



Review

Role of *de novo* cholesterol synthesis enzymes in cancer

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Abstract

Despite extensive research in the cancer field, cancer remains one of the most prevalent diseases. There is an urgent need to identify specific targets that are safe and effective for the treatment of cancer. In recent years, cancer metabolism has come into the spotlight in cancer research. Lipid metabolism, especially cholesterol metabolism, plays a critical role in membrane synthesis as well as lipid signaling in cancer. This review focuses on the contribution of the *de novo* cholesterol synthesis pathway to tumorigenesis, cancer progression and metastasis. In conclusion, cholesterol metabolism could be an effective target for novel anticancer treatment.

Key words: metabolic reprogramming, *de novo* cholesterol synthesis, cancer progress

Introduction

Over the past few decades, numerous published studies have focused on cancer cell metabolism and have determined that metabolic reprogramming is a hallmark of cancer¹⁻⁶. It is thought that reprogramming of catabolic and anabolic metabolism to harvest energy and synthesize biomass is critical for the survival and growth of cancer cells. Nearly a century ago, Otto Warburg observed that cancer cells tend to use glucose extensively through aerobic glycolysis⁷. Highly proliferative cancer cells also tend to have a high lipid content (fatty acids and cholesterol), which is important for providing energy, membrane synthesis, and lipid signaling⁸. Cancer cells often exhibit an enhanced ability to synthesize lipids and have a higher lipid uptake⁹. Most studies have reported that the upregulation of fatty acid and cholesterol related enzymes is required for tumor progression⁹⁻¹⁴. Lipid metabolism involves lipid synthesis, storage and degradation. In mammals, cholesterol is either absorbed from dietary sources or synthesized *de novo*. The liver and intestinal mucosa are the main sites of cholesterol synthesis. Up to 70-80% of cholesterol in humans is synthesized *de novo* by the liver, and 10% is synthesized *de novo* by the small intestine. Accumulating evidence demonstrates

that cholesterol plays a critical role in cancer progression¹⁵⁻¹⁹. Furthermore, intracellular cholesterol homeostasis is different among various cancer types, and cholesterol itself plays varying roles among different cancer types¹⁷. In this review, we describe normal cholesterol synthesis and cholesterol metabolic changes in cancer cells. Cholesterol biosynthesis pathways could be an attractive therapeutic target for cancer therapeutics.

Total cholesterol and cancer

Cholesterol is a primary lipid that is essential for membrane biogenesis, cell proliferation, and differentiation. Cholesterol is also the precursor of steroid hormones and sterols that induce specific biological responses. Cholesterol is mainly synthesized by the liver in humans, and is distributed throughout the body via high-density lipoprotein (HDL) and low-density lipoprotein (LDL) transporters. Acetyl-CoA is a key precursor of *de novo* cholesterol synthesis²⁰. The reduction of HMG-CoA is an important regulatory step in cholesterol synthesis. Cholesterol itself is an important metabolic intermediate that is converted into cholesteryl esters, bile acids, cholecalciferol/vitamin D, and various

steroid hormones in the appropriate tissues. Cholesterol biosynthesis, regulation of cholesterol plasma levels, and conversion to other compounds is normally carefully regulated²¹. Unlike normal cells, tumor cells upregulate intracellular cholesterol synthesis and exhibit abnormal aggregation of most metabolites.

Transcription factor and cholesterol *de novo* synthesis enzymes

Several steps are required to convert acetyl-CoA to cholesterol, which then is involved in numerous biological roles. These steps involve cholesterol synthase (ACAT, HMGCR, SQLE, OSC), acyl coenzyme A, cholesterol acyltransferases (SOAT), and ATP-binding cassette transporter A-1 (ABCA1). In a situation of decreasing cholesterol availability, inhibiting these enzymes could influence cancer cell growth. Interestingly, many inhibitors of these enzymes have effects on cancer treatment (Figure 1). SREBPs, which were reported the most transcription factors (sterol regulatory element binding proteins,) regulate cholesterol *de novo* synthesis. Also, KLF14²², ChREBP^{23,24}, LXR α ²⁵ and LRH-1²⁶ have very important roles in cholesterol metabolism. Due to the limitation of words, we just reviewed the role SREBP played on it.

SREBP

Lipid homeostasis in vertebrate cells is regulated by a series of membrane-bound transcription factors, the sterol regulatory element-binding proteins (SREBPs). SREBPs directly activate more than 30

genes specific to the synthesis and uptake of cholesterol, fatty acids, triglycerides, and phospholipids, as well as the nicotinamide adenine dinucleotide phosphate cofactor required to synthesize these molecules²⁷.

In 2016, Zhao et al. demonstrated that the hepatitis B X-interacting protein (HBXIP) upregulates SREBP-1c/SREBF1, which activates the transcription of fatty acid synthase by directly interacting with nuclear receptor coactivators and LXR. Overexpression of SREBP-1c can also activate HBXIP transcription. HBXIP enhances fat production, leading to the growth of breast cancer cells *in vitro* and *in vivo*²⁸. Therefore, direct inhibition of SREBPs, resulting in cholesterol depletion, may be an effective cancer therapeutic strategy²⁹.

HMGCR

The 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) enzyme is the rate-limiting enzyme of the cholesterol synthesis pathway. In 2016, two reports showed that autoantibody-positive anti-HMGCR myopathies and HMGCR-positive inflammatory myopathies were association with cancer^{30,31}. In a clinical study, positive cytoplasmic HMGCR expression was associated with colon cancer with distant metastasis-free disease at diagnosis. Positive HMGCR expression was significantly associated with prolonged cancer-specific survival in an unadjusted Cox regression analysis in the entire cohort and in stage III-IV disease³². Increased HMGCR expression was also observed in gastric cancer tissues. Overexpression of HMGCR promoted the growth and

migration of gastric cancer cells, while HMGCR knockdown inhibited growth, migration and tumorigenesis³³. Upregulation of HMGCR was also observed in clinical glioblastoma samples. Forced expression of HMGCR promoted the growth and migration of U251 and U373 cells, while knockdown of HMGCR inhibited their growth, migration and metastasis³⁴. HMGCR was overexpressed in prostate cancer (PC) stroma, especially in early-stage PC. These results provide insights into the molecular mechanisms underlying PC invasion³⁵. Another study found that ectopic expression of hsa-miR-195 in MCF-7 and MDA-MB-231 cells, resulting from targeting HMGCR, significantly altered cellular cholesterol and triglyceride levels as well as reduced proliferation, invasion and migration³⁶.

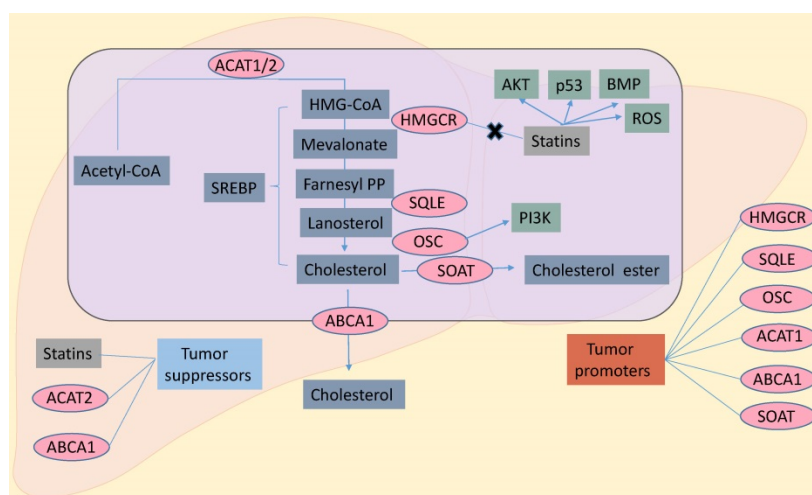


Figure 1. Cholesterol biosynthesis pathway in cancer cells. Inhibitors of HMGCR, statins could exert anti-cancer effects through AKT, p53, BMP, ROS. And OSC through PI3K promoted cancer growth. To sum up, HMGCR, SQLE, OSC, ACAT1, SOAT and ABCA1 are the contributing factors in cancers. Statins, ACAT2 and ABCA1 are inhibitors in cancers. SREBP, sterol regulatory element binding protein; ACAT1/2, acetyl-CoA acetyltransferase 1/2; SOAT, sterol-o-acyltransferase; HMGCR, hydroxy-3-methylglutaryl-coenzyme a reductase; SQLE, squalene epoxidase; OSC, oxidosqualene cyclase; ABCA1, ATP-binding cassette transporter A-1; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; ROS, reactive oxygen species; BMP, bone morphogenetic protein.

Statins are often used to lower cholesterol by inhibiting HMGCR. The multipotency of statins has been associated with cancer risk. Several studies have also found that statins play an important role in the treatment of several cancers ³⁷. In 2012, Gazzero et al. reviewed statin pharmacology, elucidating the prospect of utilizing statins in cancer treatment for hepatocellular carcinoma (HCC), colorectal carcinoma (CRC), and acute myelocytic leukemia ³⁸. A recent Danish study correlated the use of statins in cancer patients. They observed reduced cancer-related mortality for 13 cancer types among statin users. Statin use in patients with cancer is also associated with reduced cancer-related mortality ³⁹. In epithelial ovarian cancer, a retrospective study reported that the use of statins was associated with improved clinical outcomes ⁴⁰. Statin use prior to a cancer diagnosis was correlated to a reduction in all-cause and cancer-specific mortality. Consistent with these data, patients with CRC with pre-diagnosis statin use had prolonged cancer-specific survival, but no benefits were observed for patients with post-diagnosis statin use ⁴¹. Additionally, the risk of CRC was lower in statin users versus nonusers ⁴². The anticancer effect of simvastatin through the induction of apoptosis is related to AKT signaling-dependent downregulation of survival in A549 lung cancer cells ⁴³. In an analysis of 999 colon cancer patients, statin use was correlated with a reduced risk of death from any cause or from cancer. The benefit of statin use was greater for

patients whose tumors had intact bone morphogenetic protein signaling independent of *KRAS* mutation status ⁴⁴. Simvastatin also affected OCM-1 cell growth, apoptosis and cell cycle. In addition, simvastatin resulted in increased ROS levels and significantly increased apoptosis and the expression of the mitochondrion-related apoptosis protein p53 in OCM-1 cells ⁴⁵. In 2016, a surprising report found that statins preferentially inhibited the growth of cancer cells that express mutations, and p53 status impacted statin-dependent efficacy of cancer therapy ⁴⁶.

ACAT

Acetyl-CoA acetyltransferase 1 (ACAT1) is a tetrameric enzyme in the ketogenesis pathway that converts two acetyl-CoA molecules into acetyl-CoA and CoA ⁴⁷⁻⁴⁹. Fan et al. found that knockdown of ACAT1 attenuated tumor growth ⁵⁰. The inhibition of tetrameric ACAT1 by abolishing Y407 phosphorylation, or eliminating arecoline hydrobromide treatment, resulted in suppressed ACAT1 activity ⁵¹. This led to increased pyruvate dehydrogenase complex flux and oxidative phosphorylation, with attenuated cancer cell proliferation and tumor growth. These findings suggested that ACAT1 could be an effective anticancer target. Acetyl-CoA acetyltransferase 2 (ACAT2) also plays an important role in lipid metabolism. ACAT2 downregulation has been associated with a poorer cancer-specific survival prognosis in clear cell renal cell carcinoma ⁵².

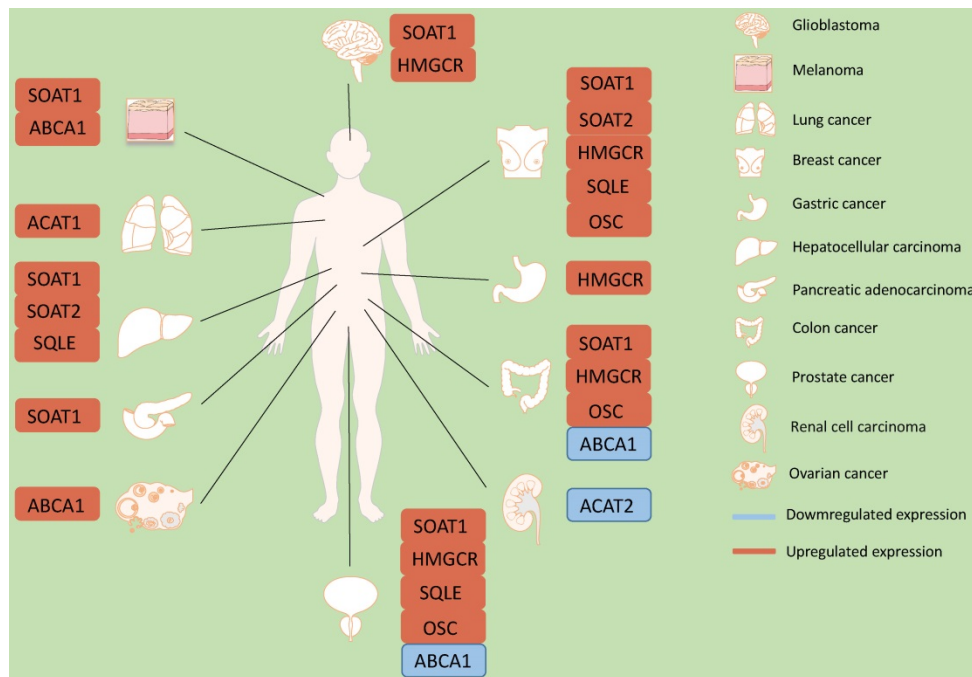


Figure 2. Role of cholesterol synthesis enzymes in different kinds of cancers. In glioblastoma, SOAT1 and HMGCR are up-regulated. In melanoma, ABCA1 and SOAT1 are up-regulated. In lung cancer, SOAT1 is up-regulated. And in breast cancer, SOAT1, SOAT2, HMGCR, SQLE and OSC are up-regulated. In gastric cancer, HMGCR is up-regulated. In hepatocellular carcinoma, SOAT2 and SQLE are up-regulated. In pancreatic adenocarcinoma, SOAT1 is up-regulated. In colon cancer, SOAT1, HMGCR and OSC are up-regulated. However, ABCA1 is down-regulated. In prostate cancer, SOAT1, HMGCR, SQLE and OSC are up-regulated. ABCA1 is down-regulated. In renal cell carcinoma, ACAT2 is up-regulated. In ovarian cancer, ABCA1 is up-regulated.

SOAT

Sterol-o-acyltransferase (SOAT), also called Acyl-CoA cholesterol acyltransferase (ACAT), is an integral membrane protein of the rough ER that catalyzes the formation of cholesteryl esters from cholesterol and long-chain fatty acids. The solubility characteristics of cholesteryl esters make them the ideal molecule for cholesterol storage, which occurs mostly in cytoplasmic lipid droplets inside cells. Thus, SOAT is a key enzyme involved in the control of intracellular cholesterol storage and in determining free cholesterol levels⁵³. SOAT plays an important role in the homeostasis of cell cholesterol metabolism and is a drug target for treatment intervention in various diseases, such as atherosclerosis, Alzheimer's disease and cancer⁵⁴.

In 2019, through proteomic and phosphor-proteomic profiling, he's group found that SOAT1 expression was higher in HCC and was associated with a poor prognosis. In addition, inhibiting SOAT1 markedly suppressed cell proliferation and migration⁵⁵. SOAT1 was also overexpressed in human castration-resistant metastatic PC tissues. These results indicate that the enzymes involved in the ketogenic pathway are upregulated in high-grade PC and could act as potential tissue biomarkers for the diagnosis or prognosis of high-grade disease⁵⁶. Li et al. found an abnormal accumulation of cholesteryl ester in human pancreatic cancer specimens and cell lines, which was mediated by SOAT1. SOAT1 expression was associated with poor outcomes. By using an SOAT1 inhibitor or shRNA knockdown, abrogated cholesterol esterification significantly suppressed tumor growth and metastasis in an orthotopic pancreatic cancer mouse model. SOAT1 inhibition was found to increase intracellular free cholesterol levels, which was associated with ER stress and apoptosis⁵⁷. Furthermore, the availability of cholesteryl esters increased the proliferation and invasiveness of normal cells, indicating that cholesteryl esters may contribute to a tumor-promoting phenotype. Another study showed that breast cancer cell lines treated with auraptene, a naturally occurring SOAT1 inhibitor, also had decreased cellular proliferation, invasion, and colony formation⁵⁸. Treatment of human prostate, pancreatic, lung, and colon cancer cell lines with avasimin, a potent SOAT1 inhibitor, significantly reduced cholesteryl ester storage in lipid droplets and increased intracellular free cholesterol levels. This led to apoptosis and the suppression of proliferation. Systemic treatment of avasimin notably suppressed tumor growth in mice and prolonged survival time⁵⁹. Similarly, SOAT1 inhibition decreased cell proliferation and invasion in two tumor cell lines⁶⁰.

The SOAT1 inhibitor CP-113818 reduced proliferation of breast cancer cells and specifically inhibited LDL-induced proliferation of ER α - cells. A greater ability to take up, store and utilize exogenous cholesterol conferred a proliferative advantage in basal-like ER α - breast cancer cells as well⁶¹.

Revitalizing the cytotoxic potential of CD8+ T cells is of great clinical interest in the cancer immunotherapy field. A novel mechanism to enhance the antitumor response of CD8+ T cells in mice by regulating cholesterol metabolism has been reported. The inhibition of cholesterol esterification in T cells, either by genetic ablation or by pharmacological inhibition of SOAT1, resulted in enhanced effects and proliferation of CD8+ T cells but not CD4+ T cells. In the absence of SOAT1, CD8+ T cells performed better than wild-type CD8+ T cells in controlling the growth and metastasis of melanoma in mice. In addition, combination therapy with avasimibe, SOAT inhibitors and anti-PD-1 antibodies had a superior effect on controlling tumor progression than single agent therapy⁶².

Human SOAT2 is mainly expressed in the intestine and fetal liver. Inhibiting SOAT2 leads to the intracellular accumulation of unesterified oxysterols and suppresses the growth of both HCC cell lines *in vitro* and as xenograft tumors. Further mechanistic studies have revealed that HCC-linked promoter hypomethylation is a major mechanism for SOAT2 gene expression induction. Specifically blocking the cholesterol metabolism pathway established in HCC may have therapeutic effects in HCC patients⁶³. The inhibition of SOAT2 expression significantly decreased leptin-induced proliferation, migration and invasion of MCF-7 and T47D cells. Additionally, leptin may enhance the proliferation, migration and invasion of breast cancer cells in an SOAT2-dependent manner through the PI3K/AKT/SREBP2 signaling pathway⁶⁴.

SQLE

Squalene epoxidase (SQLE) is involved in the first oxygenation step in the cholesterol synthesis pathway, and is therefore a good target for controlling the cholesterol synthesis process⁶⁵. Liu et al. sequenced RNA from nonalcoholic fatty liver disease (NAFLD)-induced HCC samples and revealed SQLE as the top metabolic gene overexpressed in NAFLD-induced HCC patients. In human NAFLD-induced HCC and HCC, SQLE was overexpressed and its expression was associated with poor patient outcomes. Terbinafine, an SQLE-targeting drug, markedly inhibited SQLE-induced cell growth in NAFLD-induced HCC and HCC cells and attenuated tumor development in xenograft models and SQLE

transgenic mice ^{66,67}. These findings are consistent with observations from Stopsack et al. and Brown and his colleagues. In breast cancer and PC, SQLE overexpression is more common and is an independent prognostic factor for poor prognosis ^{68,69}. Given that SQLE may be oncogenic in a growing number of cancers, molecules targeting the SQLE signaling axis may be effective therapeutics for the treatment of malignancies.

OSC

Oxidative squalene cyclase (OSC) catalyzes the transformation of the linear triterpene (3S)-2,3-oxidosqualene into cyclic compounds ⁷⁰. A previous study investigated the role of this post-squalene enzyme, which is involved in the cholesterol biosynthesis pathway, in regulating tumor angiogenesis and metastatic dissemination in mouse models of cancer. The authors showed that Ro 48-8071, a selective inhibitor of OSC ⁷¹, inhibited tumor growth in a spontaneous mouse model of pancreatic cancer and two metastatic mouse models. Remarkably, OSC inhibition suppressed metastasis formation in both the HCT116 and HPAF-II models. OSC inhibition specifically interfered with the PI3K pathway ⁷². Ro 48-8071 also potently reduced breast cancer cell viability, especially in human breast cancer cells. The administration of Ro 48-8071 to mice with tumor xenografts prevented tumor growth with no apparent toxicity. Ro 48-8071 had no effect on the viability of normal human mammary cells ⁷³. *In vivo*, Ro 48-8071 effectively inhibited the growth of human PC xenograft cells in an anti-castration setting, without any signs of toxicity in experimental animals. Importantly, Ro 48-8071 did not decrease the survival rate of normal prostate cells *in vitro* ⁷⁴. Ro 48-8071 is a potent inhibitor of cancer cell proliferation.

ABCA1

Adenosine triphosphate (ATP)-binding cassette (ABC) transporters are drug efflux pumps that can lead to multidrug resistance and to tumor treatment failure ^{75,76}. ATP-binding cassette transporter A-1 (ABCA1) mediates the export of cholesterol and phospholipids to apolipoprotein A-I for HDL assembly ⁷⁷. In addition, ABCA1 is involved in bidirectional sterol movement through the plasma membrane, and regulates cell cholesterol homeostasis ⁷⁸.

Compared with the sensitive MDA-MB-231 breast cancer cells, the overexpression of *ABCA1*, a gene involved in the lipid removal pathway in drug-resistant M14 melanoma ⁷⁹. In human PC biopsy specimens, the expression of *ABCA1* mRNA was approximately twice as high in the androgen-depleted

treatment group than in benign prostatic hyperplasia or PC ⁸⁰. Suppression of the cholesterol transporter ABCA1 inhibited ovarian cancer cell growth and migration *in vitro*. Additionally, the expression of ABCA transporters is correlated with poor outcomes in serous ovarian cancer ⁸¹. JNJ-26854165 is a new type of chemotherapy with p53 activation abilities ^{82,83}. Interestingly, ABCA1 depletion increased sensitivity to JNJ-26854165 ⁸⁴.

ABCA1 exhibits anticancer activity that inhibits the expression of the *ABCA1* gene through functional mutations in oncogenes or cancer-specific ABCA1. In 2012, one excellent study by Smith et al. revealed that the anticancer activity of ABCA1 efflux is impaired after *ABCA1* gene expression is inhibited by either an oncogenic mutation or cancer-specific ABCA1 functional deletion mutation. ABCA1 deficiency in conjunction with the high cholesterol synthesis found in cancer cells can lead to increased mitochondrial cholesterol, thereby promoting cancer cell survival ¹⁹. In LNCaP cells, a DNA methylome analysis revealed that the promoter of *ABCA1* is markedly hypermethylated. These findings suggest that the loss of cancer-specific *ABCA1* hypermethylation and protein expression directly leads to elevated levels of cholesterol in cells, thereby contributing to tumor development ⁸⁵. ABCA1 is also aberrantly expressed in colon cancer tissues and cells. Silencing ABCA1 or miR-183 promoted proliferation and inhibited apoptosis in colon cancer cells ⁸⁶.

Conclusions

In summary, cancer cells rely on cholesterol as a cellular building block for membrane formation and for the production of signaling molecules. This review highlights the importance of cholesterol, cholesterol transporters and metabolites, and key enzymes of cholesterol metabolism in cancer (Figure 1). The requirement of cholesterol for cancer cell proliferation reveals a potential cancer therapeutic target at multiple points within the cholesterol metabolism pathway to inhibit proliferation. Numerous chemical inhibitors for specific steps in the metabolism pathway already exist. Targeting cholesterol metabolism could be more a selective therapeutic modality for highly proliferative cells. Alternatively, cholesterol metabolism inhibitors could be utilized in a cell-specific and targeted manner. Cancer is a diverse set of diseases with various genetic changes. Cholesterol metabolism is also complex, with many different feedback mechanisms and regulatory points. In addition, most cholesterol metabolism enzymes have multiple isoforms, which may be connected to different lipid metabolism processes, cellular localization, or tissue distribution.

Successful treatments may depend on understanding specific metabolic abnormalities in certain types of cancer^{87,88} (Figure 1). While some cholesterol metabolites contribute to cancer development and resistance, others have therapeutic potential. Further insight on cholesterol metabolism in cancer cells will allow us to take advantage of new and effective targets to improve the survival rate of cancer patients.

Abbreviations

HDL: high-density lipoprotein; LDL: low-density lipoprotein; SREBPs: sterol regulatory element binding proteins; SR-BI: scavenger receptor class B, type I; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; CRC: colorectal cancer; ROS: reactive oxygen species; ER: estrogen receptor; PC: prostate cancer; ISC: intestinal stem cell; EC: endometrial cancer; NADPH: nicotinamide adenine dinucleotide phosphate; HBXIP: Hepatitis B X-interacting protein; FAS: fatty acid synthase; NR: nuclear receptor; SCAP: SREBP cleavage activation protein; ACAT: acetyl-coA acetyltransferase; AH: arecoline hydrobromide; PDC: pyruvate dehydrogenase complex; SOAT: sterol-o-acyltransferase (also named acyl-coA cholesterol acyltransferase); CE: cholesteryl ester; SE: steryl ester; LD: lipoprotein-depleted; HCC: hepatocellular carcinoma; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; CSS: cancer-specific survival; HMGCS1: 3-hydroxy-3-methylglutaryl-CoA synthase 1; AML: acute myelocytic leukemia; BMP: bone morphogenetic protein; SQLE: squalene epoxidase; NAFLD: nonalcoholic fatty liver disease; OSC: oxidative squalene cyclase; ATP: adenosine triphosphate; ABCA1: ATP-binding cassette transporter A-1.

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Author Contributions

Writing the manuscript and the figures, J.Y.; editing the manuscript, L.H.W and R.B.J.

Competing Interests

The authors have declared that no competing interest exists.

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