Published in final edited form as:
Curr Pharm Des. 2014 ; 20(15): 2619–2626.

Targeting SREBP-1-driven lipid metabolism to treat cancer

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Abstract

Metabolic reprogramming is a hallmark of cancer. Oncogenic growth signaling regulates glucose, glutamine and lipid metabolism to meet the bioenergetics and biosynthetic demands of rapidly proliferating tumor cells. Emerging evidence indicates that sterol regulatory element-binding protein 1 (SREBP-1), a master transcription factor that controls lipid metabolism, is a critical link between oncogenic signaling and tumor metabolism. We recently demonstrated that SREBP-1 is required for the survival of mutant EGFR-containing glioblastoma, and that this pro-survival metabolic pathway is mediated, in part, by SREBP-1-dependent upregulation of the fatty acid synthesis and low density lipoprotein (LDL) receptor (LDLR). These results have identified EGFR/PI3K/Akt/SREBP-1 signaling pathway that promotes growth and survival in glioblastoma, and potentially other cancer types. Here, we summarize recent insights in the understanding of cancer lipid metabolism, and discuss the evidence linking SREBP-1 with PI3K/Akt signaling-controlled glycolysis and with Myc-regulated glutaminolysis to lipid metabolism. We also discuss the development of potential drugs targeting the SREBP-1-driven lipid metabolism as anti-cancer agents.

Keywords

TCA cycle; PI3K/Akt; SREBP-1; ACLY; ACC; FASN; LDLR; LXR; ABCA1; SREBP-2

Introduction

Increased evidence shows that the lipogenic phenotype is a major characteristic of cancer [1-4]. Cancer cells engage in extensive *de novo* lipogenesis, producing lipids from glucose and glutamine [5, 6]. This ability of cancer cells to engage in cell autonomous generation of lipids provides a critical route by which cancer cells become independent of systemic regulation. It also provides a potential Achilles hell, as cancer cells may develop enhanced dependence on the lipogenic machinery, in an oncogene-dependent fashion. Multiple studies showed that glucose and glutamine both contribute to lipogenesis [6-9], which may open a new avenue to inhibit tumor growth by disrupting the metabolic flux from glucose, glutamine to lipogenesis. However, the detailed molecular mechanism by which the

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metabolic flux is regulated, and whether oncogenic growth signaling is tightly involved in these processes is poorly understood.

An abundant supply of lipids is required for rapid tumor cell proliferation. Phospholipids and cholesterol form the major structure of cell membranes [10-14]. Fatty acids and triglycerides provide ample energy substrates [15], and lipids are also utilized as precursors to synthesize some hormones and second messengers that mediate signal transduction pathways [10, 16]. Here, we will discuss recent advances in the understanding of lipid metabolism regulation, address how oncogenic growth signaling coordinates glucose, glutamine metabolism to lipid synthesis, and further indicate the potential druggable molecular targets in the regulatory network of lipid metabolism.

Lipogenesis pathway

PI3K/Akt signaling and C-Myc control the metabolic flux from glucose and glutamine to *de novo* lipid synthesis [5, 7, 9, 17]. Recently, SREBP-1 was revealed to be highly activated in cancers [18-20], and has been shown to play an integral role in connecting oncogenic signaling-regulated glucose and glutamine metabolism to *de novo* lipogenesis [8, 21]. Genetic and pharmacological targeting of SREBP-1 has been shown to significantly inhibit tumor cell growth, which strongly suggests that SREBP-1 is a novel molecular target in cancer [18].

SREBP-1 regulation by sterol levels

SREBPs are key transcriptional factors that control lipogenesis and lipid uptake [22]. There are two SREBP genes in mammals, SREBP-1 and -2 [23, 24]. SREBP-1 gene transcribes two isoforms SREBP-1a and -1c encoded from different promoters, which are demonstrated to mainly regulate genes that control fatty acid synthesis [22-25]. SREBP-2 is shown to regulate genes involved in cholesterol synthesis [23, 25, 26]. However, the roles of SREBP-1 and -2 significantly overlap in the regulation of lipid metabolism [25-28]. In normal tissues, SREBPs levels and activity are tightly controlled by endogenous sterol levels via negative feedback regulation [22]. SREBPs are located in the endoplasmic reticulum (ER) membrane in association with SREBPs cleave activating protein (SCAP) in which they are retained by Insulin-induced gene (Insig) when cellular sterol levels are sufficient. Once sterol levels drop, SCAP protein dissociates with Insig and escorts SREBPs to the Golgi, in which they are cleaved by site-1 and site-2 proteases (S1P and S2P) sequentially thereby releasing the N-terminus, which then enters into the nucleus to transcribe lipogenesis genes and LDLR (Fig. 1) [22, 23]. In addition, SREBP-1 has also been shown to be involved in other cellular functions, such as regulation of cell cycle and cell proliferation [29, 30]. However, it is still not clear whether the alteration of cell cycle progression when SREBP-1 is activated or inhibited is caused by the change of lipid metabolism or from separate SREBP-1 molecular functions. More detailed studies are essential in order to unravel the complete function of SREBP-1, particularly in cancer cells.

SREBP-1 is activated by PI3K/Akt signaling

In addition to regulation by sterols, SREBP-1 has been shown to be stabilized and activated by the PI3K/Akt oncogenic signaling pathway in cancer [18, 31, 32]. There are two mechanisms that could explain this regulation. The first is that activated Akt can stabilize the SREBP-1 nuclear form and promote its target gene expression through down-regulation of Fwb-7, an ubiquitin enzyme E3 which mediates SREBP-1 N-terminus degradation by inhibiting its regulator, GSK3-β [33-35]. Another mechanism is PI3K/Akt signaling through mTORC1 which regulates Lipin 1, a phosphatidic acid phosphatase, to control SREBP-1 nuclear localization and its transcriptional activity (Fig. 2) [36, 37]. These two distinct observations of regulatory mechanisms for SREBP-1 likely originate from the different organ-derived cell lines. Specifically, cancer cell lines HeLa and HepG2 were compared to the normal tissue cell lines HEK293, retinal pigment epithelial cells (RPE), NIH3T3, hepatocytes and mouse embryonic fibroblasts (MEF). Moreover, SREBP-1 mRNA and protein levels seem to be more sensitive to mTORC1 inhibition in normal tissue cells than cancer cell lines [36-39].

In cancer cells, SREBP-1 regulation appears to be more complex. A recent study showed that inhibiting mTORC1 using rapamycin has little effect on SREBP-1 nuclear localization and its abundance, but inhibiting its upstream factors like EGFR, PI3K and Akt significantly decreases SREBP-1 N-terminal levels and diminishes its abundance in the nucleus [18]. These data suggest that other oncogenic molecules beyond mTORC1 are involved in SREBP-1 regulation. It is also possible that inhibiting mTORC1 by rapamycin could maintain SREBP-1 levels via feedback activation of Akt [40]. Furthermore, mammalian target of rapamycin complex 2 (mTORC2) is possibly involved in the stability of the nucleus form of SREBP-1 according to the results from the mTOR kinase inhibitor Torin-1 [41], which inhibits both mTORC1 and mTORC2 activity [42], and significantly decreases SREBP-1 abundance in the nucleus compared to the inhibition of mTORC1 alone by rapamycin [37, 43]. Given that lipogensis is a critical source for the formation of new cellular membranes, it is not surprising that cancer cells may develop redundant molecular pathways to control SREBP-1 expression and the stability of its nuclear form to guarantee cells the ability to obtain ample lipids for their rapid growth and division. Additionally, this may partially explain the reason why targeting mTORC1 had an incremental favorable response in the clinic using rapamycin or its derivatives to treat cancer [40]. Taken together, these data suggest that directly targeting SREBP-1 may be one of the most feasible approaches to treat cancer.

SREBP-1 integrates the metabolic flux from PI3K/Akt-regulated glycolysis to lipogenesis

Addictive glycolysis is a main feature of cancers even in an oxygen-rich condition [8, 44, 45]. PI3K/Akt signaling has been demonstrated to activate glycolysis through regulating glucose transport (GLUT) and hexokinase 2 (HK2) [9, 17, 46-48]. In addition to the ATP production, glucose metabolism also contributes to NADPH and macromolecule synthesis, such as nucleic acids, amino acids and lipids [9, 49]. Cancer cells acquire glucose to synthesize fatty acids and support new membranes and lipid raft formation [1, 50, 51]. The glycolytic intermediate pyruvate enters into mitochondria and produce acetyl-CoA, which is then condensed with oxaloacetate to form citrate. To synthesize lipids, a portion of citrate is

released into the cytoplasm and then lysed by ATP citrate lyase (ACL) to produce the lipid precursor, acetyl-CoA [52, 53]. Then, acetyl-CoA carboxylase (ACC) catalyzes the irreversible carboxylation of acetyl-CoA to form malonyl-CoA [54, 55], which is then incorporated with acetyl-CoA to synthesize long-chain saturated fatty acid, palmitate, by fatty acid synthase (FASN) (Fig. 2) [1, 56]. Palmitate can be further elongated or de-saturated to produce diverse fatty acids, which can further synthesize phospholipids for new cell membrane formation, store in triglycerides for energy storage, enter into mitochondria for energy production, modify proteins by acetylation, or synthesize hormones [1, 56, 57].

Furthermore, there is a correlation between elevated glycolysis and exacerbated fatty acid synthesis [9, 21]. PI3K/Akt signaling upregulates glucose uptake and glycolysis [17, 49, 58], and also promotes fatty acid synthesis (Fig. 2) [1, 59, 60]. Meanwhile, the fatty acid synthesis pathway is tightly regulated by SREBP-1, which upregulates ACL, ACC and FASN expression [22, 23]. FASN, which controls the terminal step for the synthesis of palmitate, has been shown to be upregulated by PI3K/Akt signaling [1, 60, 61]. Multiple studies have revealed that PI3K/Akt signaling promotes fatty acid synthesis through upregulation of SREBP-1 [18, 27, 36]. Taken together, SREBP-1 has been revealed as a key player that integrates the metabolic flux from PI3K/Akt signaling regulated glycolysis to fatty acid synthesis (Fig. 2).

Glutamine metabolism and lipogenesis

In addition to glycolysis, glutamine also contributes to energy production and lipid synthesis by entering the mitochondria and integrating into the TCA cycle [7, 15, 62, 63]. The oncogene Myc upregulates glutamine transporter and glutaminase to synthesize glutamate, then enters into the mitochondria and is converted into α-ketoglutarate. Then, α-ketoglutarate can either enter into the TCA cycle through oxidative phosphorylation to produce ATP [7, 15, 62, 64, 65], or form citrate through reductive carboxylation under hypoxia or defective mitochondria condition mediated by IDH1 or IDH2, to contribute to SREBP-1-driven fatty acid synthesis (Fig. 2) [5, 6, 18, 66]. Several groups recent reported that cancer cells preferentially utilize glutamine as a precursor to synthesize fatty acid during hypoxia or in an impaired mitochondria condition [5, 6, 65, 66]. SREBP-1 could also be a key regulator of glutamine metabolism in order to synthesize lipids. Therefore, future studies demonstrating the correlation between glutamine metabolism and SREBP-1 activity is required.

Targeting the SREBP-1 regulated lipogenesis pathway is a promising therapeutic strategy to treat cancer

Over the past decade, pharmacological drug development has been moved towards the identification of molecular targets and discovery of specific small molecular compounds to antagonize these targets to treat cancer, such as EGFR, PI3K, Akt, mTOR and B-Raf [67-70]. These explorations have brought significant advances in cancer treatment. Unfortunately, resistance is frequently observed to these targeted therapies and has compromised the efficacy of the molecular targeted drugs in clinic, such as erlotinib, rapamycin, bevacizumab, PLX4032 et al. [40, 68, 71-74]. Therefore, identifying key

molecular targets and developing new effective therapeutic strategies to treat cancer is still urgent.

SREBP-1

Targeting metabolic alterations has emerged as a new strategy to treat cancer in the past few years, such as targeting glycolysis using 2-deoxyglucose (2-DG) or an HK2 inhibitor, which has shown promising results in a pre-clinical mouse model [48, 75, 76]. Lipogenesis has been shown to be highly activated in cancer and is integrated with both glucose and glutamine metabolism [6, 9, 17, 77, 78]. Thus, suppression of fatty acid synthesis could be a new approach to block cancer malignant growth [1, 79]. SREBP-1, a central regulator of the integration of PI3K/Akt signaling regulated glucose metabolism and Myc-regulated glutamine metabolism to fatty acid synthesis (Fig. 2) [8, 18, 21, 63], has emerged as a very promising druggable target. In human cancer, SREBP-1 has been shown to be highly present in glioblastoma tissues, and its active N-terminus highly localizes in the tumor cell nucleus. This is accompanied by highly expressed downstream genes ACC and FASN [18]. Genetic and pharmacological inhibition of SREBP-1 has been shown to significantly suppress tumor cell growth and lead to cell death [18]. Given the critical role of SREBP-1 in mediating PI3K/Akt signaling and Myc-regulated metabolic flux and possible other signaling pathways, developing specific inhibitors to target SREBP-1 could become a new therapeutic strategy to treat cancer, particularly in tumors with hyperactivated PI3K/Akt signaling.

ACLY, ACC and FASN

In SREBP-1-regulated fatty acid synthesis pathway, ACL, ACC and FASN have been revealed to be highly expressed in cancer (Fig. 2) [1, 18, 53, 80]. Inhibition of these key factors has shown a significant reduction of cancer cell growth *in vitro* and *in vivo* [53, 81-83]. Pharmacological and genetic inhibition of ACL, the enzyme that produces acetyl-CoA in cytoplasm and provides the precursor of lipid synthesis, has been shown to significantly inhibit cancer cell growth *in vitro* and *in vivo* [53, 81]. ACC, the enzyme that controls the rate-limiting step of fatty acid synthesis, is also highly expressed in human cancer tissues [18]. Inhibition of ACC was also shown to significantly suppress tumor growth [84]. At the terminal step in the *de novo* synthesis of fatty acids, FASN has been shown to play a key role in tumor malignant growth. It has been shown to be elevated in most cancers including prostate, breast, glioblastoma and ovarian [1, 18, 80]. Inhibitors that target FASN have been tested in preclinical models and have been shown to exert a significant inhibitory effect on tumor growth [85-87]. In normal tissues, SREBP-1 and its regulated fatty acid synthesis pathway usually display low levels of expression and activity. Therefore, targeting SREBP-1-regulated fatty acid synthesis pathway may be become a very promising strategy for treating cancer.

Inhibiting lipolysis to treat cancer

Fatty acids contribute to cell membrane formation and energy production. When fatty acid levels are excessive in cells, they are converted into triglycerides and deposit into the lipid droplet for temporary storage [88, 89]. Once cells experience a shortage of fatty acids or energy, triglycerides deposited in the lipid droplet will undergo lipolysis via sequential

lipases to release free fatty acids and maintain cellular activity [88, 90, 91]. Monoacylglycerol lipase (MAGL), which catalyzes the final step of lipolysis to convert monoacyglycerol into glycerol and one free fatty acid, has been identified to be highly activated in cancer. Pharmacological inhibition of MAGL has been shown to significantly inhibit tumor growth in a xenograft model [92]. In addition, adipose triglyceride lipase (ATGL) which hydrolytes triacylglycerol to diacylglycerol and releases one free fatty acid [90, 93], and hormone-sensitive lipase (HSL) which catalyzes diacylglycerol to release one free fatty acid and form monoacyglycerol (Fig. 3) [94, 95], may also become potential therapeutic targets. Recently, Nieman *et al.* demonstrated that adipocytes adjacent to metastatic ovarian cancer cells in the omentum through lipolysis provide fatty acid for tumor cell rapid growth [96]. This study demonstrates the importance of lipids in cancer growth. Therefore, further investigation of lipid metabolism within the tumor microenviroment certainly will provide new insights in the understanding of tumorigenesis and further identify effective approaches to treat cancer.

When free fatty acids are utilized in cells, they will be converted to acyl-CoA by acyl-CoA synthetases (ACSs), which then can either enter into the mitochondria for beta-oxidation to produce ATP, be incorporated into phospholipids or associate with proteins for acyl-modification [97]. ACS has been shown to be elevated in cancer [98]. Additionally, pharmacological and genetic inhibition of ACS has been shown to significantly suppress tumor growth and lead to cell death [99].

Cholesterol metabolism

Cholesterol is an important component of cellular membranes. It also contributes to hormone formation, and participates in important signal transduction pathways [10]. Cholesterol maintains cellular membrane integrity and fluidity, and its homeostasis is tightly regulated by uptake, *de novo* synthesis and efflux [23, 100, 101]. SREBPs and nuclear receptor Liver X Receptor (LXR) are critical factors that control cellular cholesterol levels [101, 102]. However, it is less known how cholesterol homeostasis is controlled and whether cholesterol metabolism is altered in cancer cells. Our recent study first uncovered that activated EGFR/PI3K signaling promotes cholesterol uptake by upregulating low density lipoprotein (LDL) receptor (LDLR), which was demonstrated to also be mediated by SREBP-1 (Fig. 2) [19]. This study further showed that depriving cells of cholesterol results in cell death through the activation of LXR by its synthetic agonist.

SREBP-1 mediates PI3K/Akt signaling-regulated cholesterol metabolism through upregulating LDLR

LDL is a major cholesterol-carrier in the bloodstream, which transports cholesterol from the liver to tissues in the rest of the body [103, 104]. When cellular cholesterol levels decrease, LDLR will be expressed and then inserted into the clathrin-coated pits on the cell membrane. The extracellular domain of LDLR will bind circulated LDL and promote its uptake through endocytosis. After LDL enters into cells, it will be delivered to the lysosome, in which LDL is then hydrolyzed by lipases and subsequently releases free cholesterol for cell utilization [105, 106].

One of the main features of tumor cells is high proliferation rates. It is predicted that cancer cells should maintain high levels of cholesterol in order to quickly form new membranes for its rapid division [107]. However, how cancer cells maintain its cholesterol levels are less known. Exogenous uptake and *de novo* synthesis both contribute to cellular cholesterol pools [100], but which route is preferred in cancer cells is unclear. Recently, we revealed that glioblastoma cells prefer to uptake LDL from exogenous media to obtain cholesterol and meet the demand for rapid growth and proliferation, and our data also showed that *de novo* biosynthesis is a compensatory pathway when exogenous cholesterol is scarce [19]. Our study revealed that EGFR/PI3K/Akt signaling promotes cholesterol uptake through upregulation of LDLR. We further revealed that SREBP-1 mediates this signaling pathway (Fig. 2) [19]. Collectively, the studies demonstrated that the oncogenic signaling PI3K/Akt pathway via SREBP-1 integrates glucose metabolism, lipogenesis and cholesterol uptake to provide sufficient energy and essential building blocks for rapid cancer cell growth (Fig. 2) [18, 19]. Taken together, SREBP-1 has been revealed as a central regulator of oncogenic signaling and metabolic flux. Given LDLR is highly upregulated in cancer, and its critical role for cholesterol uptake [18, 108], it could be a promising molecular target in cancer. Inhibition of LDLR should be tested in cancer cells and tumor xenograft models to determine its function in tumor growth and to provide the rationale for developing specific inhibitors or antibodies to block LDLR-mediated cholesterol uptake in order to treat cancer.

LXR/ABCA1 regulates cholesterol efflux

LXR is a key regulator of cellular cholesterol homeostasis. When endogenous cholesterol levels increase, oxysterol levels will also elevate. They then enter into the nucleus and bind to LXR to activate its transcription activity and promote the expression of its target genes, cholesterol transporter genes ATP-binding cassette, subfamily A (ABCA1) or subfamily G (ABCG1). These target genes are responsible for transporting cholesterol to the outside of cells in order to maintain cellular cholesterol homeostasis [101, 109]. Pharmacologically activating LXR has been shown to significantly reduce atherosclerotic lesions in mouse models via elevating cholesterol reverse transport [109, 110]. In cancer, activating LXR by its agonists has been shown to significantly inhibit tumor cell growth and lead to cell death *in vitro* and *in vivo* through elevating ABCA1-mediated cholesterol efflux [19, 111, 112].

Therefore, the LXR/ABCA1 axis has emerged as a promising druggable target in cancer therapy through reducing cells of cholesterol levels [19]. However, activation of LXR by its agonists unfortunately upregulates SREBP-1 gene expression and enhances fatty acid synthesis, which could decrease the efficacy of LXR agonists on tumor growth [113]. To enhance the efficacy of LXR agonists in cancer treatment, LXR agonists could be combined with inhibitors of the fatty acid synthesis pathway to increase the suppression of tumor growth. However, considering the potential toxicity of the combination of drugs, it may be a better strategy to develop a novel LXR agonist with a low effect on SREBP-1 expression in cancer treatment.

LXR and LDLR

LDLR has been shown to be regulated by SREBP-1 or SREBP-2 [26]. A recent study shows LDLR is mainly upregulated by SREBP-1 in cancer cells [19]. Intriguingly, Tontonoz's

group observed that activation of LXR significantly reduces LDLR levels in addition to elevating ABCA1-mediated cholesterol efflux. They further demonstrated that this process is mediated by the inducible degrader of LDLR (Idol), a ubiquitin ligase E3 [114]. In cancers, activation of LXR also elevates Idol expression and significantly reduces LDLR levels [18]. Taken together, these studies demonstrated that reducing cellular cholesterol levels by activation of LXR is caused by elevating ABCA1-mediated cholesterol efflux as well as reducing LDL uptake via degradation of LDLR, which strongly suggests that LXR could be a very promising molecular target in cancer treatment. In addition, development of inhibitors to block LDLR function will be a good approach to decrease cholesterol uptake and therefore treat cancer. Furthermore, cellular cholesterol levels could be significantly reduced by combining an LXR agonist with an LDLR inhibitor and will likely show a significant synergistic effect on tumor growth. In another way, developing a potent agonist of LXR with low SREBP-1 expression activity is desired but may be difficult to achieve. There is recent promising data from Freed-Pastor *et al.* shows that fatostatin, a novel SREBP-1 inhibitor, significantly suppressed tumor growth in breast cancer xenografts [115]. Combination of an SREBP-1 inhibitor, such as fatostatin, with LXR agonists could overcome the upregulation of SREBP-1 expression and result in complete inhibition of tumor growth.

SREBP-2 and cholesterol synthesis

SREBP-2 regulates *de novo* cholesterol synthesis by upregulating enzymes participating in this process [23]. Particularly, the rate-limiting enzyme HMG-CoA reductase has been explored as a significant drug target in order to reduce plasma cholesterol levels [116]. Its inhibitor statin has been shown to dramatically improve the treatment of cardiovascular diseases and significantly enhance heart attack prevention [117, 118]. Given statin's significance in reducing cholesterol levels in plasma, it has been extensively tested in cancer treatment. Unfortunately, the results are controversial for the effects of statin in the inhibition on tumor progression and in the prevention for cancer initiation [119, 120]. Recent meta-analysis of a large population showed that statin treatment does not have a significant effect on tumor growth and in prevention of cancer incidence [121, 122]. These reports are consistent with the recent study in glioblastoma treatment *in vitro* and *in vivo*, in which atorvastatin administration did not significantly inhibit tumor growth in a xenograft model [18]. However, the study demonstrated that atorvastain treatment inhibited tumor cell growth when extracellular cholesterol levels are limited [19]. It could be a good strategy to treat cancer with the combination of a statin and an LDLR inhibitor.

Perspectives

In summary, emerging data indicate that SREBP-1 plays a critical role linking oncogenic signaling with lipid metabolism. Further, recent work indicates that genetic context may impose a differential requirement for SREBP-1 in mediating tumor cell survival, hence providing the opportunity for effective, specific and less toxic targeted therapy. Although in its early stages, and with much work to do, SREBP-1 and the lipogenic machinery provide a promising new set of anti-cancer drug targets. Given that SREBP-1 activity is pretty low in normal tissues, designing specific inhibitors and less toxic drugs to inhibit the enzymes in

the SREBP-1-driven fatty acid synthesis pathway will be a promising strategy to treat cancer.

Acknowledgments

This work was supported by Rose DiGangi American Brain Tumor Association Translational Grant (DG); NIH NS072838 (DG).

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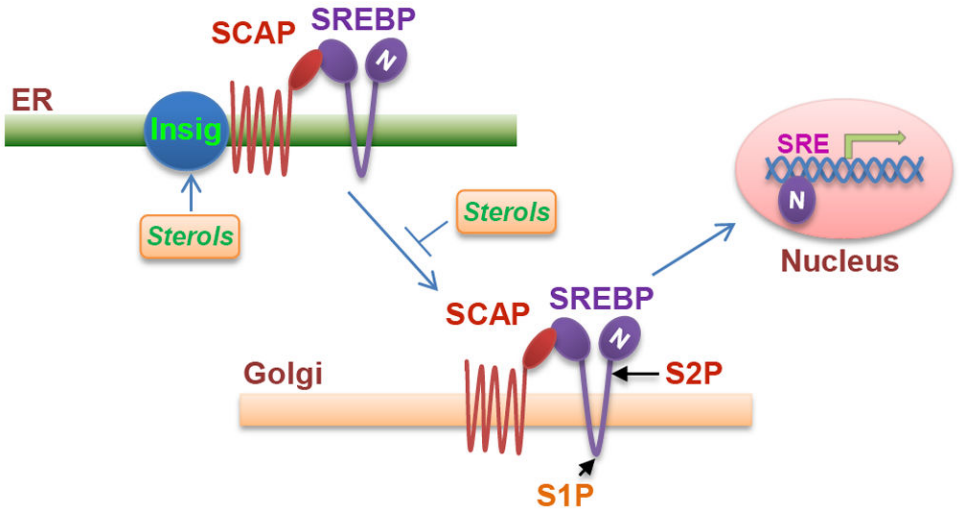

Figure 1. Model for sterols-regulated maturation of SREBPs

The precursor SREBPs locates in the ER membrane in association with SCAP, and Insig interacts with SCAP and retains the SCAP/SREBP complex in the ER membrane in the condition of high sterol levels. SCAP will dissociate from Insig and escort SREBPs translocation to the Golgi apparatus when sterol levels drop. In the Golgi, SREBPs are cleaved sequentially by the S1P and S2P proteases and then release the mature N-terminal fragment (N), which enters the nucleus to transcribe their target genes expression.

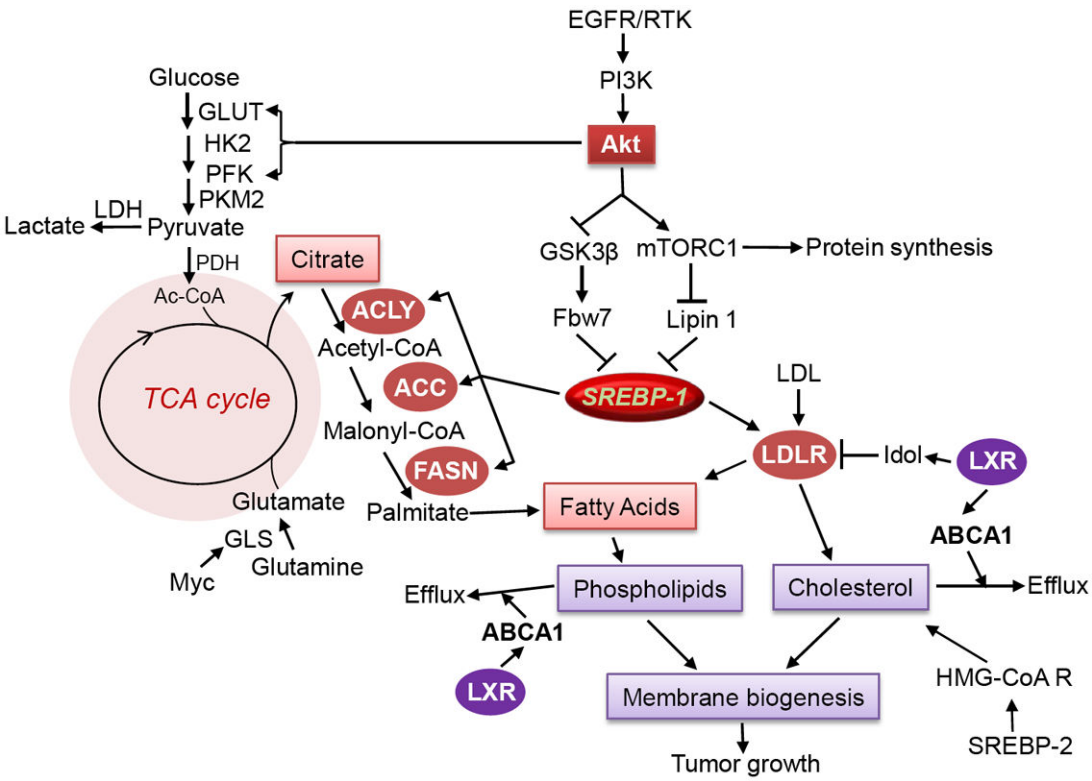

Figure 2. PI3K/Akt signaling regulates SREBP-1-mediated lipid metabolism

The scheme at the left side shows that glycolysis is promoted by PI3K/Akt signaling via promoting GLUT translocation and activating HK2 and PFK to produce pyruvate. Following, pyruvate enters into the mitochondria and generates citrate, and some portion of citrate are released into cytoplasm and hydrolysed by ACL to produce acyl-CoA, which is the precursor for lipid synthesis. In addition, glutamine incorporates into the TCA cycle through glutaminolysis regulated by the Myc oncogene, to provide an additional energy source for cell growth, and also to produce citrate as a precursor for lipid synthesis through reductive carboxylation. The scheme at right side shows that SREBP-1 plays an integral role in mediating oncogenic signaling RTK/PI3K/Akt to fatty acid synthesis and cholesterol uptake. SREBP-1 upregulates the expression of ACL, ACC and FASN to promote fatty acid synthesis, also promotes the expression of LDLR to enhance cholesterol uptake. Activation of LXR stimulates ABCA1 expression and promotes cholesterol and phospholipids efflux, also reduces LDLR levels via upregulating Idol, a ubiquitin ligase E3. GLUT, glucose transporter; HK2, hexokinase 2; PFK, phosphofructokinase; PKM2, pyruvate kinase M2; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; GLS, glutaminase; EGFR, epidermal growth factor receptor; RTK, receptor tyrosine kinase.

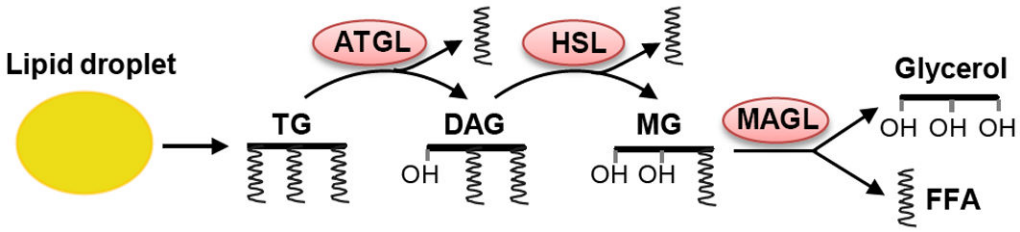

Figure 3. Lipolysis process for triacylglycerol

Triacylglycerol (TG) stored in lipid droplet is sequentially hydrolyzed by lipases ATGL, HSL and MAGL to liberate free fatty acid (FFA) and glycerol as substrates for energy production or membrane formation. ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase; MAGL, monoacylglycerol lipase.