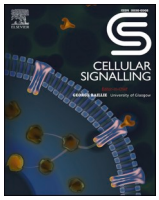
Cellular Signalling 135 (2025) 112044

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig



Targeting SREBP2 in cancer progression: Molecular mechanisms, oncogenic crosstalk, and therapeutic interventions

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ARTICLE INFO

Keywords:
Cholesterol
Sterol regulatory element binding protein 2 (SREBP2)
Cancer
Combinatorial targeted therapeutics

ABSTRACT

Cholesterol, an essential membrane component and a precursor for steroid hormones and bile acids, plays a vital role in various cellular processes. Cancer cells, in particular, exhibit a heightened demand for cholesterol to support their proliferation. This increased cholesterol requirement can be attributed to the upregulation of cholesterol biosynthesis or enhanced cholesterol uptake. Metabolic reprogramming in cancer cells allows them to sustain the energy demands associated with their aberrant growth characteristics. In normal cells, cholesterol uptake and synthesis are tightly regulated through various mechanisms within the cholesterol metabolism pathway. SREBP2 (Sterol Regulatory Element Binding Protein 2) is a critical master regulator of cholesterol homeostasis in normal cells. Dysregulation of cholesterol metabolism is intricately linked with the development of malignant phenotypes. Furthermore, emerging evidence highlights the crosstalk between SREBP2 and aberrant signaling pathways, such as PI3K/AKT/mTORC1, p53, TGF-β, c-Myc, Hippo, and FoxM1, which promote tumorigenesis. Understanding these molecular interactions between SREBP2 and signaling pathways is crucial for unraveling the mechanisms underlying cancer development. Identifying combinatorial treatment strategies targeting cholesterol metabolism holds great promise in deciphering mechanistic insights into metabolic vulnerabilities in cancer cells. Such strategies have the potential to enhance the efficacy of standard chemo/radiotherapy approaches for highly resistant cancer types. This review explores the regulation of SREBP2 in cancer and elucidates its role in dysregulated cholesterol metabolism. A detailed discussion on the implications of targeting cholesterol metabolism as a therapeutic approach for cancer treatment has also been elucidated.

1. Introduction

Cholesterol, an integral component of the cell membrane, plays a crucial role in maintaining metabolic homeostasis and membrane fluidity. Within the cell membrane, specialized microdomains called lipid rafts, enriched with cholesterol, are involved in signal transduction. These lipid rafts have been shown to play essential roles in tumor growth, apoptosis, invasion, adhesion, and migration, highlighting their significance in cancer biology. Dysregulation of cholesterol homeostasis has been implicated in the development and progression of cancer. The cholesterol biosynthesis is tightly controlled by master transcriptional factor regulators known as Sterol Regulatory Element Binding Proteins (SREBPs). These SREBPs modulate genes involved in cellular cholesterol uptake and biosynthesis. Cellular sterols act as regulators of cholesterol homeostasis and influence the localization of SREBPs to the Sterol Regulatory Element (SRE) on target genes. In cancer, the feedback inhibition mediated by sterols is often disrupted, leading to increased tumor cholesterol levels. Elevated cholesterol levels in cancer cells can modulate multiple intracellular signaling pathways and affect the production of hormones and steroids, thereby promoting cell survival [1]. One of the significant challenges in cancer treatment is the development of resistance to standard chemotherapy and

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https://doi.org/10.1016/j.cellsig.2025.112044
Received 28 April 2025; Received in revised form 17 July 2025; Accepted 31 July 2025
Available online 4 August 2025
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radiotherapy strategies, limiting their clinical efficacy and overall treatment outcomes [2]. To overcome this hurdle, the exploration of efficient chemo/radiosensitizers targeting cholesterol metabolism has gained considerable attention. Considering the intricate interrelationship between cancer and cholesterol metabolism, such approaches could prove beneficial for patients. Several preclinical studies and clinical trials have demonstrated the relevance of lipid-lowering drugs, such as statins, as potential therapeutic options in cancer treatment. This review aims to summarize and discuss the role of Sterol Regulatory Element Binding Protein 2 (SREBP2) in cholesterol metabolism, with a particular focus on its regulation in cancer. Additionally, we will explore effective drug targets that can be combined with standard chemotherapy and radiotherapy approaches for the treatment of resistant cancer types, with a specific emphasis on Head and Neck Cancer. Dysregulated activation of SREBP2 serves as a key oncogenic driver by integrating cholesterol metabolism with major cancer-promoting signaling pathways (e.g., PI3K/AKT/mTORC1, mutant p53, Hippo, c-Myc), thereby creating metabolic dependencies that support tumor survival, progression, and resistance to therapy. Targeting SREBP2 and its downstream effectors may thus represent a viable therapeutic strategy across multiple cancer types characterized by cholesterol addiction.

2. SREBP family transcription factors

The SREBP family of transcription factors plays a crucial role in regulating cholesterol and lipid metabolism and is conserved from yeast to humans. In mammals, the SREBPs are encoded by two genes, SREBF1 and SREBF2. These genes give rise to three isoforms: SREBP1a, SREBP1c, and SREBP2 [3]. In humans, SREBP1a and SREBP1c are translated from the same gene located on chromosome 17p11.2 through alternate splicing [4]. On the other hand, the SREBP2 gene is encoded on chromosome 22q13. The SREBPs exhibit diverse physiological functions. SREBP1a plays a significant role in lipid synthesis, SREBP1c is involved in fatty acid synthesis and storage, while SREBP2 primarily mediates cholesterol metabolism and regulation [5]. These SREBP isoforms serve as transcription factors that control the expression of genes involved in cholesterol and lipid homeostasis. Under conditions of cellular cholesterol depletion, SREBP2 is activated and translocate to the nucleus, where it binds to specific DNA sequences known as Sterol Regulatory Elements (SREs) present in the promoter regions of target genes. This binding leads to the transcriptional activation of genes involved in cholesterol uptake, biosynthesis, and cellular efflux, allowing the cell to restore cholesterol levels and maintain homeostasis. The intricate regulation of SREBPs ensures a delicate balance in cholesterol and lipid metabolism.

Dysregulation of SREBPs activity has been implicated in various diseases, including cancer, where it contributes to altered cholesterol metabolism and the development of malignant phenotypes. Cancer development is primarily driven by the underlying mechanisms of metabolic reprogramming, such as lipid and cholesterol biosynthesis, rather than the predominance of either SREBP1 or SREBP2, as both isoforms contribute contextually based on tumor type and microenvironmental cues. Sterol regulatory element-binding protein 1 (SREBP1), a master transcriptional regulator of lipid biosynthesis, is aberrantly activated in several cancer types, where it orchestrates metabolic reprogramming to support tumor growth, survival, and therapeutic resistance. Guan et al. (2011) [6] demonstrated that SREBP1 is a critical survival factor in liposarcoma cells, where it is activated through regulated intramembrane proteolysis (RIP). Liposarcoma cells are highly dependent on SREBP1-mediated lipogenesis, and pharmacologic disruption of SREBP1 processing effectively impairs tumor viability. These findings support the concept that SREBP1 acts as a metabolic oncogene in liposarcoma and highlight its potential as a therapeutic target in lipid-dependent tumors. In prostate cancer, SREBP1 enhances de novo fatty acid synthesis by upregulating enzymes such as Fatty acid Synthase (FASN) and Acetyl-CoA Carboxylase (ACC). This metabolic shift facilitates membrane biosynthesis and energy production essential for rapid cell proliferation and metastasis [7]. Hepatocellular carcinoma (HCC) exhibits increased SREBP1 activity mediated by neddylation via UBC12, which stabilizes the protein and promotes oncogenic lipid metabolism. This pathway is significantly upregulated in advanced HCC and correlates with poor prognosis and aggressive tumor behavior [8]. In clear cell renal cell carcinoma, transcription factor E2F1 upregulates SREBP1 expression, promoting epithelial–mesenchymal transition (EMT), lipid accumulation, and invasive properties. Elevated SREBP1 levels are associated with increased cancer cell proliferation and reduced patient survival [9]. In lung adenocarcinoma, the AKT/PRMT5/SREBP1 axis is a critical driver of tumor progression. AKT signaling activates PRMT5, which symmetrically dimethylates SREBP1, preventing its degradation and enhancing lipogenic gene expression. This contributes to tumor growth, metabolic flexibility, and resistance to targeted therapies [10]. SREBP2-mediated activation of the mevalonate pathway underlies a state of “cholesterol addiction” in cancers such as head and neck squamous cell carcinoma (HNSCC) and esophageal squamous cell carcinoma (ESCC), wherein tumor cells exhibit elevated expression of cholesterol biosynthesis genes (e.g., *HMGCR*, *SQLE*, *LDLR*) and rely on sustained cholesterol production for proliferation, survival, and therapy resistance [11,12].

2.1. Domain structure

Members of the SREBP family contain basic helix-loop-helix-leucine zipper (bHLH-Zip) domains, as described by Horton et al., (2002) [3]. The basic-helix-loop-helix superfamily of transcription factors is highly conserved and serves important functional roles. SREBPs function as homodimers and bind to specific target sites on DNA. Most bHLH proteins recognize a symmetrical E box (5’-CANNTG-3′) as a consensus hexanucleotide sequence. However, SREBP2 recognizes an asymmetrical Sterol Regulatory Element (SRE) on target genes, such as the LDL receptor, with a recognition site of 5’-ATCACCCCAC-3′ [13,14]. The domain structure of SREBPs consists of an acidic region comprising 42 residues in SREBP1a and 24 residues in SREBP1c, primarily located at the amino terminus (Fig. 1). Following this region, there is a transactivation domain rich in serine (28 %) and proline (18 %), which facilitates transactivation. Subsequently, the bHLH-Zip region, responsible for DNA binding and dimerization, is present. This is followed by a transmembrane region and finally, the regulatory COOH-terminal domain [15–17].

3. SREBP2 regulation and activation

SREBP2 is initially synthesized as a precursor molecule and is associated with the endoplasmic reticulum (ER) membrane and the outer nuclear envelope [18]. The amino-terminal part of SREBP2 contains the bHLH-Zip structure, while the carboxy-terminal region interacts with SREBP Cleavage Activating Protein (SCAP), a polytopic endoplasmic reticulum membrane protein. SREBP2 forms a heterodimeric complex with SCAP, which possesses eight transmembrane domains [5]. The polytopic membrane spanning segment of SCAP confers regulation by sterols (Fig. 2). SCAP consists of a 730-amino acid polytopic endoplasmic reticulum membranous amino domain and a 540-amino acid carboxy domain that projects into the cytosol [19]. SREBP2 regulation also involves insulin-induced genes (INSIGs). INSIG1 and INSIG2 are ER retention proteins that interact with SCAP to keep the SREBP2-SCAP complex within the ER. These proteins bind directly to oxysterols, including 22-hydroxycholesterol (22-HC), 24-HC, 25-HC, and 27-HC, enabling sterol-mediated feedback inhibition [20,21]. SREBP2 must undergo sequential proteolytic processing to become transcriptionally active. The SREBP2-SCAP complex exits the ER and is transported to the Golgi apparatus via COPII-coated vesicles. This transport is mediated by the interaction between SCAP and Sec24, a COPII complex subunit. Upon entering the Golgi apparatus, SREBP2 undergoes proteolytic

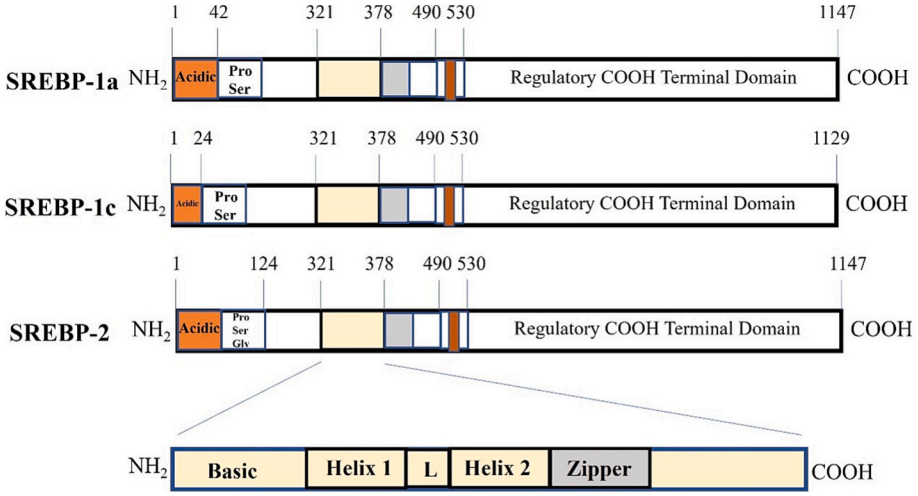

Fig. 1. Domain Structure of SREBP 1a, SREBP 1c and SREBP-2. SREBP family comprises acidic region at the N-terminus followed by the bHLH regions, transmembrane regions and regulatory C-terminus regions which have distinct structural roles.

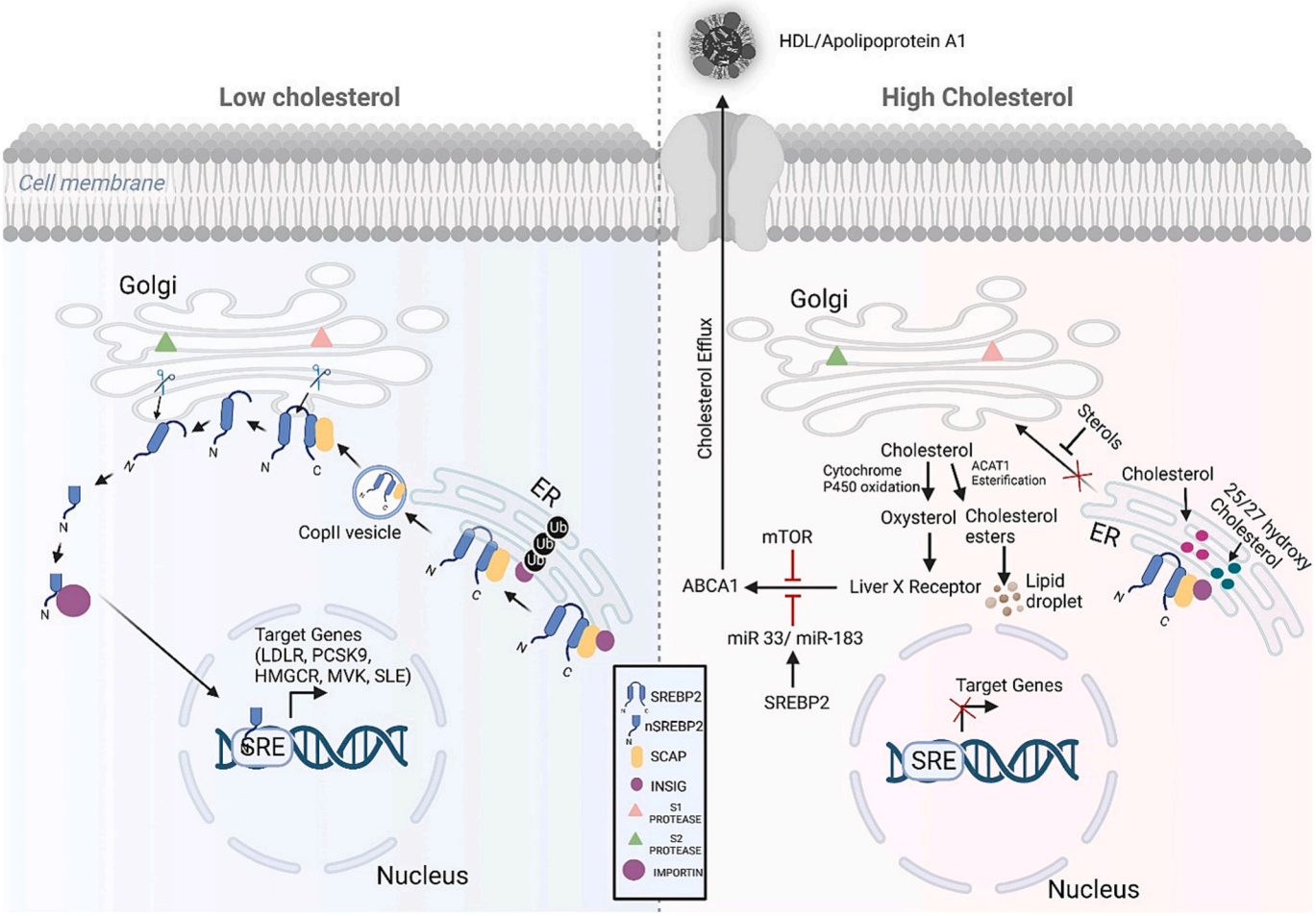

Fig. 2. SREBP2 regulation in response to sterol levels. Under conditions of low cholesterol, INSIG dissociates from SREBP2-SCAP complex and transported via COPII vesicles to the Golgi network. INSIG is ubiquitinated and degraded by the proteasome complex. In Golgi S1 proteases cleave the C terminal portion of SREBP2. The S2 protease cleaves and releases the nSREBP2 which is transported inside the nucleus via importin. Once inside the nucleus SREBP2 binds to the SRE found on the promoter region of target genes and initiates transcription of key enzymes involved in cholesterol metabolism. When cholesterol levels are high SREBP2-SCAP-INSIG complex is retained in the ER therefore transcription of target genes is inhibited. Excess cholesterol undergoes oxidation by cytochrome *p*450 to produce oxysterols which stimulates Liver X Receptors (LXR) to transcribe ATP Binding Cassette Subfamily A Member 1 (ABCA1) which promote cholesterol efflux to lipid poor Apolipoprotein A1 (APOA1) which is a major component of High-Density Lipoprotein (HDL). Simultaneously excess cholesterols are also esterified by Acetyl Co-A Acetyl Transferase 1 (ACAT1) enzyme to form cholesterol esters and subsequently lipid droplets. Further miR-33 and mTOR represses ABCA1 thereby preventing cholesterol efflux.

activation via two cleavage steps. First, Site-1 protease (S1P) cleaves the luminal loop of SREBP2 at Leu522-Ser523, releasing its N-terminal fragment [22]. This fragment is further processed by Site-2 protease (S2P), which cleaves and releases the bHLH-Zip-containing domain, allowing SREBP2 to function as a transcriptional activator. The activation process is tightly controlled by SCAP- and INSIG-mediated cholesterol and oxysterol sensing. Once activated, the mature SREBP2 fragment is transported into the nucleus by importin, which binds to its dimeric bHLH-Zip domain. Inside the nucleus, SREBP2 binds to Sterol Regulatory Elements (SREs) in the promoter regions of target genes, activating their transcription [18].

3.1. SREBP2/mevalonate pathway and cholesterol uptake

Upon activation, SREBP2 binds to the SRE (Sterol Regulatory Element) to activate the expression of enzymes involved in cholesterol metabolism, such as 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), mevalonate kinase (MVK), squalene synthase (SQS), and 24-dihydrocholesterol reductase (DHCR24). Activation of SREBP2 also increases the expression of the Low-Density Lipoprotein Receptor (LDLR) and stimulates the uptake of exogenous cholesterol (Fig. 3). In the mevalonate pathway of cholesterol biosynthesis, mediated by SREBP2, two molecules of acetyl-CoA form acetoactyl CoA through the activity of acetoacetyl thiolase. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase catalyzes the formation of HMG-CoA from acetyl-CoA and acetoacetyl CoA, which is then converted into mevalonate by HMGCR. HMGCR, a rate-limiting enzyme. High sterol levels target HMGCR for degradation by ubiquitin E3 ligase [23,24]. Mevalonate is subsequently phosphorylated to 5-phosphomevalonate by mevalonate kinase. Later, the 5-phosphomevalonate is converted into 5-pyrophosphate mevalonate by the enzyme phosphomevalonate kinase, which is further synthesized into isopentenyl pyrophosphate by the enzyme mevalonate diphosphate decarboxylase. Isopentenyl pyrophosphate is the final product of the mevalonate pathway and serves as the initial substrate for a series of reactions leading to cholesterol synthesis. Cholesterol uptake is mediated by SREBP2-mediated transcription of LDLR, which modulates the transport of cholesterol-containing low-density lipoprotein (LDL) from the bloodstream into the cell interior through clathrin-mediated endocytosis [25,26]. Once internalized, the LDL-LDLR complex enters the endosomal pathway. The acidic environment within early endosomes facilitates the dissociation of LDL from LDLR, allowing it to remain in the endosomal lumen. As endosomes mature into lysosomes, LDL is degraded by lysosomal Acid Lipase Type A (LIPA). The de-esterification of cholesterol and triglycerides is catalyzed by the LIPA hydrolase enzyme, and the end products are released from the LDL molecules [27]. Cholesterol is subsequently exported to the plasma membrane and then to the ER membrane. This export process plays a crucial role in maintaining homeostasis and regulating LDLR expression. When sufficient cholesterol is present, the transcriptional regulation of cholesterol metabolism is turned off by blocking the

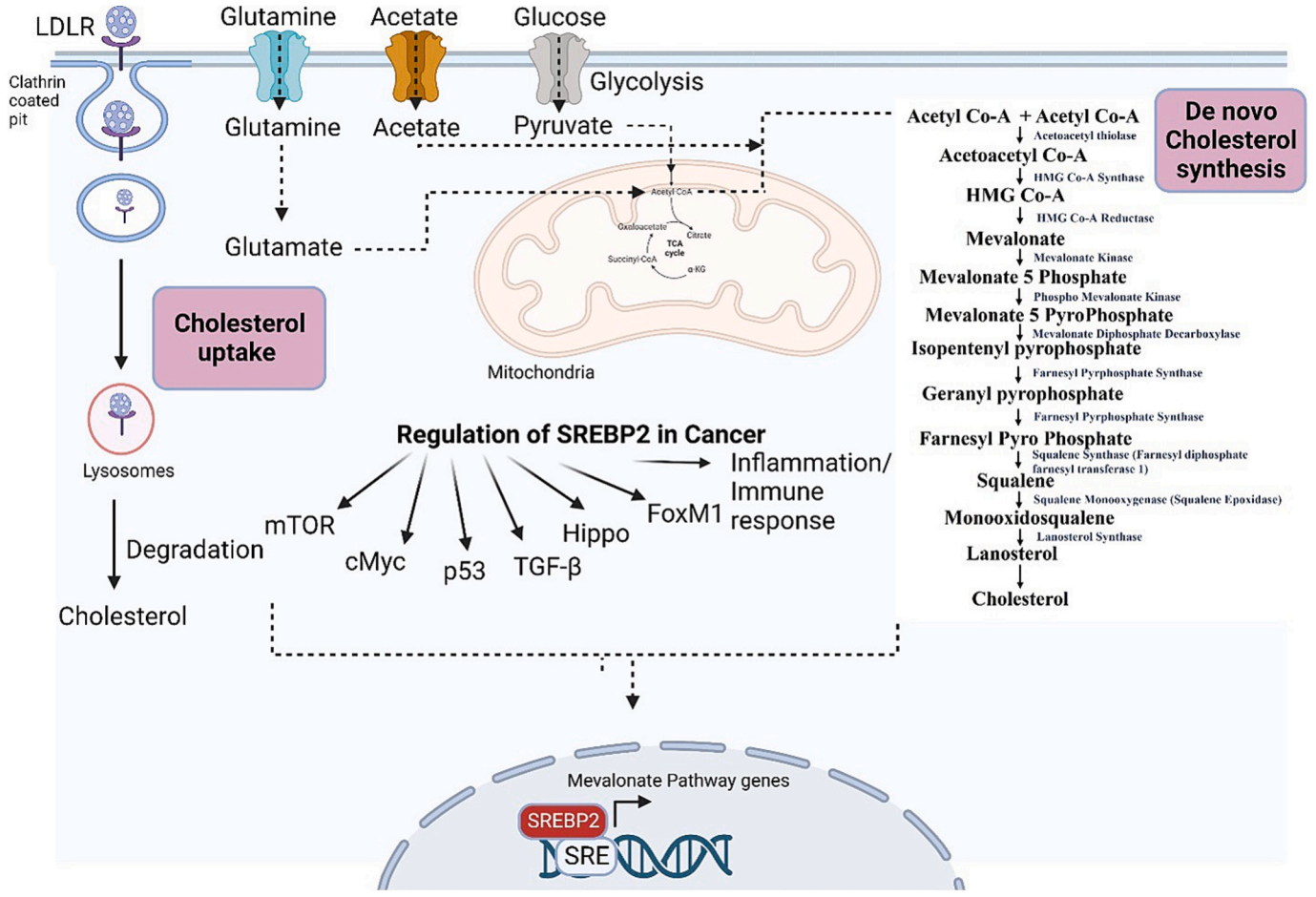

Fig. 3. SREBP2 Regulation and Activation. Acetyl Co-A which are important precursors of cholesterol synthesis is supplied by glucose by glycolysis pathway, amino acids like glutamine and glutamate and acetate. Once SREBP2 is transcriptionally active they bind to the SRE regions present on the promoters of target genes to activate their expression. Some of the SREBP2 targets include HMGCR, HMGCS, MVK, LDLR which are important enzymes in the cholesterol biosynthesis pathway. In De novo cholesterol synthesis pathway series of reactions take place to form cholesterol from acetyl Co-A mediated by several enzymes. Cholesterol uptake from blood stream takes place via LDLR (SREBP2 target) to deliver cholesterol into the cell. SREBP2 coordinates with multiple signaling mechanisms to regulate cancer progression.

activation of SREBP2, and cholesterol is esterified with fatty acids for storage as cholesterol esters in the form of lipid droplets [28]. When cholesterol levels are low, nuclear translocation of SREBP2 occurs, activating cholesterol synthesis and LDLR expression.

4. SREBP2 regulation and cancer

SREBP2 regulation occurs at multiple levels during cancer progression. One significant aspect is the aberrant expression of SREBP2 even under conditions of high sterol levels, which promotes cancer progression [29]. In addition to intrinsic regulatory mechanisms, SREBP2 activity is influenced by the tumor microenvironment, LDLR-mediated cholesterol uptake, nuclear receptors, and metabolic flux. The tumor microenvironment plays a crucial role in cancer cell metabolism. The slightly acidic extracellular pH promotes cancer cell progression and shifts the cell cycle to the G2/M phase, leading to cell proliferation and increased production of cancer cells. The acidic pH in cancer cells is a result of the anaerobic glycolytic excretion of protons and lactate through membrane proteins [30]. Under these acidic conditions, nuclear translocation of SREBP2 occurs, leading to the activation of target genes, which is an important determinant of cancer progression and survival [31]. Sterols regulate cholesterol homeostasis by influencing the de novo cholesterol synthesis pathway. The synthesis and uptake of cholesterol are also regulated at the transcriptional level through feedback inhibition of HMGCR, one of the main rate-limiting enzymes in cholesterol biosynthesis, and LDLR-mediated endocytosis of cholesterol-rich LDLs under sterol-deprived conditions [5]. Sterols synthesized by the mevalonate pathway negatively regulate HMGCR through a feedback mechanism [32,33]. Statins, commonly used cholesterol-lowering drugs, inhibit the activity of HMGCR and can inhibit cancer progression and tumor growth. Cholesterol metabolism, SREBP2, and fatty acid synthesis are interconnected. In a study conducted by Rong et al. (2017) [34], genetic deletion of SREBF2 in hepatocytes resulted in decreased expression of cholesterol biosynthesis genes, including LDLR and Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) (a protein that targets LDLR for degradation), as well as reduced SREBP1c expression and expression of all genes involved in fatty acid and triglyceride synthesis mediated by LXR activity, which is necessary for SREBF1c transcription. In the liver, cholesterol biosynthesis is also regulated by ABCA1. Excess cholesterol is exported back to lipid-poor APOA1 (a cholesterol acceptor) via ABCA1, leading to the generation of high-density lipoproteins. During excess sterol conditions, oxysterol binds to LXR, upregulating the transcription of ABCA1 expression [35]. Oxysterols are oxidation products of cholesterol mediated by the cytochrome P450 family, serving as intermediates in cholesterol catabolism [36]. Excess cholesterol can also be esterified by ACAT1 to form cholesterol esters for storage as lipid droplets [37–40]. LDLR and PCSK9, two important target genes of SREBP2, have a paradoxical role in the liver (Fig. 4). SREBP2 is involved in the expression of LDL receptor (LDLR) for cholesterol uptake. SREBP2 also stimulates the expression of PCSK9, which degrades LDLR by binding to its EGF-A domain, acting as a chaperone and directing LDLR toward intracellular degradative pathways [41–43]. PCSK9 expression is regulated by the presence or absence of sterols [44]. Another type of regulation mediated by cholesterol levels is the LXR-induced suppression of LDL uptake through the transcriptional activation of the Inducible Degrader of the LDLR (IDOL). IDOL is an E3 ubiquitin ligase that binds to the cytoplasmic domain of LDLR and targets it for degradation [45]. Apart from LXR, which belongs to the family of nuclear receptors, another class of nuclear receptor transcription factors, known as RAR-related orphan receptor gamma (RORγ), plays an important role in SREBP2-mediated cholesterol biosynthesis. Selective targeting of cancer cells by reducing their cholesterol content is important. Studies by Cai et al. (2019) [46] have shown that in triple-negative breast cancer (TNBC), inhibition of RORγ reduces tumor cholesterol content by inhibiting SREBP2 binding to target genes. SREBP2 target genes have SRE regions in their promoter regions. Studies have demonstrated that one such target of SREBP2, Isocitrate Dehydrogenase (IDH1), is dysregulated in cancer. Transcriptional activation of IDH1 promotes lipogenesis through NADPH production or reductive carboxylation, facilitating carbon flux to lipid precursors. Mutations in IDH1 result in the production of an oncometabolite, 2-hydroxyglutarate, which closely resembles α-ketoglutarate (α-KG) and promotes tumor development. Targeting the SREBP2-mediated pathway could serve as a promising approach for cancer patients [47].

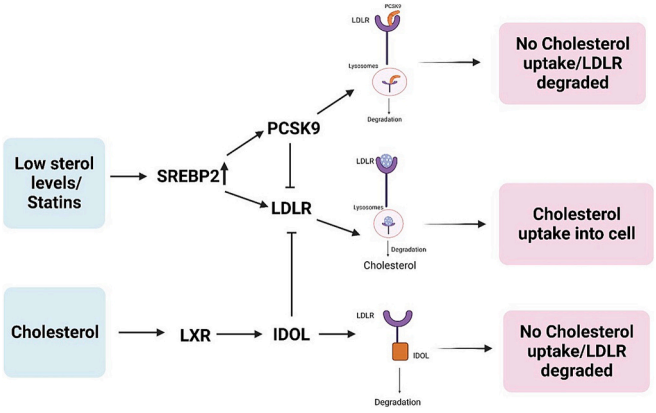

Fig. 4. Regulation of cholesterol uptake by LDLR mediated by SREBP2/Sterols. Under conditions of low sterol levels or statin mediated cholesterol lowering, SREBP2 is upregulated and induces the transcription of PCSK9 and LDLR which have opposing roles. LDLR promotes uptake of low-density lipoproteins via endocytic vesicles from bloodstream into cells wherein they are degraded by lysosomal enzymes to release cholesterol and triglycerides. PCSK9 inhibits LDLR by binding to the LDLR receptors preventing binding of LDL and target it for lysosomal degradation. LDLRs are also regulated by sterol mediated induction of LXR which leads to transcriptional activation of IDOL which bind to cytoplasmic domain of LDLR and target it for degradation.

4.1. Role of non-coding RNA in SREBP2 regulation

Non-coding RNAs play significant roles in the regulation of SREBP2 and cholesterol metabolism. MicroRNAs (miRNAs), a class of small non-coding RNAs, have been identified as key regulators of cholesterol synthesis and uptake, mediated by SREBP2. One such miRNA is miR-33a, which is located within the intronic region (intron 16) of the human SREBF2 gene. MiR-33a is involved in the regulation of cholesterol export and targets the ABCA1 gene for post-transcriptional repression. Under sterol-deprived conditions, miR-33a is transcribed to regulate cholesterol levels. Overexpression of miR-33a reduces the expression of ABCA1, thereby ameliorating LXR-mediated cholesterol efflux [48]. However, miR-33a can also enhance cholesterol efflux by elevating levels of ABCA1 [49]. The ABCA1 protein plays a critical role in maintaining cholesterol homeostasis by facilitating the export of cellular cholesterol. The role of miR-33a in cancer is paradoxical, acting as a tumor suppressor in lung, colorectal carcinoma, pancreatic cancer, and melanoma, while functioning as an oncogene in glioma [50–55]. Another miRNA, miR-183, is directly activated by SREBP2 and is found in the liver [56]. Studies with colon cancer tissues and cells have shown aberrant expression of ABCA1, with ABCA1 acting as a tumor suppressor. Overexpression of ABCA1 inhibits proliferation, while silencing ABCA1 promotes proliferation and inhibits apoptosis of colon cancer cells. miR-183 functions as an oncogene by degrading ABCA1 mRNA [57]. miR-185 and miR-342 are involved in the metabolic regulation of prostate cancer cells. They have been shown to have tumor suppressive roles and inhibit the expression of both SREBP1 and SREBP2, as well as their downstream targets, thereby reprogramming lipid and cholesterol biosynthesis in prostate cancer [58]. miR-874 acts as a tumor suppressor and has been shown to suppress the expression of SREBF2 and

phosphomevalonate kinase (PMVK) genes, leading to depletion of geranylgeranyl pyrophosphate (GGPP). This depletion activates the p53 pathway, promoting cell cycle arrest and apoptosis in breast cancer cells [59].

Apart from miRNAs, long noncoding RNAs (LncRNAs), which are longer than 200 nucleotides, have also been implicated in cancer. For example, LncRNA SNHG16 is upregulated in hepatocellular, colorectal, and ovarian cancers. It has been shown to coordinate with SREBP2 to enhance the progression of pancreatic cancer by regulating miR-195 (Fig. 5). MiR-195 is known to suppress invasion and proliferation in various cancers, including breast and pancreatic tumors [60,61]. Bioinformatic analysis has revealed that miR-195 can directly bind to SREBP2 [62]. In multiple myeloma lncRNA LINC01003 sponges miR-33a-5p by regulating PIM1 expression and promoting apoptosis [63].

5. SREBP2 and signaling pathways in cancer

SREBP2 and metabolic pathways has a pivotal role in the cancer progression and this is mediated by several regulatory networks (Fig. 6). SREBP2 mediated crosstalk with important signaling pathway and their mechanism of action is depicted in Table 1.

5.1. PI3K/AKT/mTORC1 pathway

The mammalian Target of Rapamycin (mTOR) pathway is an important mediator of cell proliferation in cancer cells and also plays a crucial role in tumor metabolism [73]. The mTOR pathway primarily regulates anabolism, energy storage, utilization, and cholesterol trafficking to lysosomes. As tumor cells require increased amounts of proteins and lipids for cellular proliferation, mTOR is aberrantly activated, playing a pivotal role in regulating metabolism [74]. Studies have reported that Mitochondrial Elongation Factor 2 (MIEF2), an important regulator of mitochondrial fission, promotes cholesterol biosynthesis by upregulating the expression of SREBP2 and its target genes, HMGCS1 and HMGCR, via activation of the AKT/mTORC1 signaling pathway in ovarian cancer cells [65]. Additionally, SREBP2 is also regulated by PI3K/AKT/mTORC1 signaling mechanisms independent of sterols. Melanomas expressing the disialylganglioside GD3 antigen induce the expression of SREBP1 and SREBP2, thereby increasing cholesterol biosynthesis. This increased expression is regulated by the PI3K/AKT/mTORC1 pathway [64]. In breast cancer, both SREBP1 and SREBP2 are activated by the PI3K/AKT/mTORC1 pathway; however, dependence on SREBP2 increases under metabolic stress conditions such as hypoxia, acidic pH, or statin treatment, which trigger compensatory cholesterol biosynthesis. Emerging studies suggest that SREBP2 may also be preferentially activated in triple-negative breast cancers (TNBC), where cholesterol metabolism becomes critical for membrane integrity and survival. Furthermore, evidence supports a **synergistic role** between SREBP1-driven fatty acid synthesis and SREBP2-mediated cholesterol biosynthesis in promoting lipid raft formation, oncogenic signaling, and therapy resistance in aggressive breast cancer subtypes.

5.2. p53 pathway

The p53 tumor suppressor gene plays a key role in regulating cancer progression by promoting cell death, cell cycle arrest, DNA repair, and more. It also has a significant role in cell metabolism, particularly in the mevalonate pathway. Research has shown that mutations in p53 can interact with nuclear SREBP2 to enhance gene transcription in the mevalonate pathway. Studies by Freed-Pastor et al. (2012) [70] have reported that missense mutations in p53 disrupt mammary acinar morphology, and tumors bearing p53 mutations rely heavily on metabolic flux through the mevalonate pathway. Inhibition of the mevalonate pathway may therefore serve as an effective target for tumors with p53 mutations. One of the p53 target genes, ABCA1, participates in exporting excess cholesterol at the plasma membrane and inhibits the conversion of SREBP2 to its mature form. Loss of ABCA1 promotes SREBP2 maturation, increasing the levels of LDLR, which mediates cholesterol uptake and is one of the target genes of SREBP2 in mouse liver [69]. The apoptosis-stimulating protein of p53 (ASPP2), an activator of p53, has been shown to promote apoptosis. ASPP2 interacts with mature SREBP2 in the nucleus and negatively regulates SREBP2 transcription along with its target genes [71]. Although preclinical studies have shown that mutant p53 enhances SREBP2 activation and mevalonate pathway upregulation, clinical validation of this axis as a stratified biomarker is still limited. Current datasets lack integrated genomic and lipidomic analyses linking p53 mutation status with SREBP2-driven therapeutic outcomes. Future studies are needed to establish the SREBP2–mutant p53 axis as a predictive marker for response to cholesterol-targeting therapies.

5.3. TGF-β pathway

The repression of SREBF2 promotes a paradoxical role in cancer

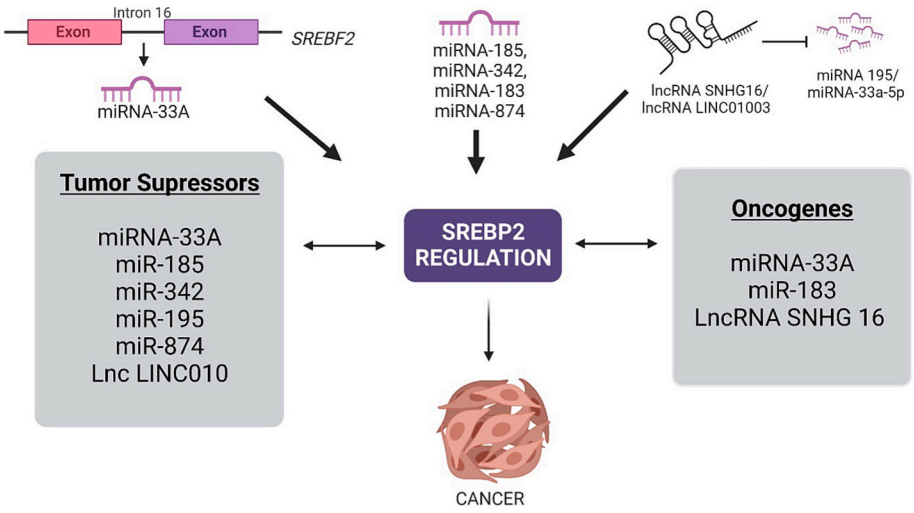

Fig. 5. Regulation of SREBP2 by noncoding RNAs in cancer. This schematic illustrates how specific microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) modulate SREBP2 expression and its associated regulatory targets. miR-33a, co-transcribed with SREBF2, represses ABCA1 post-transcriptionally, reducing cholesterol efflux. Other miRNAs (e.g., miR-183, miR-185, miR-342, miR-874) inhibit SREBP2 and downstream targets, functioning as tumor suppressors in various cancers. lncRNAs such as SNHG16 act as competing endogenous RNAs (ceRNAs), sponging miRNAs like miR-195 to relieve suppression of SREBP2.

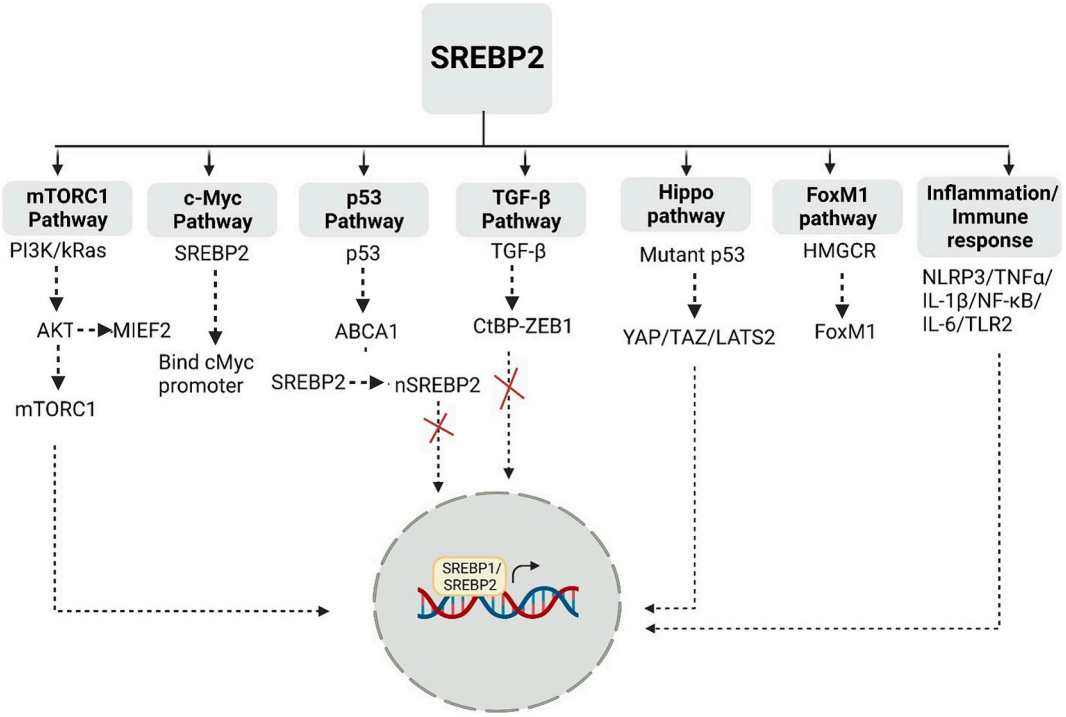

Fig. 6. Regulatory networks of SREBP2 in cancer. SREBP2 coordinate with different signaling mediators to promote tumor growth. Some of the mediators are promote cancer by aberrant activation of SREBP2 mediated transcription of target genes. While in some cases SREBP2 and its targets acts as oncogene to regulate pathways like c-Myc and FoxM1 pathway to promote cancer growth.

metastasis, stemming from the findings that the epithelial-mesenchymal transition (EMT), an important determinant of metastasis, is induced by TGF-β. The EMT-related transcription factor ZEB1 forms a complex with C-terminal binding protein (CtBP), which binds to the SREBF2 promoter and inhibits cholesterol metabolism genes such as HMGCR, FDPS, DHCR7, NPC1, and LDLR [66].

5.4. cMyc pathway

The cMyc transcription factor is aberrantly expressed in most types of cancer [75]. SREBP2 coordinates with cMyc to promote prostate cancer. It has been shown that SREBP2 interacts with the c-Myc promoter region through an SREBP2 cis-acting element in the 2′ flanking region, initiating cMyc transcription and resulting in stem cell characteristics and metastasis in prostate cancer [68]. In esophageal cancer, cMyc coordinates with SREBP2 to increase the expression of HMGCR in cancer cells [67].

5.5. Hippo pathway

The Hippo pathway plays an important role in cancer cell proliferation, with key mediators including yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) [76]. Studies have shown that aberrant SREBP2 activity leads to activation of the mevalonate pathway, resulting in the recruitment of YAP/TAZ. In breast cancer cells, this activation has been demonstrated to be induced by the oncogenic cofactor mutant p53, leading to increased expression of mevalonate pathway enzymes [77]. Furthermore, YAP associates with mature SREBP2 to enhance their transcriptional activity toward HMGCR [78]. Decreased expression of the LATS2 tumor suppressor mRNA has been correlated with increased SREBP2 target gene expression [79]. The expression of the receptor for Hyaluronan-Mediated Motility (RHAMM) is upregulated in tumor tissues. Studies have demonstrated the existence of crosstalk between the mevalonate pathway and the Hippo pathway. YAP/TEAD binds to the RHAMM promoter and promotes breast cancer migration and invasion. Simvastatin inhibits breast cancer migration by targeting YAP-activated RHAMM transcription [80].

5.6. FoxM1 pathway

The Forkhead Box M1 transcription factor (FoxM1) is highly expressed in several types of cancers, including hepatocellular carcinoma. Studies by Ogura et al. (2018) [72] have shown that FoxM1 is activated downstream of the mevalonate pathway, thus establishing a direct relationship between the mevalonate pathway and oncogenic signals.

6. Inflammation, immune response, and cholesterol homeostasis

Inflammation is a biological response of the immune system triggered against injury and infection. The molecular crosstalk between metabolic pathways and inflammation has been deciphered in multiple diseases and conditions, including cancer. Studies have shown that in proinflammatory macrophages, the activation of the NLRP3 inflammasome is promoted by the SCAP-SREBP2 complex ER to Golgi translocation. Inhibition of this translocation due to the presence of endogenous sterols suppresses NLRP3 activation [81]. The intersection of immune metabolism and cholesterol signaling via SREBP2 is increasingly recognized as a critical driver of tumor immune evasion, particularly through pathways such as NLRP3 inflammasome activation and TLR2/NF-κB signaling. This mechanistic overlap forms the rationale for ongoing trials (e.g., NCT06636734) combining statins with immune checkpoint inhibitors, as represented in Table 2, linking metabolic modulation to immunotherapy enhancement. Another study by Kusnadi et al. (2019) [82] has demonstrated that macrophage-associated TNF stimulation promotes the activation of SREBP2, which in turn binds to inflammatory and interferon response target genes, promoting inflammation. Simultaneously, type I interferon-mediated inflammation has been found to be associated with the SCAP/SREBP2 pathway [83]. TNF-

Table 1
SREBP2 and its downstream targets mediated regulatory network in cancer.

Regulatory mediators	Cancer Type	Mechanism of action
PI3K/AKT/mTORC1 pathway	Breast Cancer	Oncogenic expression of PI3K/K-Ras promote de novo lipogenesis via SREBP1 and SREBP2 activation of mTORC1 [47].
	Skin Cancer	PI3K/AKT/mTORC1 promote SREBP2 mediated metabolic reprogramming in melanoma expressing GD3 [64].
	Ovarian Cancer	MIEF2 participates in reprogramming SREBP1/SREBP2 mediated lipid metabolism via activation of AKT/mTOR signaling pathway [65].
TGF-β	Breast Cancer	TGF-β mediated CtBP-ZEB1 complex regulates cholesterol homeostasis in breast cancer by transcriptionally repressing *SREBF2* expression [66].
c-Myc	Esophageal Cancer	cMyc cooperate with SREBP2 to increase HMGCR expression [67].
	Prostate Cancer	cMyc activation promotes stem cell like features and metastasis in prostate cancer which is through SREBP2 mediated activation of cMyc and binds to 5′-flanking c-Myc promoter region [68].
p53	Liver Cancer	p53, tumor suppressor gene promote transcriptional activation of ABCA1 cholesterol transporter gene and block activation of mature SREBP2 from their precursor form [69].
	Breast Cancer	Mutant form of p53 (missense mutation) has correlation with sterol biosynthesis genes particularly mevalonate pathway in breast cancer progression [70].
	Hepatocellular Carcinoma	ASPPR, p53 activator negatively regulates SREBP2 and mevalonate pathway target genes in cancer and inhibits tumor growth [71].
FoxM1	Liver Cancer	FoxM1 has direct associated with SREBP2 mediated mevalonate pathway in hepatocellular carcinoma [72].

α and IL-1β have been shown to induce a transcriptional response mediated by NF-κB, which alters cholesterol homeostasis in endothelial cells. The NF-κB-inducible gene STARD10 is an intermediate bridge between TNF activation and SREBP2 activation [84]. The oncogene 24p3 (Neutrophil gelatinase-associated lipocalin), encoded by the LCN2 gene, has been found to modulate neutrophil activation in psoriasis. Lipocalins belong to a group of adipokines that regulate lipid metabolism and immune response. SREBP2 acts as an essential mediator of LCN2-induced keratinocyte activation by binding to the promoter region of NLRC4 [85]. Inflammatory stress induced by the administration of IL-1β and IL-6 in liver cells increases cholesterol accumulation and enhances SREBP2, LDLR, and HMGCR expression [86]. In non-alcoholic steatohepatitis (NASH), multiple factors such as inflammatory cytokine signaling (IL-1β, IL-6, TNF-α), hyperinsulinemia, and low microRNA (miR)-122 levels increase SREBP2 translocation into the nucleus. This increases LDLR and HMGCR expression, promoting LDL uptake [87].

Studies on the development of airway smooth muscle cells (ASMCs) in asthma have shown that SREBP2 activates the TLR2/NFκB/NFATc1 regulatory network and recruits TGF-β1-induced cell movement by inhibiting ABCA1 expression. Nuclear Factor activated T cell 1 (NFATc1), a member of the family of T cells, affects lymphocyte proliferation. ABCA1 controls intracellular cholesterol by promoting the efflux of free cholesterol and binding to apolipoprotein to form high-density lipoprotein (HDL) [89]. Studies have shown that disturbed flow promotes inflammation in endothelial cells, which is a crucial factor for atherosclerosis, by inducing NLRP3 inflammasome activation via SREBP2 activation [90].

7. Potential role of SREBP2 in head and neck cancers

Head and Neck Squamous Cell Carcinoma (HNSCC) is one of the most predominant cancer types, with over 850,000 people diagnosed worldwide [91]. Dysregulated metabolic reprogramming is one of the important hallmarks of HNSCC. Many of the mevalonate pathway enzymes regulated by SREBP2 are aberrant in HNSCC. It has been shown that important intermediates of the mevalonate pathway, like HMGCR, have been found upregulated in esophageal squamous cell carcinoma (ESCC) clinical samples and cell lines. Studies have demonstrated that lovastatin exhibited potent cytotoxicity and inhibited cell proliferation in ESCC [92]. It has been demonstrated that HMGCR overexpression resulted in increased cell growth and migration; however, down-regulation resulted in impaired tumorigenicity. HMGCR possibly co-ordinates with the oncogene Myc to promote cancer progression in ESCC [93]. Regulation of the mevalonate pathway in ESCC is also by SREBP2 by promoting the interaction of SREBP2 and cMyc to activate HMGCR expression [67]. Studies have demonstrated that NLRP3 inflammasome activation is promoted by the SCAP-SREBP2 complex ER to Golgi translocation [81]. Upregulation of NLRP3 was observed in biopsied HNSCC tissues, which provides a crucial role in the survival and invasiveness of HNSCC [94]. The plausible role of SREBP2 and mTOR has been demonstrated in several types of cancers [64]. In HPV (+) HNSCCs, mTOR inhibitors like rapamycin/RAD001, along with standard cisplatin or radiation therapy, have been proven beneficial [95–97]. Regulation by miR-33a has been observed in numerous HNSCC malignancies. In laryngeal cancer, miR-33a expression inhibited proliferation by down-regulating PIM1 [98]. In tongue squamous cell carcinoma, ectopic expression of miR-33a-5p reduced tumor cell proliferation and is regulated by long non-coding RNA cancer susceptibility candidate 15 [99]. In head and neck cancer, a clinical trial is assessing the impact of statins on carotid stenosis compared with placebo following radiation therapy because patients undergoing radiation treatment are at higher risk of carotid stenosis within the treated field (NCT02022293).

8. Combinatorial cancer therapeutics

Cancer treatment strategies include surgery, radiation therapy, or chemotherapy. In some cases, combinatorial therapy may prove beneficial to cancer patients. One of the important concerns governing cancer treatment is resistance. Radiotherapy is the primary treatment option for head and neck cancers. It has been observed that approximately 10–20 % of cases experience recurrence due to radiation resistance in Nasopharyngeal Cancer (NPC) [100]. Several critical determinants determine HNSCCs' response to radiation. Overexpression of EGFR and p53 somatic mutations have been associated with treatment resistance in HNSCC [101,102]. This resistance is consistent with the role of p53-EGFR interactions in DNA damage repair following exposure to radiation [102]. In the clinical trial NCT02022293, pravastatin was shown to reduce or reverse radiation-induced fibrosis and carotid artery stenosis in head and neck cancer patients, primarily through its vascular protective and anti-inflammatory effects. While the observed benefits are likely mediated through pleiotropic mechanisms independent of direct SREBP2 inhibition, the trial did not report tumor control rate or progression-free survival data. These findings suggest that statins may exert dual benefits in cancer treatment—mitigating radiation-associated toxicity while potentially enhancing tumor response through metabolic modulation, although further trials are needed to confirm direct anti-tumor efficacy. Mutant p53 also interacts with SREBP2, upregulating the mevalonate pathway, which increases oncogenic signaling [103]. Additionally, mutant EGFR increases intracellular cholesterol levels by downstream activation of SREBP2 [104]. Emerging evidence suggests that modulating ferroptosis could be a strategic approach to overcoming radiation resistance. Ferroptosis, a form of regulated cell death, occurs when redox-active iron accumulates, leading to failure in lipid peroxidation repair. The polyunsaturated fatty acid (PUFA) metabolism

Table 2
Some of the Combinatorial therapies of cholesterol metabolism/SREBP2 and its targets in cancer therapeutics.

Drugs	Cancer type	Objective	Type of study/Mechanism	Trial Outcomes
Atorvastatin	Nasopharyngeal Carcinoma (NPC)	Phase II study evaluating feasibility and safety in preventing carotid stenosis post-radiotherapy	Interventional; statin-mediated vascular protection	Pending; focuses on vascular benefit post-RT (NCT02022293)
Lovastatin + Pembrolizumab	Head and neck Cancer	Phase II study evaluating anti-tumor activity in solid tumors	Immunotherapy + statin to enhance PD-1 response via metabolic modulation	Ongoing; aims to improve checkpoint inhibitor efficacy (NCT06636734)
Lovastatin	Head and neck Cancer, Cervical cancer	Phase I trial to evaluate disease stabilization	Lipid-lowering agent affecting mevalonate pathway	Demonstrated disease stabilization in some patients [88]
Atorvastatin + Cisplatin	Head and Neck Cancer	Phase III study on reducing cisplatin-induced hearing loss	Chemoprotection via statin-mediated anti-inflammatory and endothelial effects	In progress; protective effect under investigation (NCT04915183)
Ezetimibe + Simvastatin [Vytorin]	Prostrate Cancer	Early Phase I study on growth of prostate cancer cells post-surgery	Combined cholesterol absorption and synthesis inhibition	Mechanistic focus; data pending (NCT02534376)
Atorvastatin + Ezetimibe + Evolocumab (Cholesterol Metabolism Disruption Drugs) + Folfirinox	Pancreatic Cancer	Early Phase I study to evaluate effect of cholesterol disruptors on chemo-response	Lipid-lowering triple therapy + chemotherapy	Evaluating response enhancement in advanced disease (NCT04862260)
Atorvastatin + Surgery	Prostate Cancer	Phase II trial assessing adrenal androgen suppression	Statin-mediated hormonal modulation pre-prostatectomy	Ongoing; targets hormonal axis (NCT01821404)
Rosuvastatin + Surgery	Prostate Cancer	Phase IV trial for prognosis in metastatic cancer	Androgen deprivation + statin therapy	Prognostic value being studied (NCT04776889)
Fluvastatin + Pimonidazole	Prostate Cancer	Phase II trial assessing intraprostatic tumor inhibition	Statin + hypoxia marker to assess tumor suppression	Data not yet reported (NCT01992042)
Simvastatin + Surgery	Prostate Cancer	Interventional trial on mevalonate pathway activity	Statin effect on tumor cholesterol metabolism	Ongoing; measuring molecular changes (NCT00572468)
Simvastatin + *CAF* (Cyclophosphamide, Adriamycin, and Fluorouracil)	Breast Cancer	Phase II trial to improve neoadjuvant therapy response	Statin sensitization to standard chemotherapy	Assessing margin clearance & tumor response (NCT04418089)
Simvastatin/Atorvastatin	Breast Cancer	Phase III trial on survival benefit in dyslipidemic patients	Statin impact on long-term survival	Survival data awaited (NCT03971019)
Simvastatin + Cyclophosphamide + Topotecan	Cancer (Renal cell, Neuroblastoma, etc)	Phase I trial for refractory cancers	Statin + chemotherapy in heavily pretreated patients	Safety and efficacy under evaluation (NCT02390843)
Pitavastatin + Chemotherapy	Breast Cancer	Phase II trial to test combined treatment efficacy	Lipophilic statin + standard chemotherapy	Tumor control and progression endpoints measured (NCT04705909)
Pravastatin + Idarubicin + Cytarabine	Leukemia	Phase I trial assessing chemotherapy sensitization	Statin-induced chemosensitization	Reported enhanced sensitivity in some AML patients (NCT00107523)
Zoledronic acid	Breast Cancer	Phase II trial to prevent bone marrow micrometastases	Mevalonate pathway inhibition via FDPS blockade	Ongoing; targeting dormancy/ metastasis prevention (NCT00295867)

pathway is critical in ferroptosis induction. Since PUFAs lower cholesterol levels, SREBP2 activation may increase in response to cholesterol depletion [105,106]. Promoting ferroptosis in cancer cells could be an essential strategy to counteract radiation resistance [106]. Some mevalonate pathway inhibitors have an essential role as neoadjuvant therapies for treating a wide variety of cancers in clinical trials, as depicted in Table 2. Several other targets have also been tested in preclinical studies and have proven to be beneficial. In hepatocellular carcinoma (HCC), acquired resistance to tyrosine kinase inhibitors (TKIs) such as sorafenib and lenvatinib has been linked to cancer stem cell expansion and tumor repopulation. Mechanistically, caspase 3-mediated cleavage of SREBP2 from the endoplasmic reticulum (ER) activates the sonic hedgehog signaling pathway, further driving drug resistance [107].

Statins, which inhibit the mevalonate pathway, have been explored as chemosensitizer for various cancers. Simvastatin sensitizes HCC cells to sorafenib and inhibits tumor growth [107]. Similarly, pitavastatin, a lipophilic statin, increases radiosensitivity in SQ20B radioresistant cancer cells, whereas lovastatin sensitizes lung cancer cells to radiation by inhibiting AKT and activating the AMPK pathway [108,109]. Targeting farnesyl diphosphate synthase (FDPS), a key enzyme in the mevalonate pathway, has also been shown to radiosensitize pancreatic cancer cells. FDPS overexpression is associated with radioresistance in pancreatic cancer, and its pharmacological inhibition using zoledronic acid improves radiosensitivity in pancreatic ductal adenocarcinoma (PDAC). Mechanistically, radiosensitization occurs by modulating Rac1 and Rho prenylation, impairing the DNA damage response to radiation and influencing immune modulation [110,111]. In ovarian cancer, cisplatin resistance has been linked to SREBP2 overexpression and upregulation of its target genes LDLR, FDFT1, and HMGCR in A2780-resistant cell lines [112]. In patients with HER2-positive (HER2+) breast cancer, resistance to lapatinib and trastuzumab remains a significant challenge. Studies have indicated that mevalonate pathway activation is increased in lapatinib-resistant and dual lapatinib/trastuzumab-resistant cells, suggesting that lipophilic statins and N-bisphosphonates may provide therapeutic benefits in overcoming resistance [113].

In advanced pancreatic cancer, another trial is investigating the combination of statins with chemotherapy by evaluating CA 19–9 levels, a biomarker of disease progression (NCT06241352). In breast cancer, multiple ongoing clinical trials are examining the role of statins. One trial is evaluating pitavastatin combined with conventional chemotherapy to assess tumor reduction (NCT04705909). The MASTER trial is specifically investigating the potential for statins to reduce cancer recurrence in women with early-stage breast cancer (NCT04601116). In advanced non-small-cell lung cancer (NSCLC), a trial is currently investigating the efficacy of PD-1/PD-L1 inhibitors with or without statins for tumor shrinkage (NCT05636592). In locally advanced rectal cancer, another trial evaluates the effect of rosuvastatin in combination with chemoradiation on the pathological response rate and survival (NCT02569645).

Statin use is also being explored in bladder cancer, where a trial is examining the effect of neoadjuvant treatment with simvastatin and metformin on tumor growth before surgical resection (NCT00285857).

In prostate cancer, researchers are evaluating atorvastatin and its impact on the development of castration resistance during androgen deprivation therapy (ADT) (NCT04026230). In ovarian cancer, a clinical trial is assessing the effects of simvastatin combined with carboplatin and doxorubicin on tumor progression (NCT04457089). As these trials progress, emerging data will confirm the therapeutic benefits of statin use in cancer treatment. One of the few completed studies evaluating statins for radiation-induced fibrosis in head and neck cancer patients found that pravastatin reduced or reversed fibrosis severity in 50 % of patients, as assessed by ultrasound imaging (NCT02022293). After 1 year of pravastatin treatment, a significant reduction in fibrosis thickness was observed, leading to improved patient quality of life. In addition to their direct anticancer effects, statins have been investigated for their role in reducing radiation toxicity in normal tissues. Studies have shown that statin use improves clinical outcomes in radiation-treated patients while mitigating radiation-induced damage. Research specifically examining statins for radiation-induced fibrosis has focused on prostate cancer and head and neck cancer, with promising early results. While several ongoing trials continue to explore toxicity and tumor control endpoints, the accumulated evidence suggests that statins may improve cancer therapy efficacy while reducing adverse effects [114 – 117].

Proteolysis-targeting chimeras (PROTACs) have quickly gained traction as a versatile method for degrading a wide range of oncogenic proteins. Targeted protein degradation using bifunctional small molecules, such as PROTACs, represents an emerging therapeutic strategy that enables selective elimination of intracellular proteins, offering treatment opportunities beyond the scope of conventional drug modalities [118]. These bifunctional molecules are composed of two distinct ligands—one that binds to the target protein and another that recruits an E3 ubiquitin ligase—connected by a chemical linker. The formation of a ternary complex triggers polyubiquitination of the target, leading to its degradation via the proteasome [119,120]. Studies by Luo et al., (2021) [121] demonstrated that a potent HMGCR-targeted PROTAC (21c), combining a VHL ligand and lovastatin acid, effectively degraded HMGCR in Insig-silenced HepG2 cells and formed a stable ternary complex. Oral administration of its lactone form (21b) showed strong in vivo HMGCR degradation and cholesterol reduction in mice, indicating its therapeutic potential.

Recent studies have highlighted the potential of PROTACs (Proteolysis-Targeting Chimeras) as a promising approach for targeted protein degradation in cancer. However, their clinical translation faces several key challenges, including limited bioavailability, off-target effects, and tumor-selective delivery. For example, the large molecular weight and poor solubility of many PROTAC molecules often limit their pharmacokinetics and oral bioavailability, requiring further optimization for effective in vivo applications [119]. Additionally, ensuring tumor selectivity without affecting normal tissues remains a significant hurdle, particularly in systemically administered degraders [118].

To enhance tumor selectivity of PROTACs, future strategies may involve tumor-specific E3 ligase expression profiling, targeted delivery systems (e.g., antibody-PROTAC conjugates), and environment-responsive linkers activated by hypoxia, ROS, or pH conditions within the tumor microenvironment. Beyond PROTACs, molecular glue degraders have emerged as an alternative strategy with unique advantages. Unlike PROTACs, which require a bifunctional design, molecular glues act by stabilizing interactions between an E3 ligase and the target protein, facilitating its ubiquitination and subsequent degradation. This approach may offer improved pharmacokinetics and simplified synthesis and has already demonstrated clinical potential [122]. The ubiquitin-proteasome system (UPS) tightly regulates intracellular protein turnover through substrate-specific ubiquitination mediated by E3 ligases. Molecular glue degraders (MGDs) exploit this pathway by inducing novel protein-protein interactions between E3 ligases and neo-substrates—proteins not normally recognized for degradation—via small-molecule-mediated interface stabilization. Notably, IMiDs, such as thalidomide, lenalidomide, and pomalidomide, function as MGDs by binding to cereblon (CRBN), an E3 adaptor, thereby creating a neomorphic surface that recruits transcription factors for proteasomal degradation. This mechanism has enabled degradation of traditionally "undruggable" targets, such as zinc finger and Ikaros-family transcription factors, underscoring MGDs as a versatile platform for expanding the substrate scope of UPS-based therapies [123]. Beyond IMiDs, emerging MGD strategies utilize alternative E3 ligase adaptors such as DCAF15, RNF114, KEAP1, and VHL, expanding the scope for degrading transcription factors like SREBP2. Structural features of SREBP2, including its bHLH-Zip domain and nuclear localization motifs, may serve as candidate degrons for rational MGD design using these novel ligases. Although no molecular glue has yet been identified for SREBP2, its structural domains—including the basic helix-loop-helix leucine zipper (bHLH-Zip) DNA-binding region and its nuclear import/export motifs—make it a theoretically suitable candidate for glue-based degradation. Rational design of MGDs could focus on stabilizing interactions between these motifs and E3 ligase adaptors, such as CRBN, thereby enabling SREBP2 ubiquitination and subsequent proteasomal degradation. In addition to CRBN, alternative E3 ligase adaptors are under active investigation and may provide broader substrate compatibility for SREBP2 or similar transcription factors. These non-CRBN MGDs expand the potential E3 ligase toolkit, enabling tissue- or context-specific degradation. Future work incorporating degron motif mapping, protein-protein interaction profiling, and structure-guided ligand discovery may facilitate the development of MGDs that selectively degrade SREBP2 in cholesterol-addicted cancers.

9. SREBP2 and chemotherapy/radiotherapy resistance

Resistance to chemotherapy or radiotherapy results in treatment failure and cancer recurrence caused by multiple factors. Cholesterol-driven drug resistance involves multiple molecular mechanisms that extend beyond metabolic reprogramming. Accumulation of cholesterol within lipid rafts enhances membrane rigidity and stabilizes efflux transporters such as P-glycoprotein (P-gp), reducing intracellular drug accumulation. Additionally, isoprenylation of small GTPases such as Rac1 and Rho, mediated by intermediates of the mevalonate pathway, facilitates cytoskeletal remodeling and activates DNA repair signaling pathways, thereby promoting resistance to chemotherapy and radiotherapy. Emerging evidence indicates that cholesterol homeostasis and flux, regulated in part by sterol regulatory element-binding protein 2 (SREBP2), play a central role in mediating therapy resistance across various cancer types. A unifying model suggests that SREBP2-driven cholesterol biosynthesis enhances resistance through modulation of lipid rafts, which are cholesterol-rich microdomains in the plasma membrane that organize signaling molecules and facilitate drug efflux, receptor recycling, and DNA damage repair pathway. In hepatocellular carcinoma (HCC), acquired resistance to tyrosine kinase inhibitors such as sorafenib or lenvatinib may be due to tumor cell repopulation by cancer stem cell expansion. Mechanistically, caspase 3-mediated cleavage of SREBP2 from the endoplasmic reticulum (ER) activates the sonic hedgehog signaling pathway, driving resistance. Studies have shown that Simvastatin sensitizes HCCs to sorafenib and inhibits tumor growth [107]. In ovarian cancer, cisplatin-mediated resistance is promoted by SREBP2 and differentially expressed in A2780-resistant cell lines along with their target genes LDLR, FDFT1, and HMGCR indicating an adaptive increase in cholesterol biosynthesis pathways under cisplatin stress [112]. This suggests that SREBP2-regulated gene expression contributes to chemoresistance by promoting membrane rigidity and impairing drug uptake, possibly through enhanced lipid raft formation. Treatment resistance in HER2+ breast cancer with lapatinib and trastuzumab (mAb) poses a significant challenge. Studies have shown that mediators of the mevalonate pathway are increased in lapatinib-resistant and lapatinib + trastuzumab-resistant cells, and treatment with lipophilic statins and N-bisphosphonates may provide a beneficial effect [113].

Inhibition of the mevalonate pathway by lipophilic statins like pitavastatin sensitizes radioresistant SQ20B cancer cells [108]. Lovastatin, an HMGCR inhibitor, sensitizes lung cancer cells to radiation by inhibiting AKT and activating the AMPK pathway These effects suggest that lipid metabolism impacts DNA repair fidelity, potentially through changes in membrane composition or availability of prenylation intermediates required for the activation of DNA repair enzymes. Targeting Farnesyl diphosphate synthase (FDPS), a critical mevalonate pathway enzyme radiosensitizes pancreatic cancer cells. FDPS is associated with radioresistance and is overexpressed in pancreatic cancer tumor tissues. Pharmacological inhibition of FDPS with zoledronic acid radiosensitizes pancreatic cancer cell lines [111] and pancreatic ductal adenocarcinoma [110]. Mechanistically, radiosensitization occurs by affecting Rac1 and Rho prenylation, modulating DNA damage response to radiation, and through immunomodulation. Moreover, the SREBP2-mutant p53 axis may serve as a biomarker for stratifying patients likely to benefit from cholesterol-targeting strategies, as mutant p53 has been shown to enhance mevalonate pathway activity and SREBP2 nuclear localization [70]. Targeting this metabolic vulnerability with statins or FDPS inhibitors represents a promising therapeutic avenue to overcome resistance and improve cancer treatment outcomes.

10. Conclusion

SREBP2 is a central regulator of cancer cell metabolic reprogramming, driving cholesterol biosynthesis, lipid metabolism, and tumor progression. The dysregulation of SREBP2 activation and feedback control mechanisms support uncontrolled proliferation, survival under metabolic stress, and resistance to therapy, making it a key oncogenic driver across multiple cancer types. Through its integration with oncogenic pathways such as PI3K/AKT/mTORC1, p53, TGF-β, c-Myc, and Hippo, SREBP2 helps cancer cells to bypass sterol-mediated feedback regulation, further fueling tumor growth and increasing therapeutic resistance. Given its widespread influence, targeting SREBP2 may represent a promising therapeutic strategy beyond cholesterol inhibition. Pharmacological interventions that suppress SREBP2 activation, nuclear translocation, or its downstream cholesterol metabolism effectors may provide a more comprehensive approach to disrupt tumor lipid homeostasis, induce metabolic stress, and improve treatment efficacy by disrupting oncogenic signaling. The combination of cholesterol metabolism inhibitors with standard therapies, including radiotherapy, chemotherapy, and immunotherapy, is actively being explored in preclinical and clinical settings, demonstrating the potential to overcome radioresistance, stimulate ferroptosis, and prevent cancer cell adaptation. However, statins remain the major types of drugs used in clinical studies. While statins have emerged as a potential approach to target the mevalonate pathway, alternative strategies, including FDPS, PCSK9, and oxysterol-binding receptors inhibitors, warrant further investigation. If transcription factors were considered undruggable for a long time, a new targeting strategy such as TF-Protac could be an opportunity for more targeted SREBP2 inhibition. Such strategies are underexplored, and recent insights into SREBP2's role in inflammation, immune evasion, and tumor microenvironment remodeling may provide opportunities to target the extended tumorigenic effects of SREBP2 beyond cholesterol metabolism. In summary, SREBP2 represents a metabolic vulnerability in cancer, making it a valid target for therapeutic intervention. Future research should focus on identifying precise SREBP2 inhibitors, optimizing combinatorial strategies, and understanding their interplay with other metabolic networks to improve patient outcomes and expand treatment options across multiple tumor types.

11. Future directions

Future investigations should focus on the development of isoform-specific inhibitors and heteromer-specific inhibitors that can selectively target SREBP2 without affecting SREBP1a or SREBP1c, rather than using pan-SREBP inhibitors. Such specificity may reduce off-target lipid metabolic disruptions and enhance therapeutic precision. Currently, no small molecules have been clinically validated to selectively inhibit the nuclear translocation or DNA binding of SREBP2, but several promising approaches are under exploration. For example, natural compounds like fatostatin and BF175 are known to inhibit SREBPs in general, but they lack isoform specificity and may impact both SREBP1 and SREBP2 activity. To develop SREBP2-selective compounds, future efforts should utilize structure-guided virtual screening approaches targeting unique features of the bHLH-Zip domain, which governs DNA binding and dimerization. Comparative structural analysis between SREBP2 and SREBP1 isoforms may identify isoform-specific pockets or amino acid variations that can be exploited for high-affinity binding of selective ligands. Virtual docking platforms (e.g., AutoDock) can be employed for in silico screening of small-molecule libraries against the bHLH-Zip interface of SREBP2 to predict inhibitors that may disrupt its DNA-binding activity without affecting related isoforms. HLH-Zip domain is a highly conserved but functionally distinct DNA-binding region. Advanced structural modeling, including comparative analyses of dimerization interfaces and DNA-binding motifs, may reveal druggable pockets unique to SREBP2 heteromers. Targeting conformational differences that influence heterodimer formation could yield inhibitors that specifically disrupt SREBP2-driven transcription without impairing SREBP1-mediated lipid synthesis. Additionally, proteolysis-targeting chimeras (PROTACs) tailored for SREBP2 degradation represent a promising but underdeveloped avenue. Another critical frontier is understanding tumor–stroma metabolic crosstalk, especially how SREBP2 activity in cancer-associated fibroblasts (CAFs) regulates lipid signaling and modulates the immune microenvironment. SREBP2-driven cholesterol metabolism in CAFs may alter lipid raft composition, influencing T cell receptor (TCR) signaling, MHC-I presentation, and cytokine gradients. Furthermore, the SREBP2–mevalonate axis may regulate immunosuppressive myeloid cell recruitment or PD-L1 expression on stromal cells. In vivo models incorporating conditional SREBF2 knockout in stromal compartments, coupled with single-cell transcriptomics, could unravel cell-specific functions of SREBP2. These insights may guide next-generation metabolism-immunotherapy combinations, targeting tumor and stromal SREBP2 simultaneously to enhance anti-tumor immunity.

CRediT authorship contribution statement

Rajan Radha Rasmi: Writing – original draft, Conceptualization. **Rachel Kovatich:** Writing – review & editing. **Alyssa Farley:** Writing, Methodology, Investigation. **Kunnathur Murugesan Sakthivel:** Writing – review & editing. **Vinita Takiar:** Supervision. **Mathieu Sertorio:** Supervision.

Funding

The authors declare that this study received no external funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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