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SCAP/SREBPs Are Central Players in Lipid Metabolism and Novel Metabolic Targets in Cancer Therapy

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Abstract

Lipid metabolism reprogramming emerges as a new hallmark of malignancies. Sterol regulatory element-binding proteins (SREBPs), which are central players in lipid metabolism, are endoplasmic reticulum (ER)-bound transcription factors that control the expression of genes important for lipid synthesis and uptake. Their transcriptional activation requires binding to SREBP cleavage-activating protein (SCAP) to translocate their inactive precursors from the ER to the Golgi to undergo cleavage and subsequent nucleus translocation of their NH2-terminal forms. Recent studies have revealed that SREBPs are markedly upregulated in human cancers, providing the mechanistic link between lipid metabolism alterations and malignancies. Pharmacological or genetic inhibition of SCAP or SREBPs significantly suppresses tumor growth in various cancer models, demonstrating that SCAP/SREBPs could serve as promising metabolic targets for cancer therapy. In this review, we will summarize recent progress in our understanding of the underlying molecular mechanisms regulating SCAP/SREBPs and lipid metabolism in malignancies, discuss new findings about SREBP trafficking, which requires SCAP *N*-glycosylation, and introduce a newly identified microRNA-29-mediated negative feedback regulation of the SCAP/SREBP pathway. Moreover, we will review recently developed inhibitors targeting the SCAP/SREBP pathway for cancer treatment.

Keywords

SCAP; SREBPs; Lipid metabolism; EGFR; miRNA-29; Metabolic targets

1. INTRODUCTION

Metabolic reprogramming is a new hallmark of cancer [1]. Increasing evidence has recently shown that alterations in lipid metabolism are often present in cancer cells and promote tumor growth. Lipids form the basic structures for the plasma membrane and for membranes of all cellular organelles. In addition, lipids serve as energy resources and function as important signaling molecules, regulating various cellular functions, such as migration, cell

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CONFLICT OF INTEREST

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cycle, cell division and differentiation [2–7]. Markedly increased lipid requirement is associated with the rapid growth and proliferation of tumor cells [8–12]. Lipid synthesis and uptake are highly elevated in various cancers, representing a novel characteristic of human cancers [10–14]. SREBPs, the master transcription factors in lipid synthesis and uptake pathways, have been demonstrated to be highly upregulated in a variety of cancers and may be promising molecular targets for cancer therapy [9, 11–13, 15].

2. DISCOVERY AND PROPERTIES OF THE SREBP FAMILY

SREBPs are transcription factors of the basic helix-loop-helix-leucine zipper (bHLH-Zip) class [12]. They were discovered by Brown & Goldstein's laboratory in the 1990s when they delineated the upstream regulators of low-density lipoprotein receptor (LDLR) and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) [16–20]. LDLR regulates cholesterol uptake by mediating the endocytosis of cholesterol-rich LDL [21], and HMGCR is the rate-limiting enzyme in the cholesterol biosynthesis pathway [22]. Both LDLR and HMGCR are transcriptionally regulated by a sterol-dependent mechanism through sterol regulatory-elements (SREs) located in their promoter regions [2, 23]. The NH2-terminal forms of SREBPs were purified from nuclear extracts of Hela cells and rat liver using double-stranded DNA fragments containing an SRE sequence (5′-ATCACCCCAC-3′), demonstrating that SREBPs bind to the SRE DNA fragments of LDLR and HMGCR to transcriptionally regulate their expression [16, 18]. Thereafter, Brown & Goldstein's group further uncovered feedforward and feedback molecular mechanisms that regulate SREBP transcription, translation and activation processes [2, 23]. Moreover, they identified major downstream targets of SREBPs that are involved in lipid metabolism [24].

Three SREBP isoforms are expressed in mammalian cells, SREBP-1a, SREBP-1c and SREBP-2, which are transcribed by two genes, *SREBF1* and *SREBF2* [2, 17, 19]. SREBP-1a and −1c are encoded via alternative transcription start sites (TSS) by a single gene, *SREBF1*, resulting in two isoforms with a different exon 1, and different lengths as SREBP-1a has a 24 amino acids (aa)-longer NH2-teminus than SREBP-1c [25]. SREBP-1c mainly regulates the expression of genes required for fatty acid synthesis [26], while SREBP-1a is able to regulate fatty acid and cholesterol synthesis, and cholesterol uptake [27]. SREBP-1c is the predominant isoform expressed in most tissues, whereas SREBP-1a is highly expressed in specific tissues and cells, such as intestinal epithelial, heart, macrophage and bone marrow dendritic cells [28]. SREBP-2, encoded by the *SREBF2* gene, is relatively specific to the regulation of cholesterol synthesis and uptake [17, 29]. SREBP-1c and SREBP-2 are the predominant isoforms in liver and most other tissues, and SREBP-1c is upregulated by insulin stimulation [24].

SREBPs contain three functional domains. Their NH2-terminal domain contains the bHLH-Zip motif, and an acidic transcriptional motif that binds co-activator specificity protein 1 (SP1) or nuclear transcription factor Y (NF-Y) to regulate gene expression [30]. The bHLH-Zip motif is involved in DNA binding and dimerization of the mature SREBP transcription factors. The acidic domain is essential for SREBP transcriptional activity, as its removal markedly reduces the transcriptional activity of SREBPs, although their bHLH-Zip motif can still bind to DNA [31]. The central portion of SREBPs, which is the membrane-binding

region, consists of two hydrophobic, membrane-spanning segments separated by a hydrophilic loop that extends into the lumen of the ER. The COOH-terminal segments of SREBPs contain ~590 aa and function as regulatory domains for SREBP subcellular localization and translocation [32].

3. SREBP MATURATION AND REGULATION

SREBPs are synthetized as 125 KDa inactive precursors, which bind to SREBP cleavage-activation protein (SCAP) after synthesis through their COOH-terminal domains and stay in the ER (Figure 1) [34]. The transcriptional activation of SREBPs requires that the SCAP/SREBP complex translocates from the ER to the Golgi for subsequent cleavage and release of the NH2-terminal transcription factor forms [33]. SCAP is a polytopic membrane-binding protein with 8 transmembrane helices. The long COOH-terminal extension of SCAP includes multiple copies of a WD-repeat sequence known to promote protein–protein interactions [32]. The NH2-terminal domain of SCAP binds to the ER-resident insulin-induced gene proteins (INSIGs), including INSIG1 and INSIG2, forming an INSIG/SCAP/SREBP complex that retains SREBPs in the ER (Figure 1) [35, 36]. INSIG1 is transcriptionally regulated by SREBPs and is abundant in cells [23, 24]. In contrast, INSIG2 is ubiquitously expressed at a low level in a variety of cells, suggesting that it serves as the regulator of SCAP/SREBP pathway at the basal level [35].

Brown & Goldstein revealed that SCAP/SREBP trafficking and activation is regulated by a sterol-mediated negative feedback loop (Figure 1) [2, 23]. Cholesterol or oxysterol such as 25-hydroxycholesterol can bind to SCAP or INSIGs to strengthen their association, thereby preventing SREBPs to exit from the ER [37]. When sterol level decreases, SCAP will dissociate from INSIGs and facilitate the incorporation of SCAP/SREBP into coatomer II (COPII)-coated vesicles, which then transport the complex from the ER to the Golgi. In the Golgi, SREBPs will be sequentially cleaved by two membrane-bound proteases, site-1 protease (S1P) [38] and site-2 protease (S2P) [39], releasing the transcriptionally active NH2-terminal domains that can enter into the nucleus to activate the transcription of target genes [2, 23]. Meanwhile, INSIGs are recognized by ubiquitin ligase E3, TRC8 or GP78, and rapidly degraded after dissociation from SCAP [37, 40]. Interestingly, activation of SREBPs will promote the expression of INSIG1 and lipogenic genes, to restore INSIG1 protein and cholesterol levels, leading to the re-formation of the INSIG/SCAP/SREBP complex, limiting SREBP translocation [41]. A recent study showed that both SREBPs and SCAP associate with heat shock protein 90 (HSP90) after synthesis, which maintains their stability and interaction, whereas HSP90 inhibition results in the proteasome-dependent degradation of both SREBPs and SCAP [42]. In addition, Lee *et al.* have shown that ubiquitin regulatory X domain-containing protein 8 (UBXD8) binds to INSIG1 and promotes its degradation. In turn, the binding of UBXD8 to INSIG1 can be blocked by unsaturated fatty acids, thereby stabilizing INSIG1 and inhibiting SREBP-1 activation [43].

In addition to the tight regulation of the translocation process, SREBPs are also transcriptionally regulated by various transcription factors, including the mature NH2-terminal domains of SREBP-1 and SREBP-2, forming a feedforward loop to enhance their own expression (Figure 1) [44]. Multiple SRE motifs are present in the promoters of the

SREBF1 and *SREBF2* genes [45]. Moreover, NF-κB transcriptionally regulates SREBP-1a expression [46], and liver X receptor (LXR) transcriptionally activates SREBP-1c expression [47], which plays an important role in insulin-stimulated SREBP-1c expression [48]. SREBP-1c transcription and maturation could be inhibited by unsaturated fatty acids, particularly by polyunsaturated fatty acids [49]. SREBP-2 transcription could be regulated by thyroid hormone [50]. Nevertheless, the transcriptional regulation of SREBPs, particularly in cancer cells, is not fully understood, requiring further investigation.

In addition, the stability of the nuclear forms of SREBPs (nSREBPs) is regulated by various post-translational modifications, i.e., phosphorylation, acetylation and sumoylation (Figure 1). Phosphorylation of nSREBPs by glycogen synthase kinase-3 beta (GSK3β) results in their degradation mediated by the ubiquitin ligase E3 enzyme, FBXW7 [51]. Furthermore, activation of AMP-activated protein kinase (AMPK), which acts as an energy sensor, could enhance nSREBP degradation via phosphorylation [52]. In contrast, acetylation by CREB-binding protein (CBP)/p300 acetyltransferase stabilizes nSREBPs [53–55], while nSREBPs are destabilized by sirtuin 1 (SIRT1), which removes their acetylation modification [56]. In addition, sumoylation mediated by protein inhibitor of activated STAT Y (PIASy) enhances the degradation of nSREBP-1 [57]. In summary, the stabilization of nuclear SREBP forms is tightly regulated by multiple signals.

4. ACTIVATION OF SCAP/SREBPS IN CANCER

Rapidly proliferating tumor cells consume large amounts of energy and building blocks [58]. These high demands by cancer cells are met by the reprogramming of their metabolic processes by activated oncogenic signaling pathways [59]. Lipids, functioning as essential structural components of membranes and serving as important energy resources, are critical macromolecules for tumor growth. Recent studies have demonstrated that both lipid synthesis and uptake are significantly elevated in malignancies to support tumor growth [10–14]. SREBP-1 is highly expressed in glioblastoma (GBM) [60, 61], the most deadly brain tumor [62], and in prostate [63], endometrial [64], breast cancers [65, 66], hepatocellular carcinoma (HCC) [67], ovarian cancer [68], and pancreatic cancer (Table 1) [69]. The function of SREBP-1 has been investigated in multiple cancer cell lines including colon [70], lung [71] and pancreatic cancer cell lines [72]. SREBP-2 has been shown to be upregulated in prostate cancer patient tumor tissues (Table 1) [73], and elevated by ERBB4 signaling in breast cancer cells [74]. Moreover, SREBP-2 is also activated by Akt in Chinese hamster ovary-7 (CHO-7) and CHO cells [75].

Our previous studies demonstrated that SREBP-1 is highly upregulated by oncogenic EGFR signaling in GBM [13, 60, 61, 76–81]. We found that GBM tumors bearing amplified EGFR, or expressing EGFRvIII, the constitutively active form of the receptor that lacks a portion of the extracellular ligand-binding domain, were greatly dependent on SREBP-1-mediated lipid synthesis and uptake for rapid growth [61]. EGFR/EGFRvIII activates SREBP-1 through upregulation of PI3K/Akt signaling, promoting the expression of ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), stearoyl-coenzyme A desaturase 1 (SCD1) and low density lipoprotein receptor (LDLR) to enhance fatty acid synthesis and cholesterol uptake [13, 60, 61, 80, 83].

We recently reported that glucose-mediated *N*-glycosylation of SCAP is essential for SCAP stability and dissociation from INSIG1, and mediates the activation of SREBP-1 by EGFR signaling (Figure 1) [77]. Genetically silencing SCAP expression or impairing its glycosylation via mutation significantly inhibited tumor growth and prolonged the survival of GBM-bearing mice. In contrast, overexpressing SCAP in GBM cells markedly enhanced tumor growth in mouse flank and brain (Table 1) [77]. This study demonstrated that glucose acts as an essential activator for SCAP/SREBP trafficking [77], while cholesterol functions as a key inhibitor of this process (Figure 1) [77, 82].

Oncogenic mutant of PI3K (H1047R) or K-Ras (G12V) has been shown to upregulate SREBP-1 and enhance lipogenesis through activation of mammalian target of rapamycin complex 1 (mTORC1) in breast epithelial cells [84]. Elevated mTORC1 signaling is correlated with increased mRNA and protein levels of SREBP-1 and of its downstream targets [85, 86]. In addition, loss of the tumor suppressor retinoblastoma protein (RB) promotes the transcription of SREBP-1 and SREBP-2 in an E2F-dependent manner [87]. In summary, increasing evidence demonstrates that SREBPs function as the central transition hubs that mediate signals from oncogenic pathways to the activation of lipid synthesis and uptake, promoting rapid tumor growth. Therefore, SREBPs have the potential to be efficient molecular targets for cancer therapy [13].

5. REGULATION OF SCAP/SREBPS BY MICRO-RNA

MicroRNAs (miRNAs) are small non-coding RNAs containing about 23 nucleotides. They regulate gene expression by binding to the 3'-untranslated regions (3'-UTR) of mRNAs, leading to the degradation or translation repression of the targeted mRNAs [88–90]. miRNAs have been identified and demonstrated to regulate nearly all cellular processes, i.e., cell cycle, apoptosis, autophagy, differentiation and metabolism [91–93]. The role of miRNAs in lipid metabolism has been extensively reviewed [92–96]. Here, we will focus on the role of several miRNAs, in the regulation of the SCAP/SREBP pathway.

We recently reported that miR-29 mediates a novel negative feedback loop that regulates the SCAP/SREBP-1 signaling pathway and lipid metabolism (Figure 1) [80–81]. The miRNA-29 family consists of three members, miR-29a, −29b and −29c, which share the same seed sequence [97, 98]. Analyzing a large cohort of tumor tissues from GBM patients with altered EGFR (amplification or mutation), we found that expression of all three mature miR-29s is positively correlated with *SREBF1* gene expression [80, 81]. SREBP-1, via EGFR/PI3K/Akt signaling, transcriptionally upregulated the expression of all three miR-29s in GBM cells. In turn, they could all bind to the 3'-UTR of *SREBF1* and *SCAP* mRNAs, inversely inhibiting their expression. Importantly, administration of miR-29 mimics inhibited SCAP/SREBP-1 and significantly reduced GBM tumor growth [80, 81], suggesting that miR-29s could be used to target GBM.

Both miR-185 and miR-342 have been shown to inhibit cell growth, migration and invasion *in vitro* and *in vivo* in prostate cancer cells by inhibiting SREBP-1 and −2 expression [99]. The expression of miR-185 and miR-342 is significantly downregulated in prostate cancer

cells compared to non-cancerous epithelial cells [99]. Yang *et al.* reported that miR-185 controls cholesterol homeostasis through regulating SREBP-2 expression and activity [100].

Other miRNAs have been shown to affect tumor growth, such as miR-132, which suppresses cell growth, tumorigenesis, invasion and migration as well as promotes apoptosis of glioma cells by suppressing SREBP-1c that is related to SIRT1 [101]. Repression of INSIG1 by miR-24 promotes hepatic lipid accumulation and hyperlipidemia through activation of SREBPs [102]. Moreover, Osborne *et al.* recently identified a positive feedforward loop mediated by miR-96 and miR-182 to upregulate SREBPs in mouse liver. They demonstrated that SREBP-2 transcriptionally promotes the expression of miR-96 and miR-182, which induces the degradation of FBXW, an ubiquitin E3 ligase mediating the degradation of nuclear SREBP forms [103], thereby enhancing nuclear SREBPs and increasing lipid synthesis [104].

6. INHIBITING SCAP/SREBPS TO TREAT CANCER

Given the importance of SREBPs in the regulation of lipid metabolism and cancer growth, finding specific molecules that target SCAP/SREBPs to treat cancer has recently become a highly active field of research (Table 2) [13, 41].

Two inhibitors, fatostatin and betulin, which suppress SCAP/SREBP translocation, have been extensively tested in cancer cells (Figure 1 and Figure 2) (Table 1) [105–111]. Fatostatin binds to SCAP, and inhibits its dissociation from INSIGs, thereby restricting the translocation of SREBPs to the ER and reducing lipogenesis [105, 112]. Fatostatin has been shown to inhibit cancer cell proliferation, invasion and migration, and to arrest cancer cells at the G2/M checkpoint in prostate cancer cells [109]. In addition, fatostatin alone or in combination with docetaxel suppresses the growth of androgen receptor-negative prostate cancers [111]. The combination of fatostatin and docetaxel leads to a greater proliferation inhibition and to apoptosis compared to treatment with single agents [111]. Moreover, fatostatin also inhibits the growth of pancreatic cancer MIA PaCa-2 cells by inhibiting SREBP-1 [72]. Similarly, betulin binds to SCAP and enhances its interaction with INSIGs, thereby suppressing SCAP/SREBP translocation [107]. Multiple studies have shown that betulin attenuates the growth of various cancers by inhibiting SREBP-1 [107, 110, 113–115].

Xanthohumol, a prenylated flavonoid found in hops, is a novel SREBP inhibitor (Figure 2) (Table 2) [116, 117]. Xanthohumol binds to Sec23/24 and blocks the incorporation of the SCAP/SREBP complex into COPII vesicles, thereby hindering ER-to-Golgi translocation of the complex [117]. Dietary xanthohumol reduced the maturation of hepatic SREBP-1 and transcription of its target genes [117]. Xanthohumol is also characterized as a broad-spectrum anti-tumor agent as it induces cancer cell apoptotic death and inhibits tumorigenesis through inhibition of STAT3 or NF-κB [118–125].

In addition to blocking SCAP/SREBP trafficking, suppressing the cleavage of SREBPs by inhibiting the S1P or S2P enzymes is another promising strategy to downregulate SREBP activity (Figure 1). PF-429242 is a reversible inhibitor of S1P, which significantly inhibits

SREBP processing (Table 2) [126]. PF-429242 was selected through a high throughout screeningusing purified human S1P and a fluorescent assay that analyzes cleavage of the synthetic peptide Ac-VFRSLK-MCA (Figure 2) [127]. PF-429242 suppresses the proteolytic processing and nuclear translocation of SREBPs, thereby inhibiting cholesterol and fatty acid synthesis [127]. Beth *et al.* reported that PF-429242 suppressed GBM tumor growth by inducing apoptotic cell death by inhibiting SREBP activation [128]. PF-429242 also suppresses pancreatic cancer growth by inhibiting SREBP-1 and its downstream signaling cascade, FASN, HMGCR and SCD1 [72]. Nelfinavir is an inhibitor of S2P and suppresses the proteolysis of SREBPs (Table 2) [131]. Nelfinavir was firstly identified as a HIV-1 protease inhibitor (Figure 2) [130]. Studies show that nelfinavir treatment led to the accumulation of unprocessed SREBP-1 and increase of ER stress, leading to the apoptosis of liposarcoma and inhibition of castration-resistant prostate cancer cells [132–134]. Another S2P inhibitor, 1,10-phenanthroline, has the same effects in suppressing SREBP maturation and proliferation of prostate cancer cells as nelfinavir (Figure 2) (Table 2) [133].

Transcriptional activation of lipogenic gene expression requires nuclear SREBPs to bind to CREB-binding protein (CBP)/p300 acetyltransferase and activator-recruited co-factor 105 (ARC105, also named MED15) co-activators [135]. Yang's group recently developed BF175, an inhibitor that can block the binding of MED15 to SREBP-1a, thereby inhibiting lipid synthesis and obesity in mouse models (Table 2) [136, 137]. BF175 reduces hepatic lipid content and decreases hepatic mRNA levels of *SREBFs* and their target genes in BF175 treated mice [137]. Thus, the effects of BF175 should be investigated in cancer cells.

CONCLUSION

In summary, lipid metabolism reprogramming has emerged as a novel hallmark of cancer [10–14]. Accumulating evidence has shown that SCAP/SREBPs play important roles in malignancies, connecting oncogenic signaling to lipid metabolism alterations, leading to rapid tumor growth (Figure 1) [13, 60, 61, 76–78, 80, 82]. Multiple studies have suggested that SCAP/SREBPs are very promising molecular targets in cancer treatment. A better understanding of the mechanisms underlying the trafficking and activation of SREBPs will provide optimal means to target SCAP/SREBPs. Developing effective inhibitors targeting lipid metabolism while avoiding toxicity in normal cells is the current challenge in cancer therapy. Moreover, identifying treatments that combine targeting SREBPs together with chemotherapy or immunotherapy may provide effective strategies for the treatment of cancer patients.

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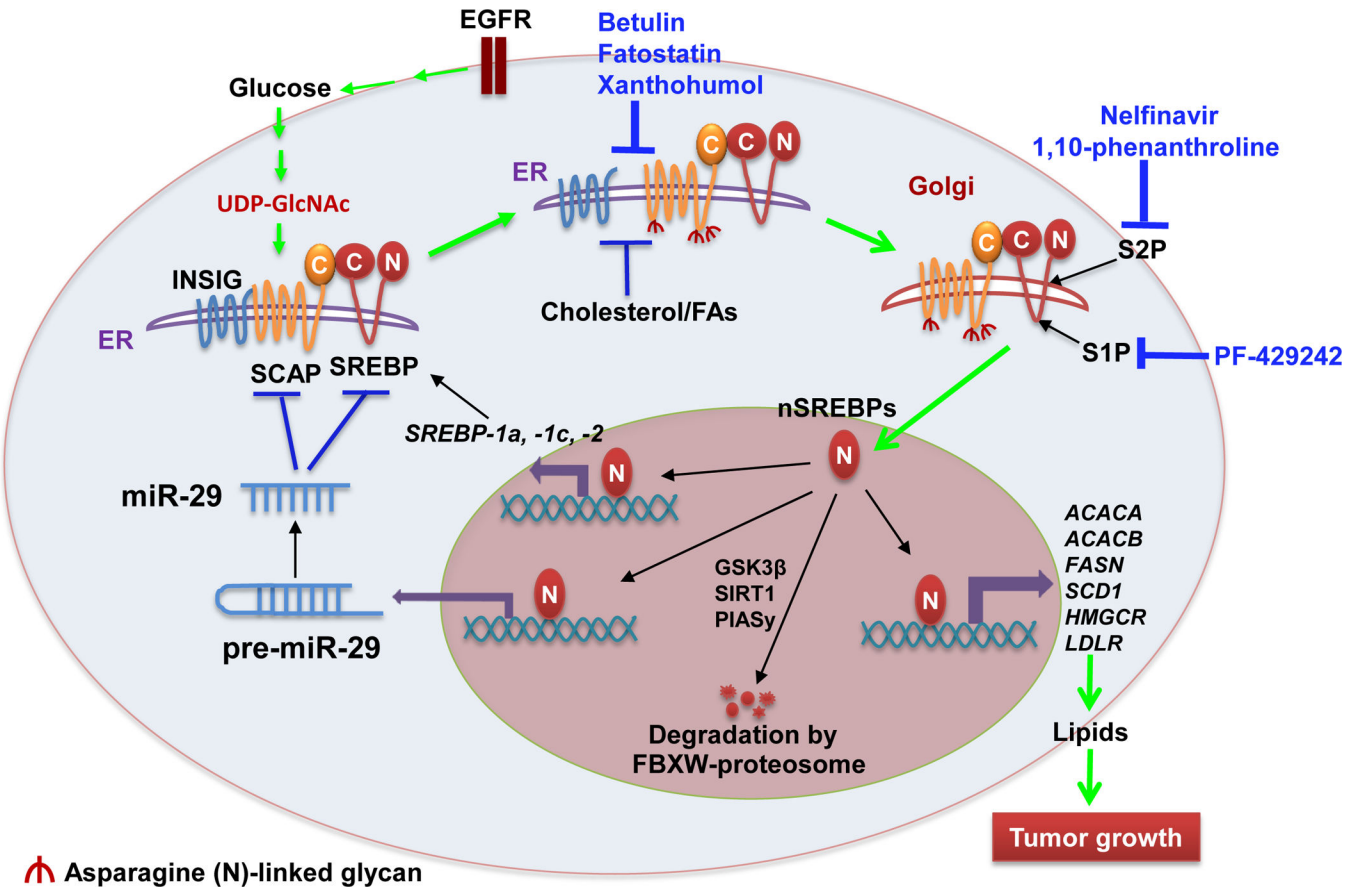

Figure 1.

Regulation of SCAP/SREBP activation in Cancer Cells.

In cancer cells, oncogenic EGFR signaling increases glucose uptake and enhances the synthesis of UDPGlcNAc, the end-product of the hexosamine synthesis pathway, promoting the *N*-glycosylation of SCAP, which enables SCAP dissociation from INSIG and leads to SCAP/SREBP trafficking from the ER to the Golgi. In the Golgi, SREBPs are sequentially cleaved by S1P and S2P proteases to release their NH2-terminal forms, which enter into the nucleus to activate the expression of key lipogenic genes, including themselves, forming a feedforward loop to activate lipid metabolism. Moreover, the newly synthesized INSIG1, cholesterol and unsaturated fatty acids mediated by SREBPs enhance the binding of INSIG and SCAP to retain SCAP/SREBP complex in the ER, forming a negative feedback loop to regulate SREBP activation. In addition, the nuclear SREBP forms are degraded by ubiquitin E3 ligase FBXW-mediated proteasome system, a process regulated by phosphorylation, acetylation and sumoylation by GSK3β, SIRT1 and PIAsy, respectively. Recently, miR-29 was found to be transcriptionally upregulated by SREBP-1, and in turn to inhibit SCAP and SREBP expression, mediating an additional negative feedback loop controlling this signaling pathway. Various inhibitors shown in blue, which inhibit SREBP translocation or maturation, have been tested in cancer cells and have shown promising anti-tumor effects. Abbreviation: ACACA, acetyl-coA carboxylase alpha; ACACB, acetyl-coA carboxylase beta; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; FAs, fatty acids; FASN, fatty acid synthase; FBXW, F-box and WD repeat domain containing; GSK3β,

glycogen synthase kinase-3 beta; HMGCR, hydroxymethylglutaryl-CoA reductase; INSIG, insulin-induced gene proteins; LDLR, low density lipoprotein receptor; PIASy, STAT Y; S1P, site-1 protease; S2P, site-2 protease; SCAP, SREBP cleavage-activating protein; SIRT1, sirtuin 1; SREBP, Sterol regulatory element-binding proteins; nSREBPs, nuclear forms of SREBPs.

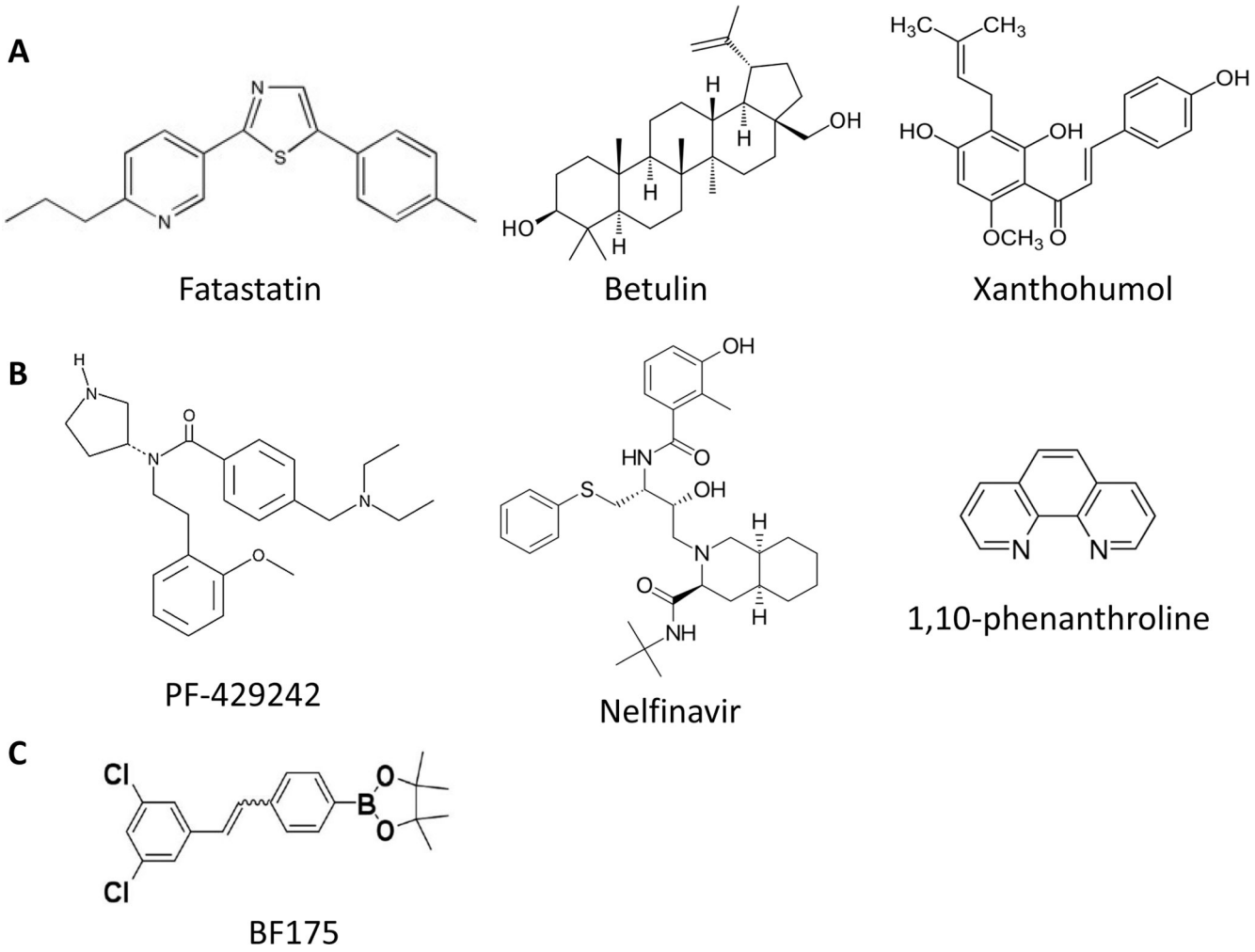

Figure 2.

The structure of inhibitors in SCAP/SREBPs pathway.

A) Inhibitors suppressing SCAP/SREBP trafficking; **B)** Inhibitor suppressing S1P or S2P;

C) Inhibitors suppressing the transcriptional activity of SREBPs.

Table 1:

Overexpression of SCAP/SREBPs in human cancers and testing their role in cancer animal models

Target	Overexpression in human cancer	References	Animal Model	Refernces
SCAP	No report	N/A	GBM xenograft mouse models by overexpression, shRNA knockdown or mutation of SCAP	[77, 108]
			SCAP knockout in diethylnitrosamine-induced mouse hepatocellular carcinoma (HCC)	[138]
SREBP-1	GBM	[60, 61]	*Testing the effects of knockdown of SREBP-1 by shRNA in mouse*	
	Prostate cancer	[63]	*xenograft models:*	
	Endometrial cancer	[64]	GBM	[78, 108, 139]
	HCC	[67]	Endometrial cancer	[64]
	Ovarian cancer	[68]	Ovarian cancer	[68]
	Pancreatic cancer	[69]	Pancreatic cancer	[69]
	Breast cancer	[65, 66]	Colon cancer	[140]
SREBP-2	Prostate cancer	[73]	*SREBP-2 xenograft model by shRNA knockdown in*	
			GBM	[108]
			Prostate cancer	[73]
			Colon cancer	[140]

Table 2:

The inhibitors targeting SCAP/SREBPs pathway in cancer cells

Drug	Mechanism	Cancer type	In Vitro Cell line (IC_{50} μM)	In vivo xenograft mouse model (drug dose)	References
Fatostatin	Inhibition of ER-Golgi translocation of SCAP/SREBPs	GBM	U87-MG (−)	U87-MG (5, 30 mg/kg)	[108]
		Prostate	LNCap(10.4), C4–2B(9.1), PC3 (15.8), DU145 (9.5)	C4–2B, PC3,DU145(15 mg/kg)	[109, 111]
		Lung	A549 (−), PC9 (−)	None	[141]
		Pancreatic	MIA PaCa-2 (14.5)	None	[72]
Betulin	Inhibition of ER-Golgi translocation of SREBPs	Prostate	LNCaP (−), PC3 (−)	None	[142]
		Breast	MCF7 (−)	MCF7 (50,100 mg/kg)	[143]
		Lung	A549 (−), PC9 (−)	A549 (20 mg/kg)	[141]
		HCC	None	Diethylnitrosamine-induced mouse HCC (50 mg/kg)	[138]
Xanthohumol	Inhibition of ER-Golgi translocation of SCAP/SREBPs by binding to Sec23/24	Normal liver	None	75 or 150 mg/kg dietary Xanthohumol inhibits SREBP-1 target gene expression in the liver in diet-induced obese mice	[117]
PF-429242	Inhibition of SREBP cleavage by inhibiting SIP	Normal liver	None	PF-429242 with 10 or 30 mg/kg inhibits the expression of SREBP target genes in mice liver	[126]
		HCC	Huh-7 (90)	None	[144]
		GBM	T98(15.0), U87-MG(15.2), A172 (27.6)	None	[128]
		Pancreatic	MIA PaCa-2 (24.5)	None	[72]
Nelfinavir	Inhibition of SREBP cleavage by inhibiting S2P	Liposarcoma	LiSa-2 (−), SW872 (−)	LiSa-2 (500 mg/kg)	[132]
		Prostate	DU145 (−), PC3 (−)	None	[134]
1,10-phenanthroline	Inhibition of SREBP cleavage by inhibiting S2P	Prostate	DU145 (−), PC3 (−)	None	[134]
BF175	Inhibition of the transcription activity of SREBPs	Normal liver	None	BF175, 0.2% per weight of diet for 8 weeks, decreases the expression of SREBP target genes in mouse liver and reduces hepatic and blood levels of lipids	[137]