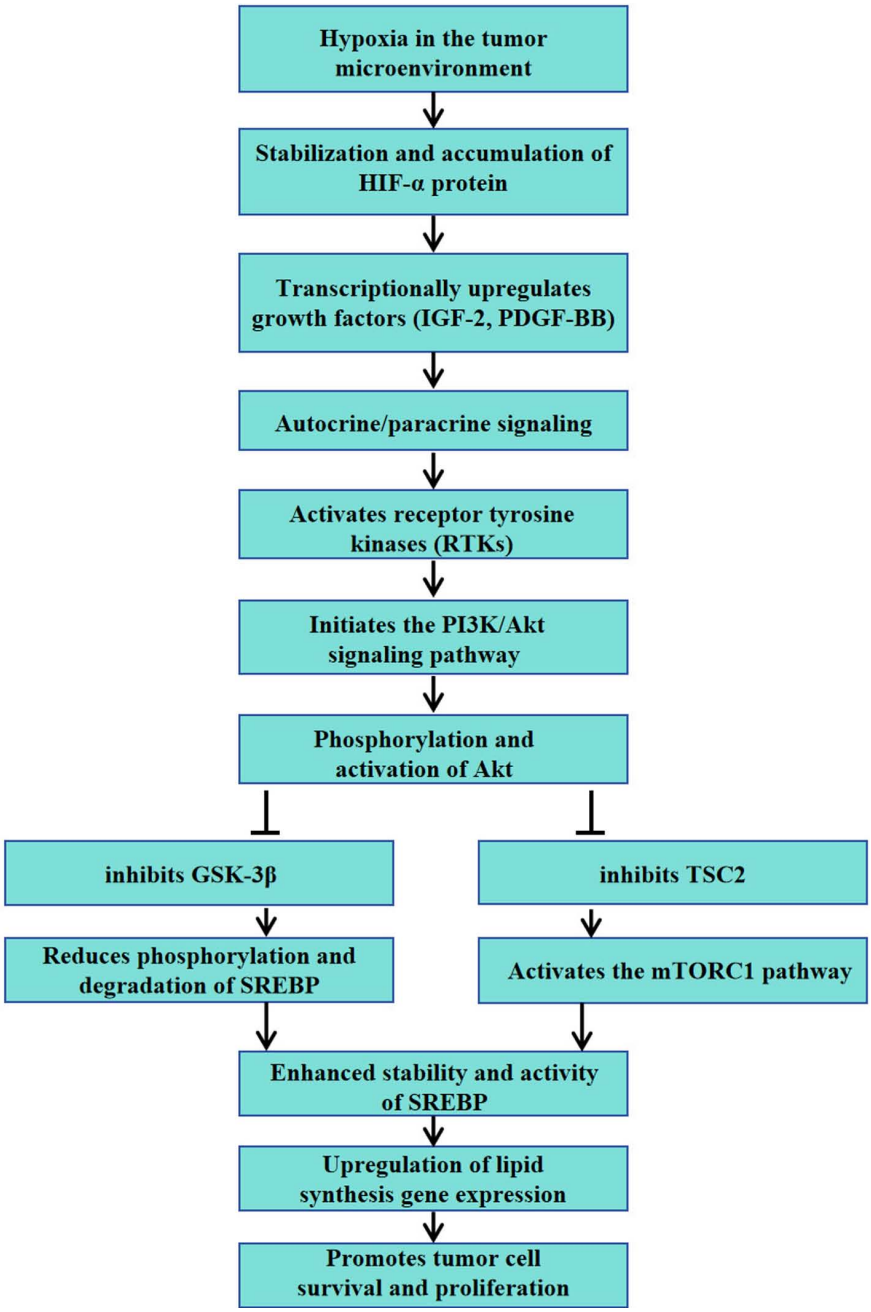

Figure 3. Schematic representation of the core molecular pathway through which HIF-α indirectly stabilizes SREBPs via the PI3K/Akt pathway. The signaling axis 'Hypoxia → HIF-α → (Growth factors/RTK) → PI3K/Akt → (Inhibition of GSK-3β and activation of mTORC1) → SREBP stabilization and activation' is a complete and experimentally validated signaling cascade. This reveals how tumor cells subtly reprogram their signaling networks and metabolic activities through HIF-α under hypoxic conditions to sustain lipid synthesis and survival advantages. HIF, hypoxia-inducible factor; SREBP, sterol regulatory element-binding proteins; RTK, receptor tyrosine kinase; GSK-3β, glycogen synthase kinase-3 beta.

activity. Dysfunction of IDH2 alters the transcriptional environment of lipid metabolism-related genes, creating favorable conditions for SREBPs to maintain its activity. This further links the succinate-SUCNR1 regulatory network with SREBPs. Upon binding to SUCNR1, succinate can also directly activate the protein kinase A (PKA)-CREB signaling axis, thereby promoting KLF4 pathway activation. This synergizes with IL-4 signaling to drive macrophage polarization toward an anti-inflammatory phenotype and enhance the expression of anti-inflammatory genes such as Arginase-1 and interleukin-10 (IL-10) (79). In mouse models, myeloid cell-specific deletion of SUCNR1 was observed to impair activation of this signaling axis, exacerbating inflammation and disrupting metabolic homeostasis. This finding further corroborates the critical role of succinate in activation of the PKA-CREB pathway via SUCNR1 to maintain metabolic and immune balance, thus providing a crucial intermediate link in the complete chain: 'extracellular metabolites → membrane receptor signaling → transcriptional reprogramming → lipid metabolism remodeling'. This metabolic cascade offers new insights for intervening in tumor metabolism, bridges metabolism and inflammation (80) and may serve as a pivotal hub connecting tumor metabolic reprogramming with the immune microenvironment.

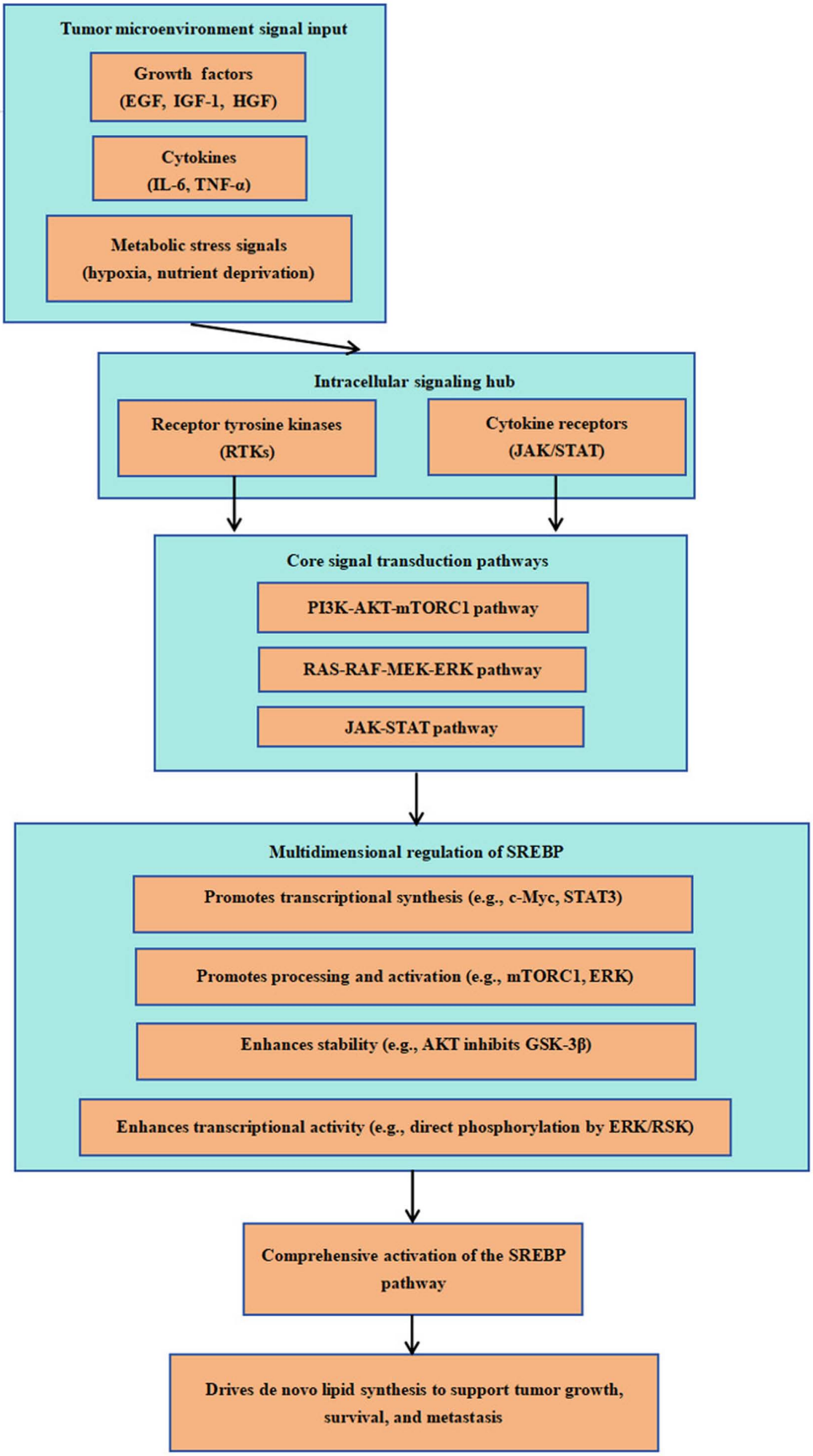

Figure 4. Systematic framework diagram of major signaling factors, core pathways and their regulatory modes on SREBPs. The tumor microenvironment activates two primary signaling axes, PI3K/AKT/mTORC1 and RAS/MAPK, through growth factors and inflammatory factors, supplemented by pathways such as JAK/STAT. It exerts 'three-dimensional' regulation on SREBPs at multiple levels, including transcription, post-translational modification, protein stability and activity. This enables SREBP-driven lipid synthesis to escape feedback inhibition by intracellular sterol levels and be integrated into the oncogenic signaling network, continuously providing tumor cells with membrane components, energy and signaling molecules. SREBP, sterol regulatory element-binding proteins; GSK-3β, glycogen synthase kinase-3 beta; TNF-α, tumor necrosis factor-α; IL, interleukin; IGF, insulin-like growth factor.

In addition to succinate, fumaratecan also influence SREBP activity through similar non-canonical pathways. Fumarate, a key metabolic intermediate in the TCA, often accumulates abnormally in the tumor cells due to functional loss or downregulation of fumarate hydratase (FH) (81). Its mechanism for regulating SREBP activity shares some commonalities with succinate but also exhibits unique pathways. It has been shown that fumarate can form a non-canonical regulatory axis by stabilizing HIF-1α (82). In FH-deficient renal cancer cells, fumarate accumulation inhibits the activity of HIF PHDs, leading to impaired degradation of HIF-1α. The stabilized HIF-1α directly binds to the promoter region of SREBP-1c, significantly increasing its transcriptional level and promoting the expression of FA synthesis-related genes. This mechanism is highly similar to the pathway by which succinate stabilizes HIF-1α through the competitive inhibition of PHDs. However, the inhibitory effect of fumarate on PHDs exhibits a dose-dependent characteristic, and the regulatory efficiency varies among different tumor types (83,84). In addition to competitively inhibiting PHDs, another key mechanism of fumarate as an oncometabolite lies in its epigenetic regulatory role. Fumarate directly affects the function of key proteins in the SREBP pathway through protein succinylation modification (85). In FH-knockout cell models, fumarate induced succinylation at the K136 site of mitochondrial malate dehydrogenase 2, resulting in a 30-50% decrease in its enzymatic activity. This further disrupts mitochondrial-cytoplasmic metabolite exchange and indirectly impairs the lipid microenvironment required for SREBP processing and maturation (86). More notably, fumarate can specifically modify the K289 site of the SCAP protein, enhancing its binding capacity to COPI-coated vesicles and promoting the transport efficiency of the SCAP-SREBP complex from the ER to the Golgi apparatus. This PTM regulation provides a novel mechanism for the non-canonical activation of SREBPs (87,88). At the epigenetic level, it has been recently demonstrated that fumarate can inhibit the activity of histone deacetylases (HDACs), leading to a global increase in histone acetylation levels (89). Among these modifications, the enrichment of H3K27ac at the promoter regions of SREBP target genes is significantly enhanced, forming an open chromatin state that favors the transcription of lipid synthesis-related genes (90). This epigenetic regulation complements the histone succinylation induced by succinate, collectively constructing a metabolite-driven transcriptional reprogramming network. Clinical sample analysis has shown that the expression levels of SREBP target genes (for example, FASN and SCD1) in FH-deficient tumor tissues are positively correlated with fumarate concentration, and inhibiting fumarate production can significantly reduce lipid droplet accumulation in tumor cells (81,91). These findings suggested that targeting fumarate metabolism may serve as a novel strategy for intervening with SREBP-driven tumor metabolic reprogramming.

Post-transcriptional regulation. The post-transcriptional regulation of SREBPs constitutes a sophisticated, multi-layered network involving coordinated actions of multiple molecules. It dynamically and precisely regulates SREBP stability and activity, ensuring rapid lipid metabolism responses to cellular demands through five core mechanisms: Ubiquitination/deubiquitination, phosphorylation/dephosphorylation, binding to lipid metabolites, miRNA regulation and protein interactions.

Ubiquitination/deubiquitination is one of the key mechanisms regulating SREBP stability. The USP20 affects lipid synthesis processes associated with the SREBP pathway by regulating HMGCR, the rate-limiting enzyme in cholesterol synthesis (92). Following feeding, glucose and insulin synergistically activate mTORC1, inducing the phosphorylation of USP20 at specific serine residues (S132 and S134), which further promotes the formation of a complex between USP20 and HMGCR, reducing the ubiquitination level of HMGCR to enhance its stability. As a key downstream enzyme in the SREBP pathway, the stable expression of HMGCR provides favorable conditions for SREBP-mediated lipid synthesis, indirectly ensuring the sustained activity of the SREBP pathway (93). Ding *et al* (94) demonstrated that USP20-targeting siRNA nanoparticles (siUSP20-NPs) silence hepatic USP20, abrogating its deubiquitinating and stabilizing effect on HMGCR and promoting its proteasomal degradation, thereby inhibiting *de novo* cholesterol synthesis. This process does not directly interfere with the SREBP pathway at the transcriptional regulatory level but inhibits lipid synthesis by regulating the activity of downstream rate-limiting enzymes. E3 ubiquitin ligases such as the SCF (Skp1-Cullin-F-box) complex can limit the excessive activation of SREBPs by mediating its modification by ubiquitination, thereby labeling it for proteasomal degradation (95). For example, FBXW7, as the substrate recognition subunit of the SCF complex, can directly bind to the phosphorylated sites of SREBP-1, promoting its ubiquitination and degradation and inhibiting the expression of lipid synthesis-related genes (96). By contrast, deubiquitinating enzymes such as USP10 interacts with SIRT6, reducing its ubiquitin-dependent degradation. SIRT6 regulates key lipid synthesis factors such as SREBP1 through direct deacetylation, thereby indirectly affecting the expression and transcriptional activity of SREBP1 to modulate lipid metabolism (97). This dynamic balance is often disrupted in tumor cells: Oncogenes such as MYC can enhance SREBP stability by upregulating USP10 expression, thus promoting lipid synthesis to meet the demand for rapid tumor proliferation (98,99); while tumor suppressor genes such as p53 accelerates SREBP degradation by inducing FBXW7 expression, leading to inhibition of tumor metabolic reprogramming (100).

Phosphorylation modification regulates the stability and transcriptional activity of SREBPs by altering their spatial conformation and protein-protein interaction capacity, with phosphorylation mediated by different kinases exerting distinctly opposite effects. Phosphorylation that inhibits SREBP stability/activity: GSK-3β is activated when cellular energy is sufficient, phosphorylating specific sites (Thr426/Ser430) of SREBP1 to provide a 'molecular tag' for Fbw7 recognition and initiate ubiquitin-dependent degradation, through an inhibitory cascade of 'GSK-3β → phosphorylation → Fbw7-mediated ubiquitination → degradation' (101) PKA can phosphorylate SREBP1a (Ser338) and SREBP1c (Ser314), which reduces their DNA-binding capacity (inhibiting transcriptional activity) as well as enhances their interaction with ubiquitin ligases (accelerating degradation), thereby dually inhibiting SREBP function (102); AMPK

inhibits its DNA-binding capacity and blocks the transcription of lipid synthesis-related genes by phosphorylating the Ser372 site of nuclear SREBPs (103). Phosphorylation that enhances SREBP stability/activity: Cyclin-dependent kinase 1 (Cdk1) forms a complex with cyclin B during cellular mitosis, which can phosphorylate the Ser439 site of SREBP1. This phosphorylation enables mature SREBP1 to maintain stability, preventing its degradation during cell division and thereby retaining active TFs to meet the lipid synthesis demand during mitosis (104). Additional studies have shown that insulin-induced phosphorylation of SREBP-1c at specific sites mediated by mTOR confers its resistance to proteasomal degradation, thereby significantly enhancing its stability and promoting *de novo* lipid synthesis (105).

Intracellular lipid metabolites can directly bind to SREBPs or their regulatory proteins and precisely regulate their levels through a feedback loop between the metabolic status and protein activity. For example, phosphatidic acid, a key intermediate in ER membrane phospholipid metabolism, binds to the N-terminal leucine zipper domain of SREBP-1c, enhancing its interaction with coactivators (for example, SRC-1) and promoting the expression of FA synthesis genes (for example, FASN and SCD1) (106,107). By contrast, sphingolipid metabolites such as ceramide competitively binds to SREBPs, inhibiting their DNA-binding capacity and forming a negative feedback regulatory loop (108). In the TME, abnormally accumulated metabolites (for example, saturated FAs) can alter the lipid-binding profile of SREBPs, reshape their target gene expression patterns, and support the lipid demand of tumor cells.

miRNAs act as 'upstream switches' in the regulatory network by directly binding to the 3'-untranslated region (3'-UTR) of SREBP mRNAs, inhibiting their translation or promoting mRNA degradation to regulate SREBP protein levels at the source (109). For example, the miR-29 family (miR-29a/b/c) can directly target the 3'UTR of SREBP-1, suppressing its expression and thereby downregulating FA synthesis-related genes (110), whereas the miR-33 family (miR-33a/b) indirectly regulates SREBP activity by inhibiting the expression of SREBP downstream target genes (for example, ABCA1), forming a metabolic feedback loop (111). In tumors, the expression of these miRNAs is often reprogrammed by oncogenic signals. For example, MYC can relieve the inhibition of SREBP-1 by suppressing miR-29 expression, thereby promoting lipid synthesis (112,113). By contrast, p53 exerts a tumor-suppressive effect by inducing miR-33 expression to inhibit the SREBP pathway (114). Additionally, miR-155 targets and degrades the mRNA of Fbw7, the ubiquitin ligase of SREBPs, leading to reduced degradation of SREBP1 thus indirectly stabilizing their levels and accelerating tumor lipid metabolic reprogramming (115).

The stability and activity of SREBPs depend on interactions with various auxiliary proteins, which further refine the regulatory network by acting as 'molecular chaperones', 'coactivators', or 'inhibitors'. Protein interactions that promote SREBP activity: SCAP, as the dedicated molecular chaperone of SREBPs, forms a complex with SREBPs and mediates their translocation from the ER to the Golgi apparatus for cleavage and activation (a prerequisite for activity activation); when intracellular cholesterol is depleted, SCAP undergoes a conformational change, dissociates from Insig-mediated inhibition, and initiates the translocation process (116). The p300/CBP, transcriptional coactivators, bind to nuclear mature SREBPs and open chromatin structure through histone acetylation modification, thereby enhancing the transcriptional activation capacity of SREBPs towards lipid synthesis-related genes (for example, FASN and ACLY) (117,118). MED15, a mediator protein, is upregulated by HIF-2α in ccRCC. It binds to SREBPs, activating FA synthesis pathway, and enhances their stability by protecting them from ubiquitin-dependent degradation (61). Protein interactions that inhibit SREBP activity: Insig1/2, ER-resident proteins, bind to the SREBP-SCAP complex when cholesterol is abundant, preventing its translocation to the Golgi apparatus. Meanwhile, they recruit ubiquitin ligases to promote SREBP degradation, leading to dual inhibition of its activity (116). CREB-H, a TF, transcriptionally upregulates the ER-anchored protein Insig, indirectly inhibiting the cleavage and activation of SREBP precursors, thus reducing the production of functional mature SREBP proteins in the nucleus (119). TRC8, an ER-associated ubiquitin ligase, synergizes with Insig to ubiquitinate the SREBP-SCAP complex, promoting its degradation and inhibiting SREBP activation (120).

These multi-layered post-transcriptional regulatory mechanisms collectively ensure the precise activation and dynamic equilibrium of SREBP in tumor cells. The post-transcriptional regulatory network of SREBP is centered on modification regulation (ubiquitination/phosphorylation), supplemented by metabolites and miRNAs, and supported by protein interactions. It achieves precise regulation of SREBP's stability and activity through the synergistic and antagonistic interactions of multiple molecules and pathways. This network not only maintains lipid metabolic homeostasis in normal cells but also undergoes adaptive reprogramming under pathological conditions such as tumorigenesis. Therefore, it serves as a key driver of tumor metabolic reprogramming, offering abundant molecular targets for therapies targeting tumor lipid metabolism.

3. Multidimensional functions of SREBP in driving malignant progression of tumors

Membrane structure and biosynthesis. The unique ER membrane-anchored structure of SREBPs serves as the foundation for their activation regulation. Whereas their aberrant biosynthesis and activation processes disrupt lipid metabolic homeostasis, continuously providing the material and signaling support required for tumor cell proliferation and invasion, and ultimately driving tumor malignant progression. In normal cells, the SCAP-SREBP complex is retained in the ER by Insig proteins when sterols are sufficient, thereby suppressing lipogenesis. However, in tumor cells, this feedback is overridden by oncogenic signals such as PI3K/AKT/mTORC1. Consequently, SREBPs undergo constitutive proteolytic activation and drive the transcription of genes involved in the synthesis of FA, cholesterol and phospholipid, that are core components of tumor cell membrane (121). This SREBP-driven lipid biosynthesis provides the structural building blocks for energy supply and rapidly dividing tumor cells, supporting membrane expansion, lipid raft formation and signal transduction platforms.

Rapidly proliferating tumor cells require vast amounts of new membranes to form daughter cells, and SREBP-driven production meets this demand. Excess cholesterol is embedded into the plasma membrane to form dense lipid raft structures, which serve as signaling platforms that enhance growth factor-mediated signal transduction and further promote tumor proliferation. Similarly, lipid droplets protect cancer cells from lipid overload-induced damage, indirectly ensuring the stable synthesis of tumor cell membranes. In addition, the large amounts of lipids synthesized under the drive of SREBPs can efficiently provide sustained energy for tumor cells in hypoxic and nutrient-depleted microenvironments through β-oxidation (122). Furthermore, intermediate products of the synthesis process, such as isoprenoids, can also act as signaling molecules to activate cell survival pathways, enhancing the adaptability of tumor cells to harsh environments and reducing apoptosis (123).

Energy storage and signal transmission. In normal cells, the lipid synthesis activity of SREBPs is strictly regulated by cholesterol levels. However, tumor cells hijack this regulatory mechanism to sustain SREBP activation, leading to massive synthesis and storage of lipids such as FAs and cholesterol, which serve as the core guarantee for tumor energy supply. The large amounts of FAs, triglycerides and cholesterol produced under SREBP control serve as energy reserve substances. When the TME is hypoxic and nutrient-depleted, these lipids are decomposed through β-oxidation to supply energy for tumor cells, ensuring their continuous proliferation (122). On the other hand, in a high-fat diet-induced HCC model, SREBP-driven lipid storage provided a buffer for tumor cells to cope with external metabolic stress. For instance, when chemotherapeutic drugs disrupt energy metabolism, stored lipids can be rapidly decomposed to supplement energy, helping tumor cells to evade apoptosis (6).

SREBPs are not only metabolic regulators but also link oncogenic networks through multiple signal transduction modes to drive tumor progression. Upon activation, SREBPs regulate the expression of lipid synthesis-related genes, affecting the composition and function of cell membranes, which in turn alters the distribution of cell surface receptors and signal transduction efficiency. For example, cholesterol synthesized under the drive of SREBP-2 can be embedded in the cell membrane to form lipid rafts, providing a clustering platform for signaling molecules such as epidermal growth factor receptor. This enhances the activation intensity of its downstream Ras/MAPK pathway, thereby promoting tumor cell proliferation (124). Meanwhile, palmitic acid, a product of FASN upregulated by SREBP-1, can stabilize β-catenin, the core protein of the Wnt pathway, through palmitoylation modification, preventing its ubiquitin-dependent degradation. Thereby, the activation of the Wnt/β-catenin signaling pathway is sustained to drive the self-renewal of cancer stem cells (125). Furthermore, SREBP-induced lipid metabolic reprogramming can also directly participate in signal transduction through metabolic intermediates: For instance, acetyl-CoA, as a substrate for histone acetyltransferases, its increased level can promote chromatin accessibility and enhance the transcriptional activity of oncogenes (for example, c-Myc) (126). While 4-hydroxynonenal generated by lipid peroxidation can modify and activate key proteins in the PI3K/AKT pathway, forming a positive feedback loop that accelerates tumor cell survival and migration (127). This metabolic-signaling crosstalk network positions SREBPs as a core hub for tumor cells to adapt to the microenvironment, evade apoptosis, and undergo invasion and metastasis. In summary, SREBPs is positioned at the center of a complex regulatory network. Their aberrant activation by upstream oncogenic signals (for example, AKT and STAT3), leads to generation of substantial lipid products that act as essential 'building materials' and 'signaling molecules'. These lipids maintain and enhance the activity of multiple oncogenic pathways, including mTOR, Ras and growth factor receptor signaling, forming a self-sustaining positive feedback loop that drives tumor malignant progression. Therefore, targeting the SREBP pathway represents a potential strategy to break this loop and inhibit tumor growth.

Redox homeostasis. Dysregulated redox homeostasis is one of the typical characteristics of tumor cells. SREBP isoforms collectively safeguard tumor redox homeostasis through distinct yet synergistic mechanisms: SREBP-1 predominantly facilitates NADPH production and SCD1-mediated ferroptosis resistance, while SREBP-2 modulates the intracellular iron pool to mitigate oxidative damage.

Excessive accumulation of reactive oxygen species (ROS) disrupts the structure of biomacromolecules in tumor cells. As a core antioxidant substance, NADPH provides electrons to antioxidant enzymes for ROS scavenging (128). SREBP-1 enhances NADPH generation by regulating related metabolic pathways, thereby maintaining redox balance (129). They induce the expression of oxidative pentose phosphate pathway enzymes such as glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, a key pathway for NADPH production. Meanwhile, SREBP-1 also promotes the expression of IDH1 and malic enzyme, all of which can catalyze reactions to generate NADPH (130,131). Adequate NADPH provides the reducing power required for SREBP-driven lipid synthesis and regenerate reduced glutathione from oxidized glutathione through antioxidant enzyme systems such as glutathione reductase. This efficiently scavenges ROS generated during tumor cell metabolism, preventing cell death from oxidative damage and ensuring the continuous proliferation of tumor cells (132).

Ferroptosis is an iron-dependent form of cell death triggered by lipid peroxidation (133). Disrupting this death mechanism is crucial for tumor survival, and SREBP-1 inhibit ferroptosis through two core pathways to maintain redox homeostasis. From one perspective, SREBP-1 activates its downstream target gene stearoyl-CoA desaturase 1 (SCD1), promoting the conversion of saturated FAs to mono-unsaturated FAs. These mono-unsaturated FAs can directly inhibit phospholipid peroxidation and reduce the accumulation of lipid peroxides, thereby blocking ferroptosis (134). This mechanism enables cancer cells to develop resistance to ferroptosis inducers in cancer cells through PI3K-AKT-mTOR pathway mutations (135). Conversely, in pancreatic cancer, SREBP-1 can bind to the promoter region of glutathione peroxidase 4 (GPX4) to regulate its transcription (136). As a key enzyme inhibiting ferroptosis, GPX4 can scavenge lipid peroxides. By maintaining the expression of GPX4, SREBP1 prevents tumor cells

from undergoing ferroptosis induced by lipid peroxidation, ensuring the stable survival of tumor cells (137). Furthermore, SREBP-2 induces overexpression of iron homeostasis-related pathways in circulating tumor cells of melanoma, reducing the intracellular iron pool, lowering the risk of iron ion-mediated oxidative damage and ferroptosis, and facilitating tumor metastasis and drug resistance (138).

SREBPs can interact with multiple oncogenic signaling pathways to coordinately regulate the redox status of tumor cells. For instance, SREBPs maintain tumor redox and survival through a reciprocal crosstalk with the NF-κB signaling pathway. Beyond its canonical role in inflammation, NF-κB synergizes with SREBP-1 to coordinate lipid-driven anti-apoptotic programs. Specifically, SREBP-1-mediated lipid metabolites, such as specific FA derivatives, trigger the nuclear translocation of NF-κB. Once activated, NF-κB reinforces the expression of pro-survival genes while retroactively modulating SREBP activity. This bidirectional feedback loop creates a robust metabolic-signaling network that sustains the malignant phenotype and redox homeostasis of tumor cells (139). SREBPs and the PI3K/AKT pathway engage in a positive feedback loop that amplifies tumor cell survival. As aforementioned, PI3K/AKT signaling promotes SREBP activation. Nonetheless, lipid products generated by SREBP-driven lipogenesis (for example, phosphatidylinositol) further stimulate PI3K/AKT, forming a self-reinforcing circuit. This crosstalk enhances NADPH production, inhibits ferroptosis, and maintains redox homeostasis in tumor cells (as detailed in the preceding paragraphs). Yi *et al* (134) reported that in tumors harboring activating mutations in PIK3CA or deletion of PTEN, the PI3K-AKT-mTOR pathway was aberrantly activated, promoting SREBP1 activation. This in turn inhibited phospholipid peroxidation through the SCD1 pathway, forming a synergistic interaction between signaling pathways and redox homeostasis regulation, thereby enhancing the survival capacity of tumor cells.

The activation process of SREBPs is highly sensitive to the intracellular redox state and can be specifically induced under oxidative stress conditions. Tumor cells upregulate the synthesis of FAs and cholesterol through SREBPs, while promoting the generation of NADPH to maintain reduced glutathione levels and enhance antioxidant capacity. This metabolic reprogramming not only meets the energy and biosynthetic demands of rapid proliferation but also helps tumor cells cope with ROS accumulation induced by high metabolic activity, thereby maintaining redox homeostasis. Therefore, SREBPs play a crucial role in coordinating lipid metabolism and antioxidant defense, further supporting the survival of tumors.

Protein isoprenylation. Protein isoprenylation is a type of PTM that involves the covalent attachment of isoprenoid groups such as farnesyl pyrophosphate (FPP) and geranyl-geranyl pyrophosphate (GGPP) to cysteine residues at the C-terminus of proteins (140). The specific role of this process in cells is to install a 'membrane anchor' for certain inherently hydrophobic proteins, aiding their localization and attachment to the cell membrane to perform functions such as signal transduction. This process promotes interactions to activate oncogenic signals (141). Aberrations in this modification are often associated with diseases, particularly in the field of oncology. For example, abnormal isoprenylation of the oncogene Ras leads to its sustained activation, driving tumor initiation and progression (142).

The mevalonate (MVA) pathway, transcriptionally controlled by SREBPs (particularly SREBP-2), generates the FPP and GGPP that are covalently attached to C-terminal cysteine residues of key oncogenic proteins (for example, Ras and Rho) via protein isoprenylation, thereby promoting their membrane localization and sustained activation of downstream oncogenic signaling (143,144). On one hand, in pancreatic ductal adenocarcinoma FPP produced by the SREBP-driven MVA pathway can mediate the farnesylation of KRAS protein (145). This isoprenylation modification guides KRAS to localize to lipid rafts in the cell membrane, enabling its sustained activation of downstream oncogenic pathways such as MEK/ERK. Thereby, accelerating tumor cell proliferation, invasion and metastasis. Moreover, KRAS mutation itself is a core driver of the progression of this type of cancer (146). On the contrary, it has been revealed that in BC, GGPP generated by the SREBP-activated MVA pathway mediated the geranylgeranylation of RhoA protein (147). The modified RhoA protein anchors more stably to the cell membrane, enhancing its interaction with downstream effector molecules and thereby sustaining the activation of the RhoA/ROCK signaling pathway. Sustained activation of this pathway promotes the rearrangement of the tumor cell cytoskeleton, endowing tumor cells with stronger motility, which facilitates tumor cell invasion and metastasis. Concurrently, it also inhibits tumor cell apoptosis and promotes tumor cell survival (148).

Beyond the direct modification of oncogenic proteins, SREBP-2-mediated protein isoprenylation exerts a profound impact on the tumor immune microenvironment. The functional status of immune cells within the TME, including T cells and macrophages, is profoundly modulated by protein isoprenylation. SREBP-2-driven flux through the MVA pathway provides the essential isoprenoid substrates required for the PTM of key signaling molecules, such as small GTPases, thereby orchestrating immune cell activation and polarization. For example, in TAMs, isoprenoid compounds generated by the SREBP-2-activated MVA pathway can modify certain signal transduction proteins in macrophages, inducing their polarization toward the M2 phenotype (149). M2-type macrophages possess immunosuppressive functions and can secrete various immunosuppressive cytokines, such as IL-10 and transforming growth factor-β (TGF-β). These cytokines inhibit the activation and proliferation of T cells, creating an immunosuppressive microenvironment that helps tumor cells escape immune surveillance and elimination, consequently promoting tumor growth and progression (150). Furthermore, SREBP-2-mediated protein isoprenylation modulates the reciprocal interaction between tumor cells and the extracellular matrix (ECM). By sustaining the MVA pathway, SREBP-2 provides the essential isoprenoid substrates for the prenylation of small GTPases (for example, Rho and Rac), which are indispensable for the cytoskeletal reorganization and ECM-dependent cell migration during metastasis. In addition, protein isoprenylation regulates the expression and function of adhesion molecules on the surface of tumor cells,

thereby influencing the adhesive capacity of tumor cells to the ECM which may also activate a series of intracellular signaling pathways, further facilitating the malignant progression of tumor cells. For example, certain isoprenylation-modified integrin proteins can enhance the adhesion of tumor cells to ECM components such as fibronectin and laminin, promoting tumor cell migration and invasion (151).

Tumor immune escape. SREBP not only drives the metabolism of tumor cells but also 'reprograms' key immune cells within the TME, shaping an immunosuppressive environment that helps tumors evade immune attacks. Tumor-infiltrating immune cells include multiple types such as regulatory T cells, $CD8^+$ T cells, macrophages and dendritic cells (DCs). SREBPs significantly enhance the immunosuppressive function of intratumoral regulatory T (Treg) cells, facilitating tumor immune escape through activation of two lipid metabolic pathways: FA synthesis and the MVA pathway. Specifically, the FASN-mediated FA synthesis pathway promotes the functional maturation of intratumoral Treg cells. Simultaneously, protein geranylgeranylation mediated by MVA metabolism upregulates PD-1 gene expression in Treg cells. PD-1 inhibits the PI3K signaling pathway, reducing IFN-γ expression in Treg cells, thereby sustaining their immunosuppressive activity. Notably, blocking the SREBP pathway in Treg cells not only impaired their immunosuppressive function but also enhanced the sensitivity to anti-PD-1 therapy in mice, strengthening the antitumor effect. Conversely, SREBPs exert a dual regulatory role on $CD8^+$ T cells, they can inhibit antitumor activity while promoting the function of specific $CD8^+$ T cell subsets (152). In HCC, regions with high SREBP1 expression are often characterized by low T cell infiltration. SREBP1 drives lipid metabolic reprogramming in tumor cells to form a physical immune barrier, impeding the migration of $CD8^+$ T cells to the tumor core (153). Whereas SREBP2 is crucial for the formation of tissue-resident memory $CD8^+$ T cells (TRM cells) within the TME. The MVA-cholesterol synthesis pathway regulated by SREBP2 generates substrates for coenzyme Q (CoQ) biosynthesis. The CoQ ensures mitochondrial respiration in $CD8^+$ T cells, which is indispensable for the metabolic homeostasis and accumulation of TRM cells. This process further enhances the tumor-controlling capacity of TRM cells and promotes the accumulation of tumor-infiltrating lymphocytes. SREBP2 can induce the differentiation of DCs into an immune-tolerant phenotype, impairing their antitumor immune-mediated functions. Lactic acid produced by melanoma activates SREBP2 in DCs within the TME, driving their differentiation into mature regulatory DCs (mRegDCs). These mRegDCs not only inhibit the antigen cross-presentation process but also promote the differentiation of T helper 2 cells and Treg cells, thereby suppressing the antitumor immune response. Notably, specific silencing or pharmacological inhibition of SREBP2 in DCs can enhance $CD8^+$ T cell activation and effectively inhibit melanoma progression (154).

4. Targeting the SREBP pathway: From laboratory to clinical practice

Direct inhibitors. Direct inhibitors targeting the SREBP pathway, notably Fatostatin, have exhibited multifaceted mechanisms of action in preclinical research. They can be primarily categorized into two types: Small-molecule inhibitors and novel peptide inhibitors. These agents block SREBP pathway activity through distinct mechanisms and demonstrate promising antitumor effects as well as therapeutic benefits for metabolic disorders in preclinical studies. The characteristics of the aforementioned direct inhibitors are summarized in Table I. As shown in the table, existing direct inhibitors are primarily divided into two categories: Small-molecular compounds (Fatostatin, PF-429242 and Betulin) and novel peptide inhibitors (Insig1/2 Loop1 peptide). The mechanisms of action of small-molecule inhibitors differ in their specific targets: Fatostatin blocks the export of the SREBP/SCAP complex from the ER by binding to SCAP; PF-429242, as an S1P protease inhibitor, blocks SREBP activation at the cleavage step; Betulin, a natural product, similarly interferes with SCAP/SREBP trafficking. For the peptide inhibitors, Insig1/2 Loop1 peptide specifically blocks the AKT-driven non-canonical SREBP activation pathway in tumors by competitively binding to phosphorylated PCK1, while having minimal impact on normal steroid feedback regulation. The experimental models, effective concentrations and primary effects of each inhibitor are listed in Table I. Overall, while traditional small-molecule inhibitors demonstrate clear *in vitro* activity, they suffer from issues of tissue selectivity and off-target toxicity; peptide inhibitors exhibit advantages in tumor specificity when delivered via nanocarrier systems, but their drug-like properties still require further optimization. These data provide an important reference for the subsequent selection and development of clinical candidate molecules.

The small-molecule inhibitor, Fatostatin, directly binds to SCAP, blocking the transport of the SREBP/SCAP complex from the ER to the Golgi apparatus. This inhibits SREBP cleavage and activation, reduces expression of key enzymes involved in lipid and cholesterol synthesis, and disrupts lipid supply to tumor cells (17). Moreover, it not only disrupts lipid metabolism by inhibiting the SREBP pathway but also possesses independent antimitotic activity. By inhibiting tubulin polymerization, it arrests the cell cycle at the G2/M phase, directly eliminating proliferative tumor cells. This dual targeting of metabolism and cell cycle may be particularly beneficial for aggressive tumors with high lipid metabolism and proliferation, such as glioblastoma (155). In glioblastoma research, Fatostatin exerted a dose-dependent inhibitory effect on the viability of U87 and U251 cells, with IC_{50} values of 21.38 and 19.44 μM, respectively. It also reduced the number of cell colonies and impairs cell proliferation capacity. Additionally, p28-functionalized PLGA nanoparticles designed by researchers to load Fatostatin can effectively cross the blood-brain barrier and target tumor sites (156). In BC cell experiments, treatment with 5 μM Fatostatin for 48 h inhibited the growth of ER^+ MCF-7 and T47D cells, inducing cell cycle arrest and apoptosis. However, it had no significant effect on the proliferation of ER^- BT20 and MDA-MB-231 cells (157). In metabolic disease models, 4-week Fatostatin treatment in C57BL/6J mice improved oral glucose tolerance, reduced body weight, liver weight, blood lipid, and blood glucose levels, and delayed the progression of metabolic dysfunction-associated steatotic liver disease (158). PF-429242 is a reversible competitive inhibitor of S1P. It blocks the interaction between SCAP

and INSIG proteins, thereby retaining SREBPs in the ER and ultimately inhibiting lipid biosynthesis (159). It is often used as a control inhibitor for SREBP activity in research. Both compounds potently inhibit cell proliferation, but PF-429242 lacks the unique antimitotic activity inherent to Fatostatin. Wang *et al* (18) demonstrated that in renal cancer cells, PF-429242 not only potently inhibited cell proliferation but also suppressed cell migration and invasion, while inducing renal cancer cell apoptosis. The study confirmed that both shRNA-mediated S1P silencing and CRISPR/Cas9-mediated S1P knockout effectively inhibit renal cancer cell proliferation and activate apoptosis. Corresponding animal experiments also revealed that intratumoral injection of S1P shRNA lentivirus significantly suppressed the growth of renal cancer cell xenografts in mice. Betulin, a natural pentacyclic triterpenoid compound, exerts its core mechanism of inhibiting the SREBP pathway by targeting a key step in SREBP activation, which is blocking the translocation of the SREBP/SCAP complex from the ER to the Golgi apparatus. This further inhibits the proteolytic maturation and nuclear translocation of SREBPs, ultimately downregulating the expression of downstream genes related to lipid synthesis (160). *In vitro* experiments on lung cancer (LC) A549 cells demonstrated that betulin exerted a dose-dependent inhibitory effect on cell proliferation and reduced intracellular cholesterol and triglyceride levels (161). In a mouse xenograft model of LC, betulin administration significantly reduced tumor volume. As a natural extract, it exhibited favorable biocompatibility in experiments with minimal impact on the normal physiological functions of mice, providing insights for the subsequent development of low-toxicity SREBP-targeted drugs (162).

The novel peptide inhibitor, Insig1/2 Loop1 is a peptide inhibitor that mimics the amino acid sequence of the first loop region of the ER transmembrane protein Insig1/2. It specifically binds to the AKT-phosphorylated PCK1 protein, blocking PCK1-Insig1/2 interaction, which inhibits phosphorylation at key Insig1/2 sites, ultimately preventing SREBP1/2 nuclear translocation and transcriptional activity. Consequently, it downregulates lipid synthesis-related gene expression and suppresses tumor cell proliferation (26). Traditional small-molecule inhibitors face challenges, while Insig1/2 loop-1 short peptides represent a novel strategy. Utilizing lipid nanoparticles (LNPs) for targeted delivery, they overcome issues of peptide drug susceptibility to degradation and low tissue enrichment. Active tumor targeting via cRGD peptides, achieve highly effective, low-toxicity treatment. Luo *et al* (163) confirmed that targeting the upstream node PCK1-Insig enables precise intervention in the aberrant non-canonical activation pathway in tumors. This approach circumvents interference with normal sterol regulation, theoretically offering higher safety. Researchers encapsulated this peptide in engineered LNPs and modified them with the cell-penetrating peptide TAT and the tumor-targeting peptide cRGD. Compared with the free peptide, the resulting formulation exhibited an ~9-fold increase in plasma half-life and a 15.1-fold enhancement in the area under the concentration-time curve. It was also retained at the tumor site for 48 h. In a mouse HCC model, this formulation alone significantly inhibited tumor growth. When combined with lenvatinib, it enhanced the antitumor effect and prolonged the survival of tumor-bearing mice. Moreover, its combination with semaglutide exerted a synergistic antitumor effect in a high-fat diet-induced HCC mouse model, completely blocking lipid supply to the tumor cells. Notably, the formulation showed no obvious toxicity to the major organs of mice.

The development of direct inhibitors targeting the SREBP pathway has advanced from early broad-spectrum small molecules to highly selective drugs based on disease-specific mechanisms. Traditional small molecules, such as betulin, fatostatin, and PF-429242, interfere with the canonical SREBP pathway by inhibiting nuclear transcriptional activity, blocking SCAP translocation, or suppressing S1P processing, respectively. However, their tissue selectivity and off-target effects remain major obstacles to clinical translation. By contrast, the novel Insig1/2 loop 1 short peptide represents a more sophisticated strategy: By competitively binding to phosphorylated PCK1, a tumor-specific activation node, it precisely blocks oncogenic signal-driven non-canonical SREBP activation. Although its peptide nature relies on advanced delivery systems, the concept of 'precisely intervening with aberrant signals while preserving normal feedback' paves a new direction for the development of safer and more effective metabolic-antitumor therapies.

Upstream pathway inhibitors. The upstream pathways of SREBPs include key regulatory nodes such as the PI3K-AKT pathway and mTORC1 pathway. Aberrant activation of these pathways drives SREBP activation, thereby promoting lipid synthesis and tumor progression. Corresponding targeted inhibitors can indirectly inhibit SREBP activity by blocking upstream signal transduction. The PI3K-AKT pathway regulates the translocation and activation of SREBPs. As a classic PI3K-specific inhibitor, LY294002 targets PI3K, an upstream activator of AKT. LY294002 blocks PI3K-mediated AKT activation, thereby disrupting the translocation of SREBP's cochaperone SCAP from the ER to the Golgi apparatus. Ultimately, it inhibits the processing and maturation of SREBP-1c and SREBP-2, downregulates the expression of their downstream genes related to cholesterol and FA synthesis, and reduces lipid synthesis in tumor cells (164). In HCC, LY294002 blocked the AKT/mTOR pathway, thereby inhibiting SREBP1 activity and lipogenesis (165). In *in vitro* experiments on human ccRCC 786-O cells, treatment with LY294002 for 48 h suppressed the mRNA expression of PI3K, Akt and mTOR in a concentration-dependent manner. This indicated that LY294002 can reduce the activation level of SREBP [that is, decreased nuclear SREBP (n-SREBP)] by inhibiting this core pathway in ccRCC cells, demonstrating its inhibitory effect on the upstream pathways of SREBP (166). Du *et al* (164) further demonstrated that LY294002 significantly inhibited statin-induced SREBP-2 processing and activation in 13A/PS cell experiments. Additionally, it suppressed IGF-1-triggered SREBP activation, thereby reducing intracellular synthesis of cholesterol and FA. Collectively, these findings highlight LY294002 effective blocking effect on the upstream pathways of SREBP. AKT Inhibitors, AKT can phosphorylate PCK1 to endow it with protein kinase function, which in turn phosphorylates Insig1/2. This phosphorylation impairs the cholesterol-binding capacity of Insig1/2, releasing the SCAP-SREBP complex to promote SREBP activation. AKT

Table I. Mechanism of action and characteristic comparison of fatostatin, PF-429242 and Insig1/2 Loop 1 short peptide.

Characteristic Dimension	Fatostatin	PF-429242	Insig1/2 Loop 1 Short Peptide
Category	Synthetic small molecule	Synthetic small molecule	Engineered polypeptide
Primary target	SCAP protein	Site-1 protease	Phosphorylated PCK1
Mechanism stage	Upstream of the pathway (endoplasmic reticulum membrane)	Midstream of the pathway (Golgi apparatus)	Upstream of the pathway, tumor-specific non-canonical activation axis
Mechanism of action	Binds to SCAP and blocks the translocation of SREBP-SCAP complex to the Golgi apparatus	Inhibits S1P protease activity and blocks the cleavage and processing of SREBP precursor	Competitively binds to phosphorylated PCK1 in tumors, prevents its interaction with Insig1/2, and thus restores the anchoring of SREBP by Insig
Inhibition mode	Prevents SREBP activation (blocks both sterol-dependent and sterol-independent pathways)	Prevents SREBP activation (mainly affects the sterol-dependent pathway)	Selectively blocks the PCK1-Insig axis-mediated sterol-independent activation (for example, AKT signaling-driven activation in tumors)
Key characteristics/ advantages	Well-defined mechanism; inhibits both SREBP-1 and SREBP-2 simultaneously; possesses independent anti-mitotic activity	Well-defined mechanism; can be used as a tool compound for investigating S1P function	High specificity and affinity; theoretically exerts minimal interference with normal sterol regulation, with higher potential safety
Main potential limitations	May exhibit SCAP-independent off-target effects; its anti-mitotic activity may induce additional cytotoxicity	S1P has other critical substrates such as ATF6; its inhibition may trigger extensive cellular stress responses	As a polypeptide, it requires nano-delivery systems (for example, lipid nanoparticles) to address issues regarding *in vivo* stability, tissue targeting, and intracellular delivery
Representative preclinical studies	Prostate cancer, glioblastoma, and fatty liver disease models	Hepatitis C virus replication, fatty liver disease, and renal cell carcinoma models	Hepatocellular carcinoma mouse models; exhibits synergistic antitumor efficacy when combined with lenvatinib and other agents

SREBP, sterol regulatory element-binding proteins; PCK1, phosphoenolpyruvate carboxykinase 1; SCAP, SREBP cleavage-activating protein; Insig, insulin-induced gene protein.

inhibitors can suppress the kinase activity of AKT, preventing the phosphorylation of PCK1 and subsequent phosphorylation of Insig1/2. This blocks the aberrant activation of SREBP at the source, reducing tumor lipid synthesis. Additionally, in triple-negative BC (TNBC) (167), AKT inhibitors suppressed its regulation of SREBP-2, preventing tumor cells from surviving through cholesterol synthesis compensation. It has been revealed that when AKT inhibitors are combined with statins, they can inhibit the SREBP-related cholesterol homeostasis pathway, leading to GGPP depletion and impaired protein geranylgeranylation in tumor cells, ultimately inducing cell death (167). The two agents exhibited a synergistic lethal effect, providing a basis for combination therapy targeting the upstream pathways of SREBP. The mTORC1 serves as a critical upstream regulatory node for SREBP. Its sustained activation maintains SREBP-1 activity, promoting lipid synthesis in tumor cells to resist ferroptosis. As a mTORC1-specific inhibitor, CCI-779 directly reduces mature SREBP-1 levels, suppresses expression of its downstream target gene SCD1, and decreases mono-unsaturated FA synthesis. This approach disrupts tumor cell resistance to ferroptosis while simultaneously severing the mTORC1-SREBP1-mediated lipogenesis pathway (168). In cancer cells harboring mutations in the PI3K-AKT-mTOR pathway, CCI-779 treatment can effectively restore the sensitivity of cancer cells to the ferroptosis inducer RSL3 and reduce the level of mature SREBP1. In animal models, the combination of mTORC1 inhibitors and ferroptosis inducers achieved nearly complete tumor regression, an effect

dependent on the inhibition of the SREBP1 pathway (134). These pathways regulate numerous cellular processes, with SREBP inhibition being one of their effects. They serve as key nodes connecting cell growth signals and metabolic reprogramming and have been extensively studied in various models of cancers and metabolic diseases.

Downstream key enzyme inhibitors. In addition to upstream pathway inhibitors, inhibitors targeting key downstream enzymes in SREBP-driven malignant tumor progression have also demonstrated significant therapeutic potential. Key enzymes in the FA synthesis pathway, such as ACC and FASN, are important downstream targets of SREBPs. As a rate-limiting enzyme in FA synthesis, ACC catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, providing substrates for FA synthesis. ACC inhibitors (for example, ND-646) suppress ACC activity to reduce malonyl-CoA production, thereby blocking FA synthesis (169). In various cancer cell experiments, ACC inhibitors significantly reduced the level of FA synthesis in tumor cells, inhibited tumor cell proliferation, and induced cell apoptosis. For instance, in non-small cell LC cells, treatment with ACC inhibitors downregulated the expression of genes related to intracellular FA synthesis, resulting in significant inhibition of cell proliferation. Moreover, when combined with chemotherapeutic drugs, the antitumor effect was enhanced (170). In HCC, ACC inhibitors suppressed FA synthesis in HepG2 cells, reduced propionyl-CoA and FA synthesis in rat livers, inhibited tumor proliferation, and enhanced survival rates in tumor-bearing rats when used alone or in combination with the multi-kinase inhibitor sorafenib (169). In summary, ACC inhibitors represented by ND-646 can effectively disrupt the essential lipid supply for rapid tumor cell proliferation by specifically targeting the rate-limiting enzyme in the first step of FA synthesis. They demonstrated promising antitumor potential in preclinical studies. This strategy provides a significant direction for developing novel therapies targeting metabolic vulnerabilities in tumors.

FASN inhibitors, FASN is a key multifunctional enzyme in the FA synthesis pathway that catalyzes the synthesis of long-chain FAs from malonyl-CoA and acetyl-CoA. FASN is highly expressed in various tumor tissues and is closely associated with malignant tumor progression and poor prognosis. FASN inhibitors (for example, C75) affect tumor cell function at three levels by reducing FA synthesis: i) Membrane structure disruption: Decreasing the phospholipid content of cell membranes and inhibiting tumor cell migration and invasion (171); ii) Energy deprivation: Blocking the supply of FAs as energy substrates and suppressing mitochondrial OXPHOS (172); iii) signaling pathway interference: Reducing the production of lipid-derived signaling molecules (for example, prostaglandins and phosphatidylinositol) and inhibiting oncogenic pathways such as NF-κB and Wnt (173,174). Chen *et al* (175) demonstrated that in addition to inhibiting cytoplasmic FASN, C75 can also bind to HsmtKAS, a key enzyme in the mitochondrial FA synthesis pathway. This action reduces lipoic acid production, impairs mitochondrial function, and leads to accumulation of ROS and decreased cell viability. Impaired mitochondrial function directly cuts off an important energy supply pathway for tumor cells, while also affecting lipid synthesis and indirectly disrupting the integrity of the tumor cell membrane. In TNBC experiments, C75 inhibited FASN activity to downregulate the expression of downstream target genes in the SREBP1 pathway, thereby reducing lipid synthesis. Concurrently, it suppressed tumor cell glycolysis and glutaminolysis, achieving 'multi-metabolic pathway blockage' (176).

In addition, key enzymes in the cholesterol synthesis pathway, such as HMGCR, are also important downstream targets of SREBPs. As a rate-limiting enzyme in the cholesterol synthesis pathway, HMGCR catalyzes the conversion of HMG-CoA to mevalonic acid, a crucial step in cholesterol synthesis. Statins, including simvastatin and atorvastatin are common HMGCR inhibitors (177). In tumor therapy, statins can reduce intracellular cholesterol levels in tumor cells and affect cell membrane fluidity and function (178), and also regulate tumor cell metabolism and proliferation by modulating the SREBP signaling pathway (143). Studies have shown that statins exhibited antitumor effects in various tumors, such as PC, BC and colorectal cancer (CRC). They can inhibit tumor cell proliferation, induce cell apoptosis, suppress tumor metastasis, and enhance therapeutic efficacy when combined with other antitumor drugs (179-181). Roy *et al* (182) further confirmed that when statins are combined with apalutamide for the treatment of advanced PC, they prolonged patients' overall survival. The statins inhibit tumor cell proliferation by regulating the androgen receptor signaling pathway. In addition, they interfere with the structure of membrane lipid rafts in tumor cells, affecting cancer cell signal transduction and forming a synergistic anticancer effect with apalutamide. It has been shown that long-term treatment with BRAF inhibitors led to epigenetic silencing of PGC-1α in melanoma cells, thereby forming a highly invasive drug-resistant subpopulation (183). As HMGCR inhibitors, statins can specifically target this subpopulation: The suppression of PGC-1α reduces the expression of RAB6B and RAB27A. Statins decrease the prenylation levels of these two RAB proteins, reducing their membrane association, leading to disruption of integrin localization and downstream signals required for growth, and ultimately inhibit the proliferation of drug-resistant melanoma cells. In addition, statins can precisely block the MVA pathway, disrupt cholesterol homeostasis in p140Cap BC cells, impair cell membrane fluidity, and interfere with lipid raft-related signal transduction, ultimately significantly reducing the survival rate of this type of BC cell. Whether used alone or in combination with chemotherapeutic drugs, statins decreased the survival rate of p140Cap BC cells (184) These downstream key enzyme inhibitors directly act on critical enzymes in the metabolic pathways regulated by SREBPs, precisely interfering with the metabolic processes of tumor cells, and providing new strategies and directions for tumor therapy.

Combination therapy strategy. Targeting the SREBP pathway reshapes tumor lipid metabolism, improves the TME, and alleviates immunosuppression. It forms multi-dimensional synergy with chemotherapy, targeted therapy and immune checkpoint inhibitors (ICIs), significantly enhancing antitumor efficacy and overcoming drug resistance. The main core mechanisms are: i) Metabolic reprogramming sensitization: Inhibiting SREBP reduces *de novo* synthesis of

FAs/cholesterol, decreases membrane fluidity and drug efflux, and increases the accumulation of chemotherapeutic/targeted drugs. Collectively it impairs tumor energy reserves and offsets drug resistance-related metabolic compensation (for example, PI3K/AKT/mTOR-driven lipid synthesis bypass) (185); ii) TME immune remodeling: Downregulating tumor PD-L1 and CD47, enhances $CD8^+$T cell infiltration and cytotoxicity; inhibits SREBP-dependent functions and PD-1 expression of intratumoral Tregs, reducing immunosuppression; promotes macrophage M1 polarization and decreases M2-type pro-tumor markers, enhancing antigen presentation (186).

Combination with chemotherapy [for example, SREBP inhibitors (Fatostatin/FGH10019) + docetaxel] can increase the proportion of membrane unsaturated lipids, enhance membrane permeability and drug accumulation; inhibit SREBP downstream targets HMGCS1/IDI1, and promote PARP cleavage and apoptosis. In PC3 xenograft tumors, the tumor inhibition rate of the combination group reached 78%, which was 40% higher than that of the monotherapy group; the accumulation of docetaxel in tumor tissues increased by 2.1-fold, the proportion of membrane unsaturated FAs increased by 65%, the level of cPARP cleavage increased by 3.5 times, and the proportion of apoptotic cells reached 45% (185). SREBP inhibitor (Pen-H) + 5-fluorouracil (5-Fu) inhibits SREBP1-mediated lipogenesis, blocks tumor metabolic compensation, and enhances DNA damage and cell cycle arrest. In a gastric cancer model, compared with monotherapy, the combined treatment of Pen-H and 5-Fu exhibited a stronger inhibitory effect on cell proliferation and tumor growth (185). SREBP1 Inhibitor + Paclitaxel/Carboplatin: Obesity upregulates SREBP1, which alters the TME and induces chemoresistance; inhibiting SREBP1 can reverse this process and restore chemosensitivity. After treatment with standard-of-care chemotherapy combined with an SREBP1 processing inhibitor, tumor recurrence is significantly reduced, and the peritoneal immune landscape is also altered (187). The combination of gemcitabine (GEM) and nab-paclitaxel (nab-PTX) can inhibit the proliferation and *de novo* lipogenesis of pancreatic cancer cells. The specific mechanism is that the combination of GEM and nab-PTX induces ATP depletion in pancreatic cancer cells and activates AMPK, which in turn inhibits the expression and nuclear translocation of SREBP1, ultimately suppressing *de novo* lipogenesis in pancreatic cancer cells (188). In combination with targeted therapy, SREBP peptide inhibitor + lenvatinib blocks the PCK1-Insig1/2 interaction to inhibit SREBP activation, cuts off the alternative lipid energy source of tumors, and overcomes anti-angiogenic resistance. In a HCC model, the tumor volume of the combination group was reduced by 35% compared with the monotherapy group, and the survival period was prolonged by 30% (163). SREBP inhibitor + PI3K/AKT/mTOR inhibitor induce dual inhibition of the upstream activation pathway and downstream metabolism of SREBP, blocking the positive feedback loop of 'PI3K activation → SREBP nuclear translocation → lipid synthesis'. In various solid tumor models, the combination overcomes monotherapy resistance and synergistically inhibits proliferation and metastasis. In a melanoma model, the tumor growth inhibition rate reached 70% (monotherapy <35%), and the Akt-SREBP positive feedback loop was blocked (31). In combination with ICIs, regorafenib + ICI: Regorafenib reverses immunosuppression and enhances ICI efficacy by regulating the IFN-γ/NSDHL/SREBP1/TGF-β1 axis. Regorafenib inhibits SREBP1 through restoring NSDHL, thereby reducing the production of the immunosuppressive factor TGF-β1, decreasing Treg infiltration, and improving the tumor immune microenvironment (189). Targeting the SREBP pathway achieves significant synergistic enhancement of the efficacy of chemotherapy, targeted therapy and ICIs through triple coordination of metabolism, immunity and signaling pathways, with particularly prominent potential in tumors with active lipid metabolism and immunosuppressive phenotypes. Future clinical trials are needed to further verify the safety and efficacy of combination regimens and optimize biomarker-guided personalized treatment strategies.

5. Challenges and future outlook

Despite the great potential of SREBPs as anticancer targets, translating SREBP-targeted strategies into clinical practice faces substantial challenges, numerous of which are rooted in the complex, context-dependent biology of SREBPs and limitations of the current tools. The major hurdles, controversies and contradictory findings in the field are discussed below, and specific recommendations for future research are provided.

Context-dependent and paradoxical functions of SREBPs across cancer types. A critical and nuanced aspect of lipid reprogramming is that while SREBP activity overwhelmingly drives tumor progression, its continuous hyperactivation can create context-dependent vulnerabilities under specific metabolic stresses. In most malignancies, including HCC, BC, ccRCC, PC, CRC and hematological malignancies, SREBP1 and SREBP2 are consistently recognized as oncogenic drivers that promote lipogenesis, proliferation, invasion and drug resistance. However, emerging evidence suggests that under certain extreme metabolic contexts, aberrant SREBP signaling may become detrimental for cancer cell survival (190,191). Mechanistically, this context-dependency may arise from: i) The dominant SREBP isoform and downstream lipid outputs (SREBP1-associated fatty-acid programs vs. SREBP2-linked cholesterol/MVA pathways); ii) tissue-specific metabolic crosstalk with other pathways such as p53 or Wnt signaling; iii) harsh metabolic microenvironments including nutrient deprivation, severe hypoxia, or lipid-induced ER stress (lipotoxicity) (121); and iv) differences in cellular stress responses, such as altered sensitivity to ferroptosis driven by polyunsaturated FA accumulation (192). This complexity means that while SREBPs are potent oncogenic drivers, targeting them requires an intricate understanding of the tumor's metabolic state, as their hyperactivation might render certain cancer cells exquisitely vulnerable to specific metabolic or oxidative stressors. Future studies must clarify these context-specific metabolic trade-offs before broad clinical application.

Major limitations of current SREBP-targeting strategies. Existing therapeutic approaches targeting SREBPs suffer from multiple critical limitations that impede clinical translation: i) Lack of tumor specificity and off-target toxicities. SREBPs are essential for physiological lipid homeostasis in liver, adipose tissue and intestinal cells; therefore systemic

inhibition causes hepatotoxicity, hyperlipidemia, metabolic disorders, or intestinal dysfunction, which severely limits safe dosing; ii) poor druggability of SREBP TFs, SREBPs are conventionally considered 'undruggable'. Thus, most current agents instead target SCAP, S1P, or downstream enzymes, which only indirectly block SREBP activity and often have off-target effects; iii) compensatory metabolic resistance. Tumors frequently activate bypass pathways such as enhanced lipid uptake, FA oxidation, or autophagy to resist SREBP inhibition, leading to therapeutic failure; iv) variable efficacy across preclinical models. Numerous SREBP inhibitors showed robust effects in cell culture but weak antitumor activity *in vivo*, partly due to poor pharmacokinetics, low tumor penetration and rapid metabolism (193); v) Lack of predictive biomarkers. There are still no validated clinical biomarkers to identify 'SREBP-addicted' tumors, which leads to potential treatment failure in unselected patients.

Specific recommendations for future research. The following focused research directions are proposed to overcome the aforementioned limitations and resolve contradictory evidence:

i) Precise biomarkers and functional stratification. Future studies should identify biomarkers that can predict functional dependence on the SREBP pathway. Such biomarkers may include specific genomic features, metabolomic signatures and lipidomic profiles. For example, lipidomic alterations associated with therapeutic resistance may enable selection of SREBP-dependent subgroups. Liquid biopsy approaches based on the tumor metabolic characteristics (for example, circulating cell-free DNA methylation profiling and lipidomics) may further support non-invasive patient stratification and response monitoring (194,195).

ii) Improved tumor-selective delivery. As selectivity is central to safety, delivery systems should be optimized to enhance intratumoral exposure while reducing normal-tissue effects. Nanocarriers (for example, pH-sensitive liposomes) and targeted delivery modalities such as antibody-drug conjugates may improve drug accumulation at the tumor sites and potentially improve therapeutic index (196,197). Beyond tumor accumulation, future research should quantify tumor penetration depth, intracellular delivery efficiency and exposure-response relationships.

iii) Rational combination strategies to prevent resistance. Single-agent SREBP inhibition may trigger adaptive metabolic rewiring. Hence, combination strategies that target complementary metabolic checkpoints or transcriptional adaptation mechanisms may enhance efficacy. For instance, combining SREBP pathway inhibition with epigenetic regulators (for example, HDAC inhibitors) or metabolic checkpoint inhibitors (for example, glutaminase inhibitors) may help overcome resistance arising from network-level compensation.

iv) Synthetic lethality and vulnerability mapping. Synthetic lethality provides a route to tumor specificity. Systematic identification of gene mutations or metabolic vulnerabilities that interact with SREBP pathway inhibition may yield tumor-selective therapeutic opportunities. Such approaches should be functionally validated using patient-derived models.

v) Temporal and spatial intervention based on tumor metabolic dynamics. SREBP activity can change during tumor progression, metastasis, and in response to prior therapies. Therefore, future studies should optimize treatment timing (for example, relative to chemotherapy or immunotherapy) and evaluate how SREBP-targeting affects therapy-resistant populations or metastasis-initiating cells.

6. Conclusion

SREBPs represent a fundamental metabolic nexus that links oncogenic signaling with the aberrant lipid phenotypes essential for tumor progression. The present review has synthesized evidence demonstrating that SREBPs are not merely passive downstream effectors, but active drivers of a self-reinforcing feedback loop that sustains membrane synthesis, redox balance and immune evasion. However, the prevailing 'one-size-fits-all' approach for targeting SREBPs is increasingly challenged by emerging evidence of cancer-type-specific functions and adaptive metabolic rewiring. The transition from broad-spectrum lipid inhibition to individualized precision medicine remains the most critical frontier. Future research must prioritize the identification of robust biomarkers to define 'SREBP-addicted' tumor subtypes and explore synthetic lethal vulnerabilities that can overcome the compensatory resistance. By shifting focus toward the spatial and temporal dynamics of SREBP signaling within the TME, next-generation interventions can move beyond the preclinical stage to achieve clinical breakthroughs. Ultimately, deciphering the contextual duality of SREBP biology is crucial for unlocking its full therapeutic potential in lipid-dependent malignancies.

In summary, SREBPs are not merely lipogenic enzymes but master integrators of oncogenic signals and metabolic outputs. Their targeting, when guided by precision medicine principles, offers a viable path to improve the outcomes in patients with lipid-addicted cancers.

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Authors' contributions

QL conceptualized the study and wrote the original draft. RW wrote the original draft. ZL, YL, LW and YZ conceptualized the study and reviewed the manuscript. JY reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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