World Journal of Surgery and Surgical Research

Research Article
Published: 25 Apr, 2024

# The Role of Cholesterol Metabolism and Its Regulation in Tumor Development

*Song W[1#], He J[2#], Wu X[3#], Su M[1,3], Hu R[1,2]* and Zhao Y[1,3]**

[1]Department of Human Histology and Embryology, Guizhou Medical University, China

[2]Characteristic Key Laboratory of Translational Medicine Research of Cardiovascular and Cerebrovascular Diseases in Guizhou Province, Guizhou Medical University, China

[3]Center for Tissue Engineering and Stem Cell Research, Key Laboratory of Regenerative Medicine in Guizhou Province, Guizhou Medical University, China

[#]These authors contributed equally to this work

## Abstract

Cholesterol and its metabolites play a crucial role in cancer development and suppression of immune responses. In recent years, a large number of experimental and clinical studies have shown that manipulation of cholesterol metabolism modulates functions in tumor biological processes, particularly oncogenic signaling pathways, ferroptosis, and the tumor microenvironment. We elucidate in detail the interactive effects produced by cholesterol metabolism and the tumor microenvironment. We also discuss therapeutic strategies aimed at interfering with cholesterol metabolism, and some new cholesterol metabolizing molecules, SREBP, SQLE and HMGCR have recently emerged as promising drug targets for cancer therapy. Here, we systematically review the role of cholesterol and its metabolites, as well as recent advances in cancer therapy targeting cholesterol metabolism.

**Keywords: Cholesterol; Metabolism; Cancer; Tumor Microenvironment; Immune**

OPEN ACCESS

***Correspondence:***
*Rong Hu, Department of Human Histology and Embryology, Guizhou Medical University, and Characteristic Key Laboratory of Translational Medicine Research of Cardiovascular and Cerebrovascular Diseases in Guizhou Province, Guizhou Medical University, Guiyang, Guizhou 550025, China,*
*Youbo Zhao, Department of Human Histology and Embryology, Guizhou Medical University, and Center for Tissue Engineering and Stem Cell Research, Key Laboratory of Regenerative Medicine in Guizhou Province, Guizhou Medical University, Guiyang, Guizhou 550025, China,*

**Received Date**: *25 Mar 2024*
**Accepted Date:** *19 Apr 2024*
**Published Date:** *25 Apr 2024*

***Citation:***
*Song W, He J, Wu X, Su M, Hu R, Zhao Y. The Role of Cholesterol Metabolism and Its Regulation in Tumor Development. World J Surg Surgical Res. 2024; 7: 1538.*



## Introduction

Cholesterol, a derivative of cyclopentane poly-hydro-phenanthrene with the chemical formula $C_{27}H_{46}O$, is the major steroidal compound in mammals and plays an important role in basic cellular life activities [1]. As an essential lipid component of mammalian cell membranes, cholesterol maintains the integrity and fluidity of cell membranes and forms cell membrane microstructures [2]. It can also act as an important regulator of cellular signaling, both through direct effects on the cell membrane and through activation of oxygenated metabolites from specific receptors (steroids, hydroxycholesterol, bile acids) [3]. Homeostasis of cholesterol metabolism in the cell is maintained by a complex network regulating cholesterol biosynthesis, uptake, efflux, conversion, esterification and cholesterol transport [4]. More importantly, cholesterol and its derived metabolites play an important role in promoting tumorigenesis as well as suppressing the tumor immune response [5]. Excess cholesterol activates the Sterol-Regulatory Element Binding Proteins (SREBPs) [6], Fatty Acid Synthase (FASN) [7,8], overexpression 3-Hydroxy-3-Methyl Glutaryl Coenzyme A Reductase (HMGCR) [8], which occurs in a variety of cancers and their pre-cancerous lesions, including hepatocellular carcinoma, gastric carcinoma, prostate carcinoma, non-small-cell lung carcinoma, and melanoma, and has been associated with cancer recurrence and death [9-11]. Cholesterol also acts as a signaling molecule that regulates morphogenetic elements, such as Hedgehog signaling [12], as well as being able to mediate a variety of signaling pathways such as Wnt/β-catenin, EGFR-STAT3 and others [13,14]. In addition, cholesterol biosynthesis affects Cancer Stem Cells (CSCs) responsible for tumor progression, recurrence and drug resistance, which could be a potential target for cancer treatment [15].

In this paper, we have elaborated on the mechanism of cholesterol synthesis, the expression and regulation of key enzyme activities and the important role that cholesterol metabolism plays in tumor development, as well as exploring the feasibility of cholesterol metabolism for the development of future clinical anti-tumor therapy.

## Cholesterol Intake

The biological functions of cholesterol are diverse, ranging from cell membrane integrity,

cell membrane signaling, and immunity to the synthesis of steroids and sex hormones, vitamin D, bile acids, and oxysterols [16-19]. Cholesterol is derived from two sources, exogenous, where the vast majority of cholesterol is derived from dietary cholesterol [20,21], and endogenous, where it is synthesized by the body itself [22]. An increase in exogenous cholesterol can feedback inhibit endogenous cholesterol synthesis [22,23]. Two main lipoproteins are involved in cholesterol transportation: namely, Low-Density Lipoprotein (LDL) and High-Density Lipoprotein (HDL) [24]. The former transports cholesterol from the liver to tissue cells throughout the body, whereas the latter transports cholesterol from tissue cells to the liver in a dynamic equilibrium [25]. In contrast, disturbances in cholesterol homeostasis are considered to be one of the manifestations of cancer, and the regulation of cholesterol homeostasis can interfere with the onset and progression of cancer [26].

## Exogenous acquisition

Cholesterol is mainly found in esterified form in meat, fish, eggs and dairy products [24]. Among them, Niemann-Pick C1-Like 1 (NPC1L1) is essential for intestinal cholesterol absorption. In the intestinal lumen, cholesterol binds to bile salt micelles and is transported through the intestinal epithelium at the Brush Border Membrane (BBM) *via* NPC1L1 in response to lattice protein-mediated endocytosis [14,27,28]. Binding of cholesterol to the amino-terminal structural domain of NPC1L1 induces dissociation of the carboxyl terminus from the Plasma Membrane (PM), exposing the endocytosis motif Y1306VNxxF (where x represents any amino acid) for NUMB recognition [29]. NUMB recruits AP2/Clathrin to generate Clathrin-encapsulated vesicles and initiates endocytosis of NPC1L1, while NPC1L1 interacts with Flotillin-1/2 proteins to form cholesterol-rich membrane microstructural domains, and in this vesicular transport mode NPC1L1 transports large amounts of cholesterol to the Endocytosis Recycling Chamber (ERC) [30]. NPC1L1 can bind different amounts of cholesterol molecules in response to changes in cholesterol levels *via* its Sterol Sensing Domains (SSDs) [31], and triggers Clathrin-mediated auto endocytosis and its action on cholesterol molecules in the vicinity of the endoplasmic reticulum. Internalized cholesterol in the small intestine is then transported to the endoplasmic reticulum where it is modified by Acyl-CoA Cholesterol Acyltransferase 2 (ACAT2) to cholesteryl esters, which are secreted into the interstitial space of the cells in the form of Chytridiales Microsomes (CMs) or High-Density Lipoproteins (HDLs), migrate to the lamina propria, enter the luminal ducts of the lymphatic system, and pass through the portal vein to the liver or through the thoracic duct into the circulation [22,32,33]. In addition, absorbed cholesterol can be exported from the cell *via* adenosine triphosphate-binding cassette transporter G5/G8 (ABCG5/ABCG8) heterodimer and re-secreted back into the intestinal lumen [34].

Current studies have shown that NPC1L1 influences colorectal cancer development and prognosis and can be used as an independent prognostic marker for colorectal cancer cancers [35,36], furthermore, cells entering the Drug-Tolerant Persister (DTP) state in Multidrug-Resistant (MDR) cancer cells counteracted chemotherapy-triggered oxidative stress by promoting NPC1L1-regulated vitamin E uptake, and the use of the NPC1L1 inhibitor ezetimibe treatment can further enhance the effect of combination therapy by inducing methuosis [37].

## Endogenous synthesis

The liver is the main site of cholesterol biosynthesis, delivering endogenously synthesized and exogenously obtained cholesterol to the blood as Very Low-Density Lipoprotein (VLDL) [38,39]. Cholesterol synthesis is a multistep reaction process with extremely high energy expenditure, requiring 18 acetyl coenzyme a, 36 ATP, 16 NADPH and 11 oxygen molecules for the synthesis of one cholesterol molecule [1,39]. This biosynthetic pathway converts acetyl coenzyme a to cholesterol through nearly 30 enzymatic reactions, including the mevalonate pathway, squalene biosynthesis and subsequent conversion [40]. Two acetyl coenzyme molecules in the cytoplasm condense to form Acetoacetyl coenzyme a, which reacts with a third acetyl coenzyme a to produce 3-Hydroxy-3-Methylglutaryl Coenzyme a (HMG-CoA), which is reduced to mevalonate by the 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase (HMGCR), and a series of enzymatic reactions converts the mevalonate to Farnesyl Pyrophosphate (FPP), the precursor of stanols and all non-sterol isoprenoids [41]. The condensation of two FPP molecules to squalene refers to the production of sterols, and FPP also produces Geranylgeranyl pyrophosphate (GGPP), both FPP and GGPP can pentenoic acid and activate a number of oncogenic proteins, such as small GTP-binding proteins [42,43]. Cells largely fulfill their cholesterol requirement through de novo synthesis of acetyl coenzyme a, which is particularly important for cancer cells to maintain dysregulated cell proliferation [44] (Figure 1).

HMGCR, the predominant rate-limiting enzyme in cholesterol biosynthesis, is highly regulated at the transcriptional, translational and post-translational levels [45]. Mammalian HMGCR is an Endoplasmic Reticulum (ER)-localized glycoprotein comprising a hydrophobic N-terminal structural domain that spans the cell membrane 8-fold and a larger soluble N-terminal structural domain that projects into the cytoplasm [46-48]. HMGCR expression is upregulated in ovarian, hepatocellular, and breast cancers [49-51]. Overexpression of HMGCR promotes cancer cell growth and migration, while HMGCR knockdown inhibits tumorigenesis [52]. Statins, as competitive HMG-CoA Reductase (HMGCR) inhibitors, not only lower cholesterol and improve cardiovascular risk, but also have anticancer properties [53], and statins have been targeted for the treatment of a wide range of drug-resistant solid and hematologic cancers [54,55]. Early-stage T-cell Acute Lymphoblastic Leukemia (ETP ALLs) shows increased biosynthesis of phospholipids and sphingolipids and is particularly sensitive to inhibition of the rate-limiting enzyme HMG-CoA reductase in the mevalonate pathway, mechanistically inhibiting oncogenic AKT1 signaling by the restriction of cholesterol synthesis and inhibiting the expression of MYC through the loss of leukemia stem cell-specific distal regulation of MYC enhancer chromatin [56]. In addition to being a substrate for HMGCR, HMG-CoA can be catalyzed by HMG-CoA-Lyase (HMGCL) to produce acetoacetate, a ketone body necessary for activation of MEK in certain tumor types [57]. HMG-CoA reductase also has a transmembrane sterol-sensing structural domain that plays a role in activating the degradation of the enzyme, which is also regulated at the transcriptional level by the regulation by Sterol Regulatory Element Binding Protein #2 (SREBP-2) [58].

## Homeostatic imbalance

Disturbed cholesterol homeostasis plays a key role in the development of several diseases, such as Cardiovascular Disease (CVD), neurodegenerative diseases and cancer [59]. Especially in cancer, the therapeutic idea of targeting cholesterol metabolism for cancer treatment has been widely tested in the clinic in recent years [60]. Cholesterol deficiency was found to be present in T cells within

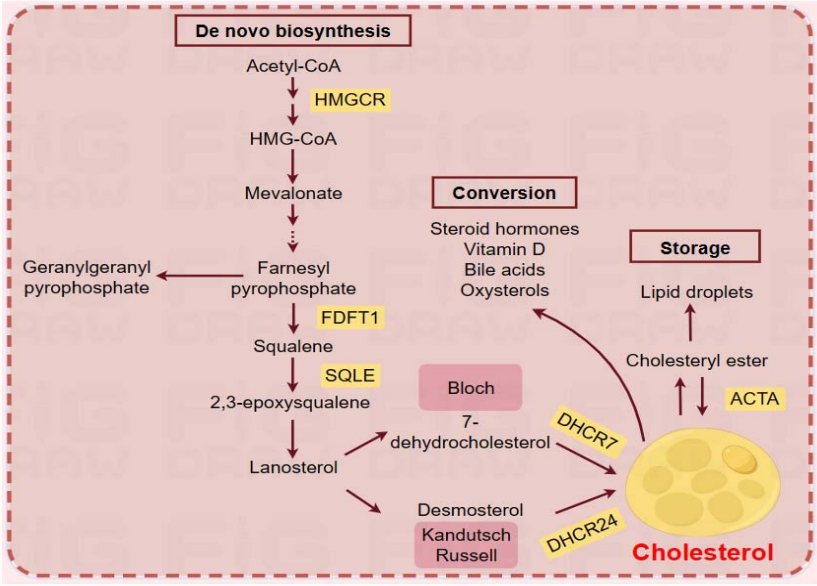


**Figure 1:** *De novo* biosynthesis, conversion, and storage of cholesterol in organisms.

tumors, whereas immunosuppressive myeloid and tumor cells showed significant upregulation of cholesterol, and low cholesterol levels inhibited T cell proliferation while inducing autophagy-mediated apoptosis, particularly in cytotoxic T lymphocytes [61]. In the tumor microenvironment, oxysterols mediate reciprocal alterations in the LXR and SREBP2 pathways, contributing to T-cell cholesterol deficiency and subsequently leading to aberrant metabolism that drives T-cell exhaustion and dysfunction [62,63]. LXRβ deficiency in Chimeric Antigen Receptor T (CAR-T) cells improves antitumor function against solid tumors [64].

Adrenal and gonadal steroidogenesis begins with the translocation of cholesterol to mitochondria, which is mediated by the Recombinant Steroidogenic Acute Regulatory Protein 1 (STARD1), which contains a mitochondrial import sequence and a cholesterol-binding START structural domain [65], and cholesterol translocation to mitochondria *via* STARD1 is the alternative pathway of Bile Acid (BA) production in the rate-limiting step [66]. High expression of STARD1 promotes primary BA synthesis through the mitochondrial pathway, and its products stimulate hepatocyte self-renewal, stemness, inflammation, and Hepatocellular Carcinoma (HCC) development [67-69].

Proprotein Convertase Subtilisin/Kexin type-9 (PCSK9), the highest up-regulated of the cholesterol-related genes, acts as a regulator of cholesterol homeostasis, and plays a role in increasing circulating Low-Density Lipoprotein (LDL) - cholesterol (LDLc) levels by enhancing the sorting and escorting of LDL Receptor (LDLR) to lysosomes on the cell surface. Cholesterol (LDLc) levels, which involves the binding of the catalytic structural domain of PCSK9 to the EGF-A structural domain of the LDLR, and also requires the presence of the C-terminal Cys/His-rich structural domain, its binding to secreted cytosolic cyclase-associated protein 1, and potentially another membrane-bound "protein X "PCSK9 deficiency inhibits the growth of APC/KRAS mutant CRC cells *in vitro* and *in vivo via* the GGPP-KRAS/MEK/ERK axis, whereas PCSK9 overexpression induces carcinogenesis [70-72]. Knockdown of the mouse PCSK9 gene in concomitant cells was significantly attenuated in a cytotoxic T-cell-dependent manner, enhancing the efficacy of immunotherapy targeting the checkpoint protein PD1, and inhibition of PCSK9 by gene deletion or use of a PCSK9 antibody increased the expression of the Major Histocompatibility Complex I (MHC I) proteins on the surface of the tumor cells, facilitating a powerful intra-tumor infiltration [73].

## Regulatory Components and Key Enzymes in the Regulation of Cholesterol Metabolism and the Role in Cancer

### SREBPs

SPEBPs are important modules in the regulation of cholesterol metabolism, which not only play an important role in metabolic diseases, but also have been found to play a key role in the development of tumors [74,75]. SREBPs are involved in the formation of the energy supply, lipid supply, immune environment, and inflammatory milieu of the tumor cells and act as a protective shield to support the malignant proliferation of tumor cells [76]. SREBPs belong to the family of membrane-bound proteins and are basic helix-loop-helix leucine zipper transcription factors. The isoforms are SREBP-1a, SREBP-1c, and SREBP-2. Of these, SREBP-1a and SREBP-1c are encoded by the same gene, while SREBP-2 is encoded by a separate gene [77,78]. SREBP-1 is mainly regulated by caloric restriction [79], whereas SREBP-2 is stimulated by thyroid hormones and itself [80]. SREBP-2 is also preferentially involved in gene transcription in cholesterol biosynthesis [81]. Under physiological conditions, activation of SREBPs is tightly regulated by sterol-triggered negative feedback loops in the ER [82]. Classical activation is mainly mediated by Insulin-Inducible Genes (INSIG) and SREBP Cleavage-Activating Protein (SCAP) [83-85]. Extracellular cholesterol is carried by LDL and binds to the LDLR on the cell surface. Upon binding, cholesterol is transported into the cell and broken down by lysosomes into intracellular cholesterol [86,87]. Intracellular cholesterol binds to the sterol transporter ATP-Binding Cassette subfamily A member 1 (ABCA1)/ATP-Binding Cassette subfamily G member 1 (ABCG1) and is translocated to the extracellular space, accomplishing cholesterol uptake and efflux [88,89]. miR-33 embedded introns are co-transcribed with SREBPs, which can inhibit the expression of

ABCA1 and ABCG1, thereby inhibit cholesterol reversal [90]. Excess cholesterol in cells binds to SREBP-mediated fatty acids and esterifies them to cholesteryl esters to avoid negative cholesterol regulation, and these measures provide a large amount of energy and nutrients and protection for tumor cell proliferation [91-93].

SREBPs are also involved in the activation of M1-type macrophages [94]. M1-type macrophages use glycolysis as the main mode of energy supply. Disruption of the tricarboxylic acid cycle in M1 macrophages leads to the accumulation of citric and succinic acids, which activate HIF1α, which in turn leads to the release of pro-inflammatory factors [95,96]. LPS induces, through a TLR4 signaling dependent and independent pathway NF-κB activation, which induces the expression of SREBPs and promotes lipid synthesis and accumulation [97]. Acetyl-CoA synthetase (ACLY) acts as a downstream gene of SREBPs and participates in lipid synthesis, driving the release of ROS, NO, PGE2 [98,99]. SREBPs also activate Nlrp1a and Nlrp1c, leading to the release of pro-inflammatory factors [100,101]. The role of SREBPs is not limited to macrophages, but is also broadly involved in T-cell function as well as in the specific functions of innate and adaptive immunity [102,103]. SREBPs are required in the metabolic reprogramming of CD8+ T cells in response to mitogenic signals, and their absence in CD8+ T cells renders them ineffective against matricellular cells, leading to reduced proliferative capacity *in vitro* and attenuated clonal expansion during viral infection [104]. In dendritic cells, cholesterol accumulation accelerates the development of autoimmunity at the transcriptional level through Nod-Like Receptor 3 (NLRP3) isoforms [105,106].

## FDFT1

FDFT1 is a key enzyme molecule in the endogenous cholesterol synthesis pathway, which generates squalene through the condensation of two FPPs [107], an enzyme consisting of 416 amino acids with a molecular weight of 47-kDa, and is found almost exclusively in the endoplasmic reticulum [108]. Abnormal expression of FDFT1 occurs in a wide variety of cancers, which can be serve as a new candidate biomarker and a novel target for cancer therapy [109]. In addition to its role as a structural element in cholesterol biosynthesis, the product of the FDFT1 reaction, PSDP, has an additional function as a bioactive lipid that directly inhibits phospholipase D and leukocyte activity, thereby down-regulating intracellular signaling and attenuating the magnitude of the acute inflammatory response, thereby decreasing the risk of damage to host tissues, an activity that exhibits PSDP's role in the inflammatory response in neutrophils as a mediator property [110].

Most studies have reported that upregulation of FDFT1 is required for tumor progression because cholesterol is essential for cell proliferation and lipid rafts are required for signaling, invasion, and migration of cancer cells. FDFT1 is highly expressed in sphere-forming breast cancer and neuroblastoma stem cells, which exhibit a very high capacity for auto-renewal and differentiation, as well as resistance to cancer therapy [111,112]. And in colorectal cancer FDFT1 exerts tumor suppressor function by negatively regulating AKT/mTOR/HIF1α signaling [113]. FDFT1 not only serves as an important gene for predicting the prognosis of patients with colorectal cancer, but currently FDFT1 has been identified as a ferroptosis gene [114,115]. The expression of FDFT1 is significantly increased during cell proliferation, which suggests that FDFT1 is involved in proliferative signaling in cancer cells. Specifically, FDFT1 regulates the cell cycle, in which inhibition of FDFT1 significantly hinders the period of synthesis in cell cycle. In addition, FDFT1 activates the NF-κB pathway, leading to increased levels of anti-apoptotic proteins such as Bcl-xL, Bcl-2, and Bax, and to decreased levels of pro-apoptotic proteins such as caspase-3, thus blocking the apoptotic signaling pathway [116]. In Squalene Epoxidase (SQLE)-deficient cancer cells, high expression of FDFT1 increased intracellular squalene levels, thereby protecting the cell membrane from lipid peroxidation by ROS and further preventing cells from entering the iron death pathway [117].

## EBP

EBP is an endoplasmic reticulum membrane protein that converts yeast sterols to dehydro-plant sterols or yeast sterols to plat sterols. The products of these two reactions are involved in cholesterol biosynthesis, autophagy, and oligodendrocyte formation through one of two parallel pathways, termed the Bloch and Kandutsch/Russell pathways, respectively [118]. Inhibition of EBP leads to the accumulation of its substrate's enzyme sterols and enzyme enols, which promotes autophagy in tumor cells [119,120]. Notably, EBP binds a large number of structurally diverse pharmacologically active compounds, including antidepressants, antipsychotics, opioid analgesics, sterol biosynthesis inhibitors, and antitumor reagents [121].

The Hedgehog (Hh) pathway plays a central role in vertebrate embryonic development and carcinogenesis, and G-protein-coupled receptor-like protein Smoothing (SMO) is one of the major members of the Hh pathway. Covalent modification of cholesterol on the 95$^{th}$ asparagine (D95) of human SMO, which is regulated by Hh and PTCH1, is essential for SMO activation. EBP acts as an SMO-interacting protein, and overexpression of EBP inhibits SMO cholesterolylation and Hh pathway activity, whereas genetic disruption of EBP enhances SMO cholestrerolization and downstream signaling. EBP-mediated SMO inhibition of cholesterolylation is independent of its isomerase activity but dependent on the C-terminus of EBP required for SMO binding [122]. In contrast, in colorectal cancer, inhibition of EBP leads to cancer cell death through depletion of downstream sterols [123]. EBP inhibitors have been shown to have a favorable inhibitory effect on the proliferation of the human prostate cancer PC-3 cell line [124]. Accumulation of EBP at the mRNA and protein levels is observed in Mesenchymal Lymphoma Kinase (ALK+) tumors [125].

## SQLE

Squalene Epoxidase (SQLE) controls cholesterol biosynthesis by converting squalene to 2,3-diene oxide [126]. In human cells, the gene encoding SQLE is located in the chromosome 8q24.1 region [127]. SQLE is a direct target of SREBP2, and the SQLE protein also contains a cholesterol-sensing domain that regulates the proteasomal degradation of SQLE, so that, like HMGCR, SQLE activity is precisely regulated by intracellular cholesterol levels in the form of feedbacks, which makes it the second rate-limiting step in cholesterol synthesis [128]. Its loss leads to the accumulation of the upstream metabolite squalene. Although squalene is usually undetectable, squalene alters cellular lipid distribution, protects cancer cells from ferroptosis and provides a growth advantage for tumors under conditions of oxidative stress and in tumor xenografts [117]. SQLE is considered an oncogene that promotes oncogenic signaling, and indeed, frequent SQLE amplification and differential expression have been reported in cancer [129,130]. Given that the correlation between gene transcripts and protein abundance in tumors is likely to be low, and that small molecule SQLE inhibitors target proteins rather than mRNAs, it is

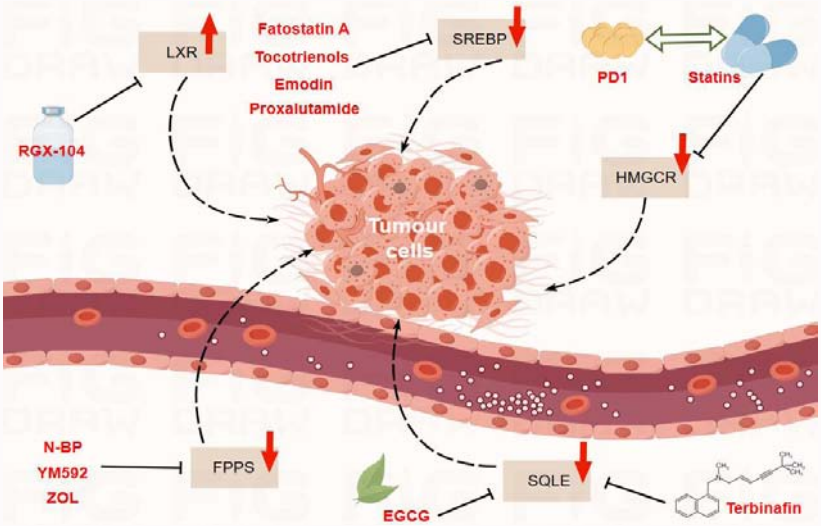


**Figure 2:** Targeting regulatory elements and key enzymes of cholesterol metabolism for cancer therapy.

important to study the expression of SQLE proteins in cancers and assess their significance in patient prognosis [131].

SQLE promotes CRC cell proliferation by inducing cell cycle progression and inhibiting apoptosis, whereas inhibition of SQLE reduces the levels of Calcitriol (the active form of vitamin D3) and CYP24A1, followed by an increase in the intracellular Ca2+ concentration, followed by an inhibition of MAPK signaling, leading to the suppression of CRC cell growth [132]. The concomitant use of the SQLE inhibitor terbinafine can inhibit CRC growth by synergizing with oxaliplatin and 5-fluorouracil [133]. In prostate cancer PTEN/p53 defects upregulate SQLE through activation of SREBP2 transcription and also enhance the protein stability of SQLE by inhibiting the PI3K/Akt/GSK3β-mediated proteasomal pathway, thus the synergistic relationship that exists between SQLE and PTEN/p53 deficiencies in order to increase cholesterol biosynthesis for tumor cell growth and survival [134]. SQLE expression is specifically elevated in HCC and is strongly associated with poor clinical outcomes. SQLE significantly promotes HCC growth, epithelial-mesenchymal transition, and metastasis both *in vitro* and *in vivo*, and the effect of SQLE on HCC is associated with STRAP-dependent activation of TGF-β/SMAD signaling [135]. Activation of SQLE by nuclear receptor subfamily 4 group A member 2 (NR4A2) dysregulates cholesterol homeostasis in microglia, oxidative stress promotes tumor growth *via* NR4A2-SQLE activity in microglia, and targeting SQLE enhances therapeutic effects of immune checkpoint blockade *in vivo* [136]. In addition, SQLE increases the NADP+/NADPH ratio, which triggers DNA Methyltransferase 3A (DNMT3A) expression, DNMT3A-mediated epigenetic silencing of Phosphatase Tensin Homologs (PTEN), and activation of oncogenic targets of the rapamycin pathway [129].

### DHCR24

DHCR24 is the final enzyme in the cholesterol biosynthesis pathway and is involved in the formation of lipid rafts and catalyzes the reduction of the Δ24 double bond in congeners to produce cholesterol [137,138]. DHCR24 is involved in a variety of cellular functions such as oxidative stress, cellular differentiation, anti-apoptotic function and anti-inflammatory activity [139].

DHCR24 expression is higher in breast cancer than in normal breast, especially in luminal and HER2-positive breast cancer tissues. DHCR24 overexpression enhances breast cancer stem-like cell populations and the number of acetaldehyde dehydrogenase-positive cells, and DHCR24 promotes the growth of cancer stem-like cells by augmenting the Hedgehog signaling pathway [140]. DHCR24 is a direct target of the stem cell regulator SOX9, and in a Diffuse Large B-Cell Lymphoma (DLBCL) cell line xenograft model, knockdown of SOX9 resulted in reduced levels of DHCR24, decreased cholesterol content, and reduced tumor load, meaning that SOX9 can drive lymphomas through the DHCR24 and cholesterol biosynthesis pathways, and the SOX9-DHCR24-cholesterol biosynthesis axis could be a new therapeutic target for DLBCLs [141]. Since Serine/arginine-Rich Splicing Factor 3 (SRSF3) regulation may be beneficial for the treatment of Colorectal Cancer (CRC), silencing SRSF3 significantly inhibited the proliferation and migration of CRC cells through inhibition of its target gene, DHCR24, and the novel SRSF3 inhibitor, SFI003, exhibited potent antitumor efficacy *in vitro* and *in vivo*, driving apoptosis in CRC cells through the SRSF3/DHCR24/ROS axis [142]. Persistent Hepatitis C Virus (HCV) infection induces hepatocyte tumorigenicity, and HCV-induced high expression of DHCR24 exhibits resistance to oxidative stress and apoptosis while leading to reduced acetylation of p53 at lysine residues 373 and 382 in the nucleus, suggesting that DHCR24 is elevated in response to HCV infection and inhibits p53 stress by stimulating the MDM2 (cytoplasmic p53-specific E3 ubiquitin ligase)-p53 complex accumulation in the cytoplasm and inhibiting the p53 stress response by suppressing p53 acetylation in the nucleus [143]. Thus, DHCR24 could be an important target for HCV-associated HCC therapy.

## Interaction between Cholesterol Metabolism and Tumor Microenvironment

Cancer development and progression is consistent with changes in the surrounding mesenchyme. Cancer cells can shape their microenvironment by secreting various cytokines, chemokines, and other factors, which leads to reprogramming of the surrounding cells, enabling them to play a decisive role in tumor survival and progression. Immune cells are an important component of the tumor mesenchyme and play a crucial role in this process [144,145].

In recent years, a growing body of evidence has emphasized the complex interplay between energy metabolism and immune cell

responses [146]. Indeed, the emerging field of research in immune metabolism aims to elucidate the bidirectional causal relationship between metabolic reprogramming and immune dysfunction in various pathological conditions such as metabolic syndrome, autoimmune diseases and cancer. From this perspective, alterations in energy metabolism toward the tumor microenvironment have recently been implicated as a fuel for tumor cell proliferation and as a coordinator of cancer-associated inflammation and immune escape [147].

Tumors contain a variety of tumor-infiltrating immune cells. Cholesterol-rich and cholesterol-containing tumor tissues in tumor-infiltrating CD8+ T cells positively correlate with up-regulated T-cell expression of PD-1, 2B4, TIM-3, and LAG-3, and cholesterol induces the expression of immune checkpoints by increasing ER stress in CD8+ T cells, while the endoplasmic reticulum stress sensor, XBP1, is activated and regulates the transcription of PD-1 and 2B4, whereas inhibition of XBP1 or lowering cholesterol in CD8+ T cells effectively restored antitumor activity [5]. Macrophages have intrinsic tumor suppressor activity, but Tumor-Associated Macrophages (TAMs) adopt an alternative phenotype in the tumor microenvironment characterized by tumor-promoting immunosuppressive and trophic functions, where cancer cells promote macrophage membrane cholesterol efflux and depletion of lipid rafts, and increased cholesterol efflux facilitates IL-4-mediated reprogramming, including inhibition of IFN-γ-induced gene expression, and gene deletion of ABC transporter proteins mediating cholesterol efflux, restoring tumor-promoting functions of TAMs and slowing tumor progression [148]. The unfavorable microenvironment in tumor tissues disrupts endoplasmic reticulum homeostasis and induces the Unfolded Protein Response (UPR), Chronic UPR in cancer cells and tumor-infiltrating leukocytes may contribute to evasion of immune surveillance, Whereas the UPR component, X-Box-Binding Protein 1 (XBP1), facilitates cholesterol synthesis and secretion, which activates Myeloid-Derived Suppressor Cells (MDSCs) and induces immune suppression, Cholesterol is delivered in the form of delivered as extracellular vesicles and internalized by MDSCs through macrophage phagocytosis, and genetic or pharmacological depletion of XBP1 significantly reduces MDSC abundance and triggers a potent antitumor response when lowering tumor cholesterol levels [149]. Cholesterol deficiency in tumors leads to T-cell exhaustion through inhibition of mTORC1 signaling, and increasing cholesterol levels in Chimeric Antigen Receptor (CAR)-T cells by blocking LXR improves antitumor function [64].

Cancer-derived cholesterol metabolites, especially oxysterols, have different effects on the function of different tumor-infiltrating immune cells. For neutrophils,22HC binds CXCR2 and recruits Gr-1-high neutrophils to cancer cells. 24HC attracts Ly6G- and CD11b-positive neutrophils. 27HC increases neutrophils and γδ T-cells but decreases CD8 T-cells, which promotes breast cancer metastasis. For macrophages, 25HC attracts macrophages by directing cytoskeletal reorganization. Thus, this may contribute to cancer metastasis and may also promote cancer metastasis by upregulating the expression of Matrix Metallopeptidases (MMPs). For dendritic cells, potential oxysterols that activate LXRα inhibit CCR7 expression and thus DC function. For CD8 T cells, some oxysterols may activate LXR signaling and inhibit effector functions. For MDSCs, as yet unidentified factors recruit lox-1-positive MDSCs to exert pro-tumorigenic functions [41].

## Targeting Cholesterol to Treat Diseases

### LXR

LXR agonist, RGX-104, potently inhibits the growth of a variety of mouse and human tumors. Depletion of MDSCs by up-regulation of the LXR transcriptional target APOE subsequently increased T cell activation. Importantly, this observation was further validated in cancer patients in a phase I clinical trial. In addition, LXR activation can augment other immunotherapies such as overt T-cell transfer and checkpoint blockade therapy in mouse models [150]. In addition, RGX-104 also partially cleared the immunosuppressive effects of radiotherapy in a mouse model of Non-Small Cell Lung Cancer (NSCLC) [151].

### SREBP

Adiponectin, a specific inhibitor of SREBP activation, is a diarylthiazole derivative that binds to SCAP and inhibits the translocation of SREBP-1 and SREBP-2 from the ER to the Golgi [152]. In prostate cancer, adiponectin inhibits cell proliferation and colony formation in androgen-responsive or insensitive cancer cells and leads to G2/M cell cycle arrest and cell death, which is mediated by blocking SREBP-regulated metabolic pathways and AR signaling networks [153]. Furthermore, adiponectin can reverse progesterone resistance by inhibiting the SREBP-1/NF-kB pathway in endometrial cancer [154]. In addition to inhibiting SREBP activity, it also inhibits mitotic microtubule spindle assembly and cell division in invasive cancers [155]. Tocotrienol, a minor form of vitamin E, degrades mature SREBP-2 without affecting LXR activity to maintain cholesterol homeostasis in prostate cancer [156]. Rhodopsin, an anthraquinone from many plants, inhibits SREBP-2 transcriptional activity, cholesterol metabolism and Akt signaling pathways, and sensitizes HCC cells to the anticancer effects of sorafenib in vitro and in xenograft models [157]. A newly developed AR antagonist, apalutamide, significantly inhibited proliferation and migration, induced cysteine protease-dependent apoptosis, and reduced lipid droplet levels in PCa cells by modulating the levels of ACL, ACC, FASN, and SREBP-1. In addition, proxalutamide reduced AR expression in PCa cells, which may overcome resistance to AR-targeted therapy [158].

### HMGCR

Targeting HMGCR, a key enzyme in cholesterol synthesis, is considered one of the strategies for the treatment of cancer [159]. Originally used for the treatment of cardiovascular diseases, statins have become a standard of care for the treatment of cancer patients with high cholesterol levels [160]. Statins competitively inhibit HMG-CoA reductase its controlled conversion of HMG-CoA to mevalonate [161]. In TME, statins can reduce tumor cell proliferation, promote apoptosis, induce autophagy, reduce migration and invasion, and promote anti-inflammatory immunomodulation by affecting key proteins such as Ras, RhoA/C, Rac, and Rab [162]. Smooth muscle tumor experiments showed that simvastatin treatment not only inhibited cell proliferation and promoted apoptosis, but also inhibited extracellular matrix protein levels [163]. And synergistic effects have been observed when statins are combined with anti-PD1 therapy [164].

### FPPS

Nitrogen containing Bisphosphonates (N-BPs) as FPPS inhibitors are another major class of inhibitors targeting the mevalonate pathway. Compared to the original non-nitrogen-containing bisphosphonates,

N-BPs have an increased affinity for hydroxyapatite and interfere with FPPS in the mevalonate pathway [165]. The third generation N-BPs, Zoledronic acid (ZOL) and minodronate (YM529), are more potent inhibitors of FPPS than the first generation of bisphosphonates and have been found to inhibit cell growth, induce apoptosis, inhibit angiogenesis, and reduce tumor cell adherence to bone, among other possible mechanisms, in a variety of cancers [166]. Due to its strong inhibitory effect on osteoclasts, N-BP is used for the treatment of osteolytic bone metastases, and in is also commonly used in the advanced treatment of prostate and breast cancer [81].

### SQLE

Given the dysregulation of SQLE in cancer and its tumor-promoting function, targeting SQLE is considered a new and promising antitumor therapy. Terbinafine, a pioneer SQLE inhibitor used in antitumor therapy (Figure 2), was shown to reduce the overall risk of death in a retrospective cohort study of prostate cancer patients receiving systemic administration of terbinafine [167], and another study showed that terbinafine reduced PSA levels in three-quarters of patients with advanced prostate cancer [168]. In Non-Alcoholic Fatty Liver Disease (NAFLD)-induced HCC, terbinafine enhances SQLE degradation *via* autophagy and then reverses PTEN expression, which in turn inhibits the AKT/mTOR signaling pathway [129]. For other types of SQLE inhibitors, such as natural compounds and derivatives, their specific properties may make them potential antitumor agents or developed as clinically safe SQLE inhibitors, such as (-)-Epigallocatechin 3-O-gallate (EGCG) extracted from green tea has been shown to be a potent and safe inhibitor of SQLE, even when consumed at high doses, few side effects have been reported [169]. The antitumor effect of EGCG has been extensively studied, but it is unclear whether the association between SQLE and EGCG contributes to this effect [170], which is worthy of further in-depth study.

## Conclusion

Cholesterol plays a key role in maintaining the structural and functional properties of the bilayer, and a large body of evidence suggests that elevated cholesterol levels are associated with the development of cancer. Cancer cells require a constant supply of cholesterol to maintain aberrant proliferation, and much of this cholesterol is ensured by *de novo* synthesis of acetyl coenzyme a in the endoplasmic reticulum. Consistent with this view is the idea that the immune system and its immune function can be regulated by alterations in a variety of mechanisms and can play a wide range of roles in the organism.

The reprogramming of cholesterol metabolism in tumors is driven by endogenous and exogenous factors. Endogenous factors include activation of oncogenes and inactivation of oncogenes, while exogenous factors include endoplasmic reticulum stress, microenvironmental acidification, and inflammatory factors. Numerous clinical and preclinical studies have shown that cholesterol metabolism in tumor cells and immune cells can be interfered with to achieve the goal of tumor treatment. Cholesterol metabolism modulation therapy can also be combined with existing clinical therapies to improve the efficacy of tumor treatment. Further understanding of the biology of mitochondrial cholesterol regulation, sterol regulatory element binding proteins, and the regulation of enzymes involved in cholesterol-regulated metabolism in cancer cells could be an attractive target for intervening in the biology of cancer cells and provide an opportunity for the design of new cancer therapeutic approaches.

Despite the exciting advances in the field, many fundamental questions remain to be addressed, such as: Is it possible to modulate specific cholesterol pathways to achieve both anti-tumor and immune-promoting effects? What are the most effective combinatorial strategies for attacking cancer cells with different approaches? Can some of the drugs currently used to treat metabolic diseases be repositioned as antitumor agents? These salient questions reflect the urgent need for more mechanistic studies of cholesterol metabolism in cancer, which may pave the way for the next generation of clinical therapies.

## Funding

This work was financially supported by National Natural Science Foundation of China (82203871, 32260165, 82060151, 82160151, 82171343); Key Laboratory for Research on Autoimmune Diseases of Higher Education schools in Guizhou Province (Qianjiaoji[2023]016); The Science and Technology Foundation of Guizhou Province to Min Su (Qiankehezhicheng[2020]4Y230); The project funded by China Postdoctoral Science Foundation (2022M720928); Guizhou Provincial Science and Technology Projects (zk (2022)-404); Guizhou Provincial Education Department Youth Science and Technology Talent Project (KY [2022]244).

## References

1. Luo J, Yang H, Song BL. Mechanisms and regulation of cholesterol homeostasis. Nat Rev Mol Cell Biol. 2020;21(4):225-45.
2. Brown MS, Radhakrishnan A, Goldstein JL. Retrospective on cholesterol homeostasis: The central role of scap. Annu Rev Biochem. 2018;87:783-807.
3. Jefcoate CR, Lee J. Cholesterol signaling in single cells: lessons from STAR and sm-FISH. J Mol Endocrinol. 2018;60(4):R213-35.
4. Xu H, Zhou S, Tang Q, Xia H, Bi F. Cholesterol metabolism: new functions and therapeutic approaches in cancer. Biochim Biophys Acta Rev Cancer. 2020;1874(1):188394.
5. Ma X, Bi E, Lu Y, Su P, Huang C, Liu L, et al. Cholesterol induces CD8+ T cell exhaustion in the tumor microenvironment. Cell Metab. 2019;30(1):143-56.e5.
6. Osborne TF, Espenshade PJ. Lipid balance must be just right to prevent development of severe liver damage. J Clin Invest. 2022;132(11):e160326.
7. Wang X, Sun B, Wei L, Jian X, Shan K, He Q, et al. Cholesterol and saturated fatty acids synergistically promote the malignant progression of prostate cancer. Neoplasia. 2022;24(2):86-97.
8. Liang J, Yu D, Luo C, Bennett C, Jedrychowski M, Gygi SP, et al. Epigenetic suppression of PGC1α (PPARGC1A) causes collateral sensitivity to HMGCR-inhibitors within BRAF-treatment resistant melanomas. Nat Commun. 2023;14(1):3251.
9. Cao D, Yang J, Deng Y, Su M, Wang Y, Feng X, et al. Discovery of a mammalian FASN inhibitor against xenografts of non-small cell lung cancer and melanoma. Signal Transduct Target Ther. 2022;7(1):273.
10. Li Y, Yang W, Zheng Y, Dai W, Ji J, Wu L, et al. Targeting fatty acid synthase modulates sensitivity of hepatocellular carcinoma to sorafenib *via* ferroptosis. J Exp Clin Cancer Res. 2023;42(1):6.
11. Ferraro GB, Ali A, Luengo A, Kodack DP, Deik A, Abbott KL, et al. Fatty acid synthesis is required for breast cancer brain metastasis. Nat Cancer. 2021;2(4):414-28.
12. Zhang Y, Beachy PA. Cellular and molecular mechanisms of Hedgehog signaling. Nat Rev Mol Cell Biol. 2023;24(9):668-87.

13. Zheng S, Lin J, Pang Z, Zhang H, Wang Y. Aberrant cholesterol metabolism and wnt/β-catenin signaling coalesce *via* frizzled5 in supporting cancer growth. Adv Sci (Weinh). 2022;9(28):2200750.

14. Hu B, Zou T, Qin W, Shen X, Su Y, Li J, et al. Inhibition of EGFR overcomes acquired Lenvatinib resistance driven by STAT3-ABCB1 signaling in hepatocellular carcinoma. Cancer Res. 2022;82(20):3845-57.

15. Gao S, Soares F, Wang S, Wong CC, Chen H, Yang Z, et al. CRISPR screens identify cholesterol biosynthesis as a therapeutic target on stemness and drug resistance of colon cancer. Oncogene 2021;40(48):6601-13.

16. Tan JX, Finkel T. A phosphoinositide signaling pathway mediates rapid lysosomal repair. Nature. 2022;609(7928):815-21.

17. Canfrán-Duque A, Rotllan N, Zhang X, Andrés-Blasco I, Thompson BM, Sun J, et al. Macrophage-derived 25-Hydroxycholesterol promotes vascular inflammation, atherogenesis, and lesion remodeling. Circulation. 2023;147(5):388-408.

18. Bassi G, Sidhu SK, Mishra S. The expanding role of mitochondria, autophagy and lipophagy in steroidogenesis. Cells. 2021;10(8):1851.

19. Warren T, McAllister R, Morgan A, Rai TS, McGilligan V, Ennis M, et al. The interdependency and co-regulation of the vitamin D and cholesterol metabolism. Cells. 2021;10(8):2007.

20. Zhong VW, Van Horn L, Cornelis MC, Wilkins JT, Ning H, Carnethon MR, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. JAMA 2019;321(11):1081-95.

21. Frascoli M, Ferraj E, Miu B, Malin J, Spidale NA, Cowan J, et al. Skin γδ T cell inflammatory responses are hardwired in the thymus by oxysterol sensing *via* GPR183 and calibrated by dietary cholesterol. Immunity. 2023;56(3):562-75.e566.

22. Ko CW, Qu J, Black DD, Tso P. Regulation of intestinal lipid metabolism: Current concepts and relevance to disease. Nat Rev Gastroenterol Hepatol. 2020;17(3):169-83.

23. Stellaard F. From dietary cholesterol to blood cholesterol, physiological lipid fluxes, and cholesterol homeostasis. Nutrients. 2022;14(8):1643.

24. Brandts J, Ray KK. Novel and future lipid-modulating therapies for the prevention of cardiovascular disease. Nat Rev Cardiol. 2023;20(9):600-16.

25. Xiao X, Kennelly JP, Ferrari A, Clifford BL, Whang E, Gao Y, et al. Hepatic non-vesicular cholesterol transport is critical for systemic lipid homeostasis. Nat Metab. 2023;5(1):165-81.

26. Gu J, Zhu N, Li HF, Zhao TJ, Zhang CJ, Liao DF, et al. Cholesterol homeostasis and cancer: A new perspective on the low-density lipoprotein receptor. Cell Oncol (Dordr). 2022;45(5):709-28.

27. Liu H, Liu J, Liu Z, Wang Q, Liu J, Feng D, et al. Lycopene reduces cholesterol absorption and prevents atherosclerosis in ApoE(-/-) mice by downregulating HNF-1α and NPC1L1 expression. J Agric Food Chem. 2021;69(35):10114-20.

28. Yang XY, Yu H, Fu J, Guo HH, Han P, Ma SR, et al. Hydroxyurea ameliorates atherosclerosis in ApoE(-/-) mice by potentially modulating Niemann-Pick C1-like 1 protein through the gut microbiota. Theranostics. 2022;12(18):7775-87.

29. Li PS, Fu ZY, Zhang YY, Zhang JH, Xu CQ, Ma YT, et al. The clathrin adaptor numb regulates intestinal cholesterol absorption through dynamic interaction with NPC1L1. Nat Med. 2014;20(1):80-6.

30. Xiao J, Dong LW, Liu S, Meng FH, Xie C, Lu XY, et al. Bile acids-mediated intracellular cholesterol transport promotes intestinal cholesterol absorption and NPC1L1 recycling. Nat Commun. 2023;14(1):6469.

31. Hu M, Yang F, Huang Y, You X, Liu D, Sun S, et al. Structural insights into the mechanism of human NPC1L1-mediated cholesterol uptake. Sci Adv. 2021;7(29):eabg3188.

32. Zhang R, Liu W, Zeng J, Meng J, Jiang H, Wang J, et al. Niemann-Pick C1-like 1 inhibitors for reducing cholesterol absorption. Eur J Med Chem. 2022;230:114111.

33. Long T, Liu Y, Li X. Molecular structures of human ACAT2 disclose mechanism for selective inhibition. Structure. 2021;29(12):1410-18.e4.

34. Matsuo M, Ogata Y, Yamanashi Y, Takada T. ABCG5 and ABCG8 are involved in vitamin K transport. Nutrients. 2023;15(4): 998.

35. Zhang R, Zeng J, Liu W, Meng J, Wang C, Shi L, et al. The role of NPC1L1 in cancer. Front Pharmacol. 2022;13:956619.

36. Kwon RJ, Park EJ, Lee SY, Lee Y, Hwang C, Kim C, et al. Expression and prognostic significance of Niemann-Pick C1-Like 1 in colorectal cancer: A retrospective cohort study. Lipids Health Dis. 2021;20(1):104.

37. Zhang Z, Qin S, Chen Y, Zhou L, Yang M, Tang Y, et al. Inhibition of NPC1L1 disrupts adaptive responses of drug-tolerant persister cells to chemotherapy. EMBO Mol Med. 2022;14(2):e14903.

38. Wang Y, Yutuc E, Griffiths WJ. Cholesterol metabolism pathways - are the intermediates more important than the products? Febs J. 2021;288(12):3727-45.

39. Patel KK, Kashfi K. Lipoproteins and cancer: the role of HDL-C, LDL-C, and cholesterol-lowering drugs. Biochem Pharmacol. 2022;196:114654.

40. Göbel A, Rauner M, Hofbauer LC, Rachner TD. Cholesterol and beyond - the role of the mevalonate pathway in cancer biology. Biochim Biophys Acta Rev Cancer. 2020;1873(2):188351.

41. Huang B, Song BL, Xu C. Cholesterol metabolism in cancer: mechanisms and therapeutic opportunities. Nat Metab. 2020;2(2):132-41.

42. Kobayashi K, Baba K, Kambayashi S, Okuda M. Effect of simvastatin on cell proliferation and Ras activation in canine tumor cells. Vet Comp Oncol. 2021;19(1):99-108.

43. Muehlebach ME, Holstein SA. Geranylgeranyl diphosphate synthase: Role in human health, disease and potential therapeutic target. Clin Transl Med. 2023;13(1):e1167.

44. Garcia-Ruiz C, Conde de la Rosa L, Ribas V, Fernandez-Checa JC. Mitochondrial cholesterol and cancer. Semin Cancer Biol. 2021;73:76-85.

45. Jo Y, DeBose-Boyd RA. Post-translational regulation of HMG CoA reductase. Cold Spring Harb Perspect Biol. 2022;14(12):a041253.

46. Schumacher MM, DeBose-Boyd RA. Post translational regulation of HMG CoA reductase, the rate-limiting enzyme in synthesis of cholesterol. Annu Rev Biochem. 2021;90:659-79.

47. Zhong S, Li L, Liang N, Zhang L, Xu X, Chen S, et al. Acetaldehyde dehydrogenase 2 regulates HMG-CoA reductase stability and cholesterol synthesis in the liver. Redox Biol. 2021;41:101919.

48. Björkhem I, Lund E, Rudling M. Coordinate regulation of cholesterol 7 alpha-hydroxylase and HMG-CoA reductase in the liver. Subcell Biochem. 1997;28:23-55.

49. Saito Y, Yin D, Kubota N, Wang X, Filliol A, Remotti H, et al. A therapeutically targetable TAZ-TEAD2 pathway drives the growth of hepatocellular carcinoma *via* ANLN and KIF23. Gastroenterology. 2023;164(7):1279-92.

50. Yao X, Xie R, Cao Y, Tang J, Men Y, Peng H, et al. Simvastatin induced ferroptosis for triple-negative breast cancer therapy. J Nanobiotechnology. 2021;19(1):311.

51. Yarmolinsky J, Bull CJ, Vincent EE, Robinson J, Walther A, Smith GD, et al. Association between genetically proxied inhibition of HMG-COA reductase and epithelial ovarian cancer. JAMA. 2020;323(7):646-55.

52. Pokhrel RH, Acharya S, Ahn JH, Gu Y, Pandit M, Kim JO, et al. AMPK promotes antitumor immunity by downregulating PD-1 in regulatory T cells *via* the HMGCR/p38 signaling pathway. Mol Cancer. 2021;20(1):133.

53. Jiang W, Hu JW, He XR, Jin WL, He XY. Statins: A repurposed drug to fight cancer. J Exp Clin Cancer Res. 2021;40(1):241.

54. Nie Y, Yun X, Zhang Y, Wang X. Targeting metabolic reprogramming in chronic lymphocytic leukemia. Exp Hematol Oncol. 2022;11(1):39.

55. Hu N, Chen C, Wang J, Huang J, Yao D, Li C. Atorvastatin ester regulates lipid metabolism in hyperlipidemia rats via the PPAR-signaling pathway and HMGCR expression in the liver. Int J Mol Sci. 2021;22(20):11107.

56. Rashkovan M, Albero R, Gianni F, Perez-Duran P, Miller HI, Mackey AL, et al. Intracellular cholesterol pools regulate oncogenic signaling and epigenetic circuitries in early T-cell precursor acute lymphoblastic leukemia. Cancer Discov. 2022;12(3):856-71.

57. Zhou S, Xu H, Tang Q, Xia H, Bi F. Dipyridamole enhances the cytotoxicities of trametinib against colon cancer cells through combined targeting of HMGCS1 and MEK pathway. Mol Cancer Ther. 2020;19(1):135-46.

58. Chen L, Ma MY, Sun M, Jiang LY, Zhao XT, Fang XX, et al. Endogenous sterol intermediates of the mevalonate pathway regulate HMGCR degradation and SREBP-2 processing. J Lipid Res. 2019;60(10):1765-75.

59. Duan Y, Gong K, Xu S, Zhang F, Meng X, Han J. Regulation of cholesterol homeostasis in health and diseases: from mechanisms to targeted therapeutics. Signal Transduct Target Ther. 2022;7(1):265.

60. Hoppstädter J, Dembek A, Höring M, Schymik HS, Dahlem C, Sultan A, et al. Dysregulation of cholesterol homeostasis in human lung cancer tissue and tumor-associated macrophages. Ebio Medicine. 2021;72:103578.

61. Ma S, Lv M, Chen X, Zang G, Tang Z, Zhang Y, et al. Avasimibe can cooperate with a DC-targeting and integration-deficient lentivector to induce stronger HBV specific T cytotoxic response by regulating cholesterol metabolism. Antiviral Res. 2023;216:105662.

62. Yan C, Zheng L, Jiang S, Yang H, Guo J, Jiang LY, et al. Exhaustion-associated cholesterol deficiency dampens the cytotoxic arm of antitumor immunity. Cancer Cell. 2023;41(7):1276-93.

63. Singh PK, Mehla K. LXR Signaling-mediated cholesterol metabolism reprogramming regulates cancer cell metastasis. Cancer Res. 2023;83(11):1759-61.

64. Chaves-Filho AB, Schulze A. Cholesterol atlas of tumor microenvironment provides route to improved CAR-T therapy. Cancer Cell. 2023;41(7):1204-6.

65. Tugaeva KV, Titterington J, Sotnikov DV, Maksimov EG, Antson AA, Sluchanko NN. Molecular basis for the recognition of steroidogenic acute regulatory protein by the 14-3-3 protein family. FEBS J. 2020;287(18):3944-66.

66. Larsen MC, Lee J, Jorgensen JS, Jefcoate CR. STARD1 functions in mitochondrial cholesterol metabolism and nascent HDL formation. Gene expression and molecular mRNA imaging show novel splicing and a 1:1 mitochondrial association. Front Endocrinol (Lausanne). 2020;11:559674.

67. Papa S, Bubici C, Syn WK. STARD1: A new rising StAR in cholesterol-mediated hepatocarcinogenesis. Hepatobiliary Surg Nutr. 2021;10(6):910-2.

68. Torres S, Baulies A, Insausti-Urkia N, Alarcon-Vila C, Fucho R, Solsona-Vilarrasa E, et al. Endoplasmic reticulum stress-induced upregulation of STARD1 promotes acetaminophen-induced acute liver failure. Gastroenterology. 2019;157(2):552-68.

69. Conde de la Rosa L, Garcia-Ruiz C, Vallejo C, Baulies A, Nunez S, Monte MJ, et al. STARD1 promotes NASH-driven HCC by sustaining the generation of bile acids through the alternative mitochondrial pathway. J Hepatol. 2021;74(6):1429-41.

70. Ding Z, Pothineni NVK, Goel A, Lüscher TF, Mehta JL. PCSK9 and inflammation: Role of shear stress, pro-inflammatory cytokines, and LOX-1. Cardiovasc Res. 2020;116(5):908-15.

71. Seidah NG, Prat A. The multifaceted biology of PCSK9. Endocr Rev. 2022;43(3):558-82.

72. Wong CC, Wu JL, Ji F, Kang W, Bian X, Chen H, et al. The cholesterol uptake regulator PCSK9 promotes and is a therapeutic target in APC/KRAS-mutant colorectal cancer. Nat Commun. 2022;13(1):3971.

73. Liu X, Bao X, Hu M, Chang H, Jiao M, Cheng J, et al. Inhibition of PCSK9 potentiates immune checkpoint therapy for cancer. Nature. 2020;588(7839):693-8.

74. Cheng C, Geng F, Cheng X, Guo D. Lipid metabolism reprogramming and its potential targets in cancer. Cancer Commun (Lond). 2018;38(1):27.

75. Romani P, Brian I, Santinon G, Pocaterra A, Audano M, Pedretti S, et al. Extracellular matrix mechanical cues regulate lipid metabolism through Lipin-1 and SREBP. Nat Cell Biol. 2019;21(3):338-47.

76. Jiang T, Zhang G, Lou Z. Role of the sterol regulatory element binding protein pathway in tumorigenesis. Front Oncol. 2020;10:1788.

77. Amemiya-Kudo M, Shimano H, Hasty AH, Yahagi N, Yoshikawa T, Matsuzaka T, et al. Transcriptional activities of nuclear SREBP-1a, -1c, and -2 to different target promoters of lipogenic and cholesterogenic genes. J Lipid Res. 2002;43(8):1220-35.

78. Toth JI, Datta S, Athanikar JN, Freedman LP, Osborne TF. Selective coactivator interactions in gene activation by SREBP-1a and -1c. Mol Cell Biol. 2004;24(18):8288-300.

79. Zhao Q, Lin X, Wang G. Targeting SREBP-1-mediated lipogenesis as potential strategies for cancer. Front Oncol. 2022;12:952371.

80. Shin DJ, Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through Sterol Regulatory Element-Binding Protein-2 (SREBP-2). J Biol Chem. 2003;278(36):34114-8.

81. Xue L, Qi H, Zhang H, Ding L, Huang Q, Zhao D, et al. Targeting SREBP-2-regulated mevalonate metabolism for cancer therapy. Front Oncol. 2020;10:1510.

82. Guo D, Bell EH, Chakravarti A. Lipid metabolism emerges as a promising target for malignant glioma therapy. CNS Oncol. 2013;2(3):289-99.

83. Yan R, Cao P, Song W, Qian H, Du X, Coates HW, et al. A structure of human Scap bound to Insig-2 suggests how their interaction is regulated by sterols. Science. 2021;371(6533):eabb2224.

84. Jiang SY, Yang X, Yang Z, Li JW, Xu MQ, Qu YX, et al. Discovery of an insulin-induced gene binding compound that ameliorates nonalcoholic steatohepatitis by inhibiting sterol regulatory element-binding protein-mediated lipogenesis. Hepatology. 2022;76(5):1466-81.

85. Wu X, Yan R, Cao P, Qian H, Yan N. Structural advances in sterol-sensing domain-containing proteins. Trends Biochem Sci. 2022;47(4):289-300.

86. Kim JY, Wang LQ, Sladky VC, Oh TG, Liu J, Trinh K, et al. PIDDosome-SCAP crosstalk controls high-fructose-diet-dependent transition from simple steatosis to steatohepatitis. Cell Metab. 2022;34(10):1548-60.

87. Zhang X, Huo Z, Luan H, Huang Y, Shen Y, Sheng L, et al. Scutellarin ameliorates hepatic lipid accumulation by enhancing autophagy and suppressing IRE1α/XBP1 pathway. Phytother Res. 2022;36(1):433-47.

88. Moon SH, Huang CH, Houlihan SL, Regunath K, Freed-Pastor WA, Morris JPt, et al. p53 represses the mevalonate pathway to mediate tumor suppression. Cell. 2019;176(3):564-80.

89. Zhang X, Zhao H, Sheng Q, Liu X, You W, Lin H, et al. Regulation of microRNA-33, SREBP and ABCA1 genes in a mouse model of high cholesterol. Arch Anim Breed. 2021;64(1):103-8.

90. Peng C, Lei P, Li X, Xie H, Yang X, Zhang T, et al. Down-regulated of SREBP-1 in circulating leukocyte is a risk factor for atherosclerosis: A case control study. Lipids Health Dis. 2019;18(1):177.

91. Chang TY, Chang CC, Ohgami N, Yamauchi Y. Cholesterol sensing, trafficking, and esterification. Annu Rev Cell Dev Biol. 2006;22:129-57.

92. Cheng C, Ru P, Geng F, Liu J, Yoo JY, Wu X, et al. Glucose-mediated N-glycosylation of SCAP is essential for SREBP-1 activation and tumor growth. Cancer Cell. 2015;28(5):569-81.

93. Kawamura S, Matsushita Y, Kurosaki S, Tange M, Fujiwara N, Hayata Y, et al. Inhibiting SCAP/SREBP exacerbates liver injury and carcinogenesis in murine nonalcoholic steatohepatitis. J Clin Invest. 2022;132(11):e151895.

94. Yao JM, Ying HZ, Zhang HH, Qiu FS, Wu JQ, Yu CH. Exosomal RBP4 potentiated hepatic lipid accumulation and inflammation in high-fat-diet-fed mice by promoting M1 polarization of Kupffer cells. Free Radic Biol Med. 2023;195:58-73.

95. Hinds Jr TD, Kipp ZA, Xu M, Yiannikouris FB, Morris AJ, Stec DF, et al. Adipose-specific PPARα knockout mice have increased lipogenesis by PASK-SREBP1 signaling and a polarity shift to inflammatory macrophages in white adipose tissue. Cells. 2021;11(1):4.

96. Araki M, Nakagawa Y, Saito H, Yamada Y, Han SI, Mizunoe Y, et al. Hepatocyte- or macrophage-specific SREBP-1a deficiency in mice exacerbates methionine- and choline-deficient diet-induced nonalcoholic fatty liver disease. Am J Physiol Gastrointest Liver Physiol. 2022;323(6):G627-39.

97. Hu J, Wang H, Li X, Liu Y, Mi Y, Kong H, et al. Fibrinogen-like protein 2 aggravates nonalcoholic steatohepatitis *via* interaction with TLR4, eliciting inflammation in macrophages and inducing hepatic lipid metabolism disorder. Theranostics. 2020;10(21):9702-20.

98. Husain A, Chiu YT, Sze KM, Ho DW, Tsui YM, Suarez EMS, et al. Ephrin-A3/EphA2 axis regulates cellular metabolic plasticity to enhance cancer stemness in hypoxic hepatocellular carcinoma. J Hepatol. 2022;77(2):383-96.

99. Xu H, Luo J, Tian H, Li J, Zhang X, Chen Z, et al. Rapid communication: Lipid metabolic gene expression and triacylglycerol accumulation in goat mammary epithelial cells are decreased by inhibition of SREBP-1. J Anim Sci. 2018;96(6):2399-407.

100. Huang YQ, Tang YX, Qiu BH, Talukder M, Li XN, Li JL. Di-2-Ethylhexyl Phthalate (DEHP) induced lipid metabolism disorder in liver *via* activating the LXR/SREBP-1c/PPARα/γ and NF-κB signaling pathway. Food Chem Toxicol. 2022;165:113119.

101. Im SS, Yousef L, Blaschitz C, Liu JZ, Edwards RA, Young SG, et al. Linking lipid metabolism to the innate immune response in macrophages through sterol regulatory element binding protein-1a. Cell Metab. 2011;13(5):540-9.

102. Kidani Y, Elsaesser H, Hock MB, Vergnes L, Williams KJ, Argus JP, et al. Sterol regulatory element-binding proteins are essential for the metabolic programming of effector T cells and adaptive immunity. Nat Immunol. 2013;14(5):489-99.

103. Webb LM, Sengupta S, Edell C, Piedra-Quintero ZL, Amici SA, Miranda JN, et al. Protein arginine methyltransferase 5 promotes cholesterol biosynthesis-mediated Th17 responses and autoimmunity. J Clin Invest. 2020;130(4):1683-98.

104. Liu C, Chikina M, Deshpande R, Menk AV, Wang T, Tabib T, et al. Treg cells promote the SREBP1-dependent metabolic fitness of tumor-promoting macrophages *via* repression of CD8(+) T Cell-Derived Interferon-γ. Immunity. 2019;51(2):381-97.

105. Xu Y, Tertilt C, Krause A, Quadri LE, Crystal RG, Worgall S. Influence of the cystic fibrosis transmembrane conductance regulator on expression of lipid metabolism-related genes in dendritic cells. Respir Res. 2009;10(1):26.

106. Westerterp M, Gautier EL, Ganda A, Molusky MM, Wang W, Fotakis P, et al. Cholesterol accumulation in dendritic cells links the inflammasome to acquired immunity. Cell Metab. 2017;25(6):1294-304.

107. Coman D, Vissers L, Riley LG, Kwint MP, Hauck R, Koster J, et al. Squalene synthase deficiency: Clinical, biochemical, and molecular characterization of a defect in cholesterol biosynthesis. Am J Hum Genet. 2018;103(1):125-30.

108. Tansey TR, Shechter I. Squalene synthase structure and regulation. Prog Nucleic Acid Res Mol Biol. 2001;65:157-95.

109. Tüzmen Ş, Hostetter G, Watanabe A, Ekmekçi C, Carrigan PE, Shechter I, et al. Characterization of Farnesyl Diphosphate Farnesyl Transferase 1 (FDFT1) expression in cancer. Per Med. 2019;16(1):51-65.

110. Bonnans C, Levy BD. Lipid mediators as agonists for the resolution of acute lung inflammation and injury. Am J Respir Cell Mol Biol. 2007;36(2):201-5.

111. Ehmsen S, Pedersen MH, Wang G, Terp MG, Arslanagic A, Hood BL, et al. Increased cholesterol biosynthesis is a key characteristic of breast cancer stem cells influencing patient outcome. Cell Rep. 2019;27(13):3927-38.

112. Liu M, Xia Y, Ding J, Ye B, Zhao E, Choi JH, et al. Transcriptional profiling reveals a common metabolic program in high-risk human neuroblastoma and mouse neuroblastoma sphere-forming cells. Cell Rep. 2016;17(2):609-23.

113. Weng ML, Chen WK, Chen XY, Lu H, Sun ZR, Yu Q, et al. Fasting inhibits aerobic glycolysis and proliferation in colorectal cancer *via* the Fdft1-mediated AKT/mTOR/HIF1α pathway suppression. Nat Commun. 2020;11(1):1869.

114. Nie J, Shan D, Li S, Zhang S, Zi X, Xing F, et al. A novel ferroptosis related gene signature for prognosis prediction in patients with colon cancer. Front Oncol. 2021;11:654076.

115. Shao Y, Jia H, Huang L, Li S, Wang C, Aikemu B, et al. An original ferroptosis-related gene signature effectively predicts the prognosis and clinical status for colorectal cancer patients. Front Oncol. 2021;11:711776.

116. Ha NT, Lee CH. Roles of farnesyl-diphosphate farnesyltransferase 1 in tumor and tumor microenvironments. Cells. 2020;9(11):2352.

117. Garcia-Bermudez J, Baudrier L, Bayraktar EC, Shen Y, La K, Guarecuco R, et al. Squalene accumulation in cholesterol auxotrophic lymphomas prevents oxidative cell death. Nature. 2019;567(7746):118-22.

118. Madan B, Virshup DM, Nes WD, Leaver DJ. Unearthing the Janus-face cholesterogenesis pathways in cancer. Biochem Pharmacol. 2022;196:114611.

119. Long T, Hassan A, Thompson BM, McDonald JG, Wang J, Li X. Structural basis for human sterol isomerase in cholesterol biosynthesis and multidrug recognition. Nat Commun. 2019;10(1):2452.

120. Segala G, David M, de Medina P, Poirot MC, Serhan N, Vergez F, et al. Dendrogenin A drives LXR to trigger lethal autophagy in cancers. Nat Commun. 2017;8(1):1903.

121. Nes WD, Zhou W, Dennis AL, Li H, Jia Z, Keith RA, et al. Purification, characterization and catalytic properties of human sterol 8-isomerase. Biochem J. 2002;367(3):587-99.

122. Qiu ZP, Hu A, Song BL. The 3-beta-hydroxysteroid-Delta(8), Delta(7)-isomerase EBP inhibits cholesterylation of smoothened. Biochim Biophys Acta Mol Cell Biol Lipids. 2021;1866(12):159041.

123. Theodoropoulos PC, Wang W, Budhipramono A, Thompson BM, Madhusudhan N, Mitsche MA, et al. A medicinal chemistry-driven approach identified the sterol isomerase EBP as the molecular target of TASIN colorectal cancer toxins. J Am Chem Soc. 2020;142(13):6128-38.

124. Berardi F, Abate C, Ferorelli S, de Robertis AF, Leopoldo M, Colabufo NA, et al. Novel 4-(4-aryl)cyclohexyl-1-(2-pyridyl)piperazines as Delta(8)-Delta(7) sterol isomerase (emopamil binding protein) selective ligands with antiproliferative activity. J Med Chem. 2008;51(23):7523-31.

125. Villalva C, Trempat P, Greenland C, Thomas C, Girard JP, Moebius F, et al. Isolation of differentially expressed genes in NPM-ALK-positive anaplastic large cell lymphoma. Br J Haematol. 2002;118(3):791-8.

126. Ge H, Zhao Y, Shi X, Tan Z, Chi X, He M, et al. Squalene epoxidase promotes the proliferation and metastasis of lung squamous cell carcinoma cells though extracellular signal-regulated kinase signaling. Thorac Cancer. 2019;10(3):428-36.

127. Nagai M, Sakakibara J, Wakui K, Fukushima Y, Igarashi S, Tsuji S, et al. Localization of the Squalene Epoxidase gene (SQLE) to human chromosome region 8q24.1. Genomics. 1997;44(1):141-3.

128. Padyana AK, Gross S, Jin L, Cianchetta G, Narayanaswamy R, Wang F, et al. Structure and inhibition mechanism of the catalytic domain of human squalene epoxidase. Nat Commun. 2019;10(1):97.

129. Liu D, Wong CC, Fu L, Chen H, Zhao L, Li C, et al. Squalene epoxidase drives NAFLD-induced hepatocellular carcinoma and is a pharmaceutical target. Sci Transl Med. 2018;10(437):9840.

130. Li L, Zhang Q, Wang X, Li Y, Xie H, Chen X. Squalene epoxidase-induced cholesteryl ester accumulation promotes nasopharyngeal carcinoma development by activating PI3K/AKT signaling. Cancer Sci. 2020;111(7):2275-83.

131. Hong Z, Liu T, Wan L, Fa P, Kumar P, Cao Y, et al. Targeting squalene epoxidase interrupts homologous recombination *via* the ER stress response and promotes radiotherapy efficacy. Cancer Res. 2022;82(7):1298-12.

132. He L, Li H, Pan C, Hua Y, Peng J, Zhou Z, et al. Squalene epoxidase promotes colorectal cancer cell proliferation through accumulating calcitriol and activating CYP24A1-mediated MAPK signaling. Cancer Commun (Lond). 2021;41(8):726-46.

133. Li C, Wang Y, Liu D, Wong CC, Coker OO, Zhang X, et al. Squalene epoxidase drives cancer cell proliferation and promotes gut dysbiosis to accelerate colorectal carcinogenesis. Gut. 2022;71(11):2253-65.

134. Shangguan X, Ma Z, Yu M, Ding J, Xue W, Qi J. Squalene epoxidase metabolic dependency is a targetable vulnerability in castration-resistant prostate cancer. Cancer Res. 2022;82(17):3032-44.

135. Zhang Z, Wu W, Jiao H, Chen Y, Ji X, Cao J, et al. Squalene epoxidase promotes hepatocellular carcinoma development by activating STRAP transcription and TGF-β/SMAD signaling. Br J Pharmacol. 2023;180(12):1562-81.

136. Ye Z, Ai X, Yang K, Yang Z, Fei F, Liao X, et al. Targeting microglial metabolic rewiring synergizes with immune-checkpoint blockade therapy for glioblastoma. Cancer Discov. 2023;13(4):974-1001.

137. Luu W, Zerenturk EJ, Kristiana I, Bucknall MP, Sharpe LJ, Brown AJ. Signaling regulates activity of DHCR24, the final enzyme in cholesterol synthesis. J Lipid Res. 2014;55(3):410-20.

138. Wu J, Guo L, Qiu X, Ren Y, Li F, Cui W, et al. Genkwadaphnin inhibits growth and invasion in hepatocellular carcinoma by blocking DHCR24-mediated cholesterol biosynthesis and lipid rafts formation. Br J Cancer. 2020;123(11):1673-85.

139. Zerenturk EJ, Sharpe LJ, Ikonen E, Brown AJ. Desmosterol and DHCR24: Unexpected new directions for a terminal step in cholesterol synthesis. Prog Lipid Res. 2013;52(4):666-80.

140. Qiu T, Cao J, Chen W, Wang J, Wang Y, Zhao L, et al. 24-Dehydrocholesterol reductase promotes the growth of breast cancer stem-like cells through the Hedgehog pathway. Cancer Sci. 2020;111(10):3653-64.

141. Shen Y, Zhou J, Nie K, Cheng S, Chen Z, Wang W, et al. Oncogenic role of the SOX9-DHCR24-cholesterol biosynthesis axis in IGH-BCL2+ diffuse large B-cell lymphomas. Blood. 2022;139(1):73-86.

142. Zhang Y, Wang M, Meng F, Yang M, Chen Y, Guo X, et al. A novel SRSF3 inhibitor, SFI003, exerts anticancer activity against colorectal cancer by modulating the SRSF3/DHCR24/ROS axis. Cell Death Discov. 2022;8(1):238.

143. Nishimura T, Kohara M, Izumi K, Kasama Y, Hirata Y, Huang Y, et al. Hepatitis C virus impairs p53 *via* persistent overexpression of 3beta-hydroxysterol Delta24-reductase. J Biol Chem. 2009;284(52):36442-52.

144. Hinshaw DC, Shevde LA. The tumor microenvironment innately modulates cancer progression. Cancer Res. 2019;79(18):4557-66.

145. DeBerardinis RJ. Tumor microenvironment, metabolism, and immunotherapy. N Engl J Med. 2020;382(9):869-71.

146. Bader JE, Voss K, Rathmell JC. Targeting metabolism to improve the tumor microenvironment for cancer immunotherapy. Mol Cell. 2020;78(6):1019-33.

147. Bleve A, Durante B, Sica A, Consonni FM. Lipid metabolism and cancer immunotherapy: Immunosuppressive myeloid cells at the crossroad. Int J Mol Sci. 2020;21(16):5845.

148. Goossens P, Rodriguez-Vita J, Etzerodt A, Masse M, Rastoin O, Gouirand V, et al. Membrane cholesterol efflux drives tumor-associated macrophage reprogramming and tumor progression. Cell Metab. 2019;29(6):1376-89.

149. Yang Z, Huo Y, Zhou S, Guo J, Ma X, Li T, et al. Cancer cell-intrinsic XBP1 drives immunosuppressive reprogramming of intratumoral myeloid cells by promoting cholesterol production. Cell Metab. 2022;34(12):2018-35.

150. Tavazoie MF, Pollack I, Tanqueco R, Ostendorf BN, Reis BS, Gonsalves FC, et al. LXR/ApoE activation restricts innate immune suppression in cancer. Cell. 2018;172(4):825-40.

151. Liang H, Shen X. LXR activation radiosensitizers non-small cell lung cancer by restricting myeloid-derived suppressor cells. Biochem Biophys Res Commun. 2020;528(2):330-5.

152. Shao W, Machamer CE, Espenshade PJ. Fatostatin blocks ER exit of SCAP but inhibits cell growth in a SCAP-independent manner. J Lipid Res. 2016;57(8):1564-73.

153. Li X, Chen YT, Hu P, Huang WC. Fatostatin displays high antitumor activity in prostate cancer by blocking SREBP-regulated metabolic pathways and androgen receptor signaling. Mol Cancer Ther. 2014;13(4):855-66.

154. Ma X, Zhao T, Yan H, Guo K, Liu Z, Wei L, et al. Fatostatin reverses progesterone resistance by inhibiting the SREBP1-NF-κB pathway in endometrial carcinoma. Cell Death Dis. 2021;12(6):544.

155. Gholkar AA, Cheung K, Williams KJ, Lo YC, Hamideh SA, Nnebe C, et al. Fatostatin inhibits cancer cell proliferation by affecting mitotic microtubule spindle assembly and cell division. J Biol Chem. 2016;291(33):17001-8.

156. Krycer JR, Phan L, Brown AJ. A key regulator of cholesterol homoeostasis, SREBP-2, can be targeted in prostate cancer cells with natural products. Biochem J. 2012;446(2):191-201.

157. Kim YS, Lee YM, Oh TI, Shin DH, Kim GH, Kan SY, et al. Emodin sensitizes hepatocellular carcinoma cells to the anti-cancer effect of sorafenib through suppression of cholesterol metabolism. Int J Mol Sci. 2018;19(10):3127.

158. Gu Y, Xue M, Wang Q, Hong X, Wang X, Zhou F, et al. Novel strategy of proxalutamide for the treatment of prostate cancer through coordinated blockade of lipogenesis and androgen receptor axis. Int J Mol Sci. 2021;22(24):13222.

159. Dorsch M, Kowalczyk M, Planque M, Heilmann G, Urban S, Dujardin P, et al. Statins affect cancer cell plasticity with distinct consequences for tumor progression and metastasis. Cell Rep. 2021;37(8):110056.

160. Iannelli F, Lombardi R, Milone MR, Pucci B, De Rienzo S, Budillon A, et al. Targeting mevalonate pathway in cancer treatment: Repurposing of statins. Recent Pat Anticancer Drug Discov. 2018;13(2):184-200.

161. Fracassi A, Marangoni M, Rosso P, Pallottini V, Fioramonti M, Siteni S, et al. Statins and the Brain: More than lipid lowering agents? Curr Neuropharmacol. 2019;17(1):59-83.

162. King RJ, Singh PK, Mehla K. The cholesterol pathway: Impact on

immunity and cancer. Trends Immunol. 2022;l43(1):78-92.

163. Malik M, Britten J, Borahay M, Segars J, Catherino WH. Simvastatin, at clinically relevant concentrations, affects human uterine leiomyoma growth and extracellular matrix production. Fertil Steril. 2018;110(7):1398-407.

164. Christie CF, Fang D, Hunt EG, Morris ME, Rovini A, Heslop KA, et al. Statin-dependent modulation of mitochondrial metabolism in cancer cells is independent of cholesterol content. Faseb J. 2019;33(7):8186-201.

165. van Beek E, Pieterman E, Cohen L, Löwik C, Papapoulos S. Farnesyl pyrophosphate synthase is the molecular target of nitrogen-containing bisphosphonates. Biochem Biophys Res Commun. 1999;264(1):108-111.

166. Green JR. Antitumor effects of bisphosphonates. Cancer. 2003;97(3 Suppl):840-47.

167. Ji J, Sundquist J, Sundquist K. Use of terbinafine and risk of death in patients with prostate cancer: A population-based cohort study. Int J Cancer. 2019;144(8):1888-95.

168. Kalogirou C, Linxweiler J, Schmucker P, Snaebjornsson MT, Schmitz W, Wach S, et al. MiR-205-driven downregulation of cholesterol biosynthesis through SQLE-inhibition identifies therapeutic vulnerability in aggressive prostate cancer. Nat Commun. 2021;12(1):5066.

169. Abe I, Seki T, Umehara K, Miyase T, Noguchi H, Sakakibara J, et al. Green tea polyphenols: Novel and potent inhibitors of squalene epoxidase. Biochem Biophys Res Commun. 2000;268(3):767-71.

170. Li F, Qasim S, Li D, Dou QP. Updated review on green tea polyphenol epigallocatechin-3-gallate as a cancer epigenetic regulator. Semin Cancer Biol. 2022;83:335-52.