# Cholesterol metabolism and cancer: Molecular mechanisms, immune regulation and an epidemiological perspective (Review)

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**Abstract.** Cholesterol and its metabolites exert multifaceted and profound effects on cancer initiation, progression and therapeutic response as well as patient prognosis. The present review systematically summarizes the oncogenic role of cholesterol metabolism in malignancies. Cancer cells extensively remodel cholesterol homeostasis through enhanced synthesis, increased uptake and impaired efflux, thereby sustaining proliferative signaling, suppressing ferroptotic cell death, promoting autophagic survival and facilitating epithelial-mesenchymal transition, collectively fueling tumor invasion and metastasis. Within the tumor immune microenvironment, cholesterol exhibits dual immunoregulatory roles; it potentiates T-cell antitumor function while its oxidized derivatives contribute to T-cell exhaustion. Therapeutic targeting of cholesterol metabolism represents a promising strategy to trigger ferroptosis, reverse chemoresistance and reinvigorate antitumor immunity. Nevertheless, epidemiological evidence regarding the correlation between cholesterol levels and cancer risk remains contentious, underscoring the context-dependent and complex nature of cholesterol in oncology. Targeting cholesterol metabolism may thus offer a novel integrative approach for cancer therapy, meriting further mechanistic and clinical investigation.

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*Abbreviations:* TME, tumor microenvironment; EMT, epithelial-to-mesenchymal transition; HMGCR, HMG-CoA reductase; SREBPs, sterol regulatory element binding proteins; SQLE, squalene epoxidase; ACAT1, acetyl-CoA acetyltransferase 1; ABCA1, ATP-binding cassette transporter A1; LDLR, low-density lipoprotein receptor; TC, total cholesterol; VLDL, very low-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; MVA, mevalonate; IPP, isopentenyl pyrophosphate; FDPS, farnesyl diphosphate synthase; GGPP, geranylgeranyl pyrophosphate; FPP, farnesyl pyrophosphate; 25-HC, 25-hydroxycholesterol; LR, lipid raft; GPX4, glutathione peroxidase 4; PD-L1, programmed death-ligand 1; FSP1, ferroptosis suppressor protein 1; HCD, high cholesterol diet

*Key words:* cancer, cholesterol, molecular mechanisms, treatment, prognosis

**Contents**



## 1. Introduction

Cholesterol is an essential component of mammalian cell membranes and is indispensable for maintaining normal cellular functions (1). The synthesis of cholesterol is maintained through a dynamic homeostatic process, with intracellular cholesterol levels being precisely regulated by a sophisticated feedback system involving synthesis, uptake, efflux, transport, esterification and enzymatic conversion (2). Cancer cells frequently exhibit an elevated demand for cholesterol to facilitate their growth (3). Specifically, they augment the uptake of exogenous cholesterol and lipoproteins and reprogram cholesterol metabolism by regulating genes related to cholesterol synthesis, efflux and intake to increase cholesterol influx and decrease efflux (4,5). Additionally, tumors can elevate cholesterol levels within the tumor microenvironment (TME) by stimulating cholesterol efflux from monocytes and macrophages via intercellular signaling (6). Furthermore, cholesterol serves as a precursor for biologically active metabolites, such as oxysterols (7), steroid hormones (8) and lipid rafts (LRs) (9), which collectively promote cancer

cell proliferation, angiogenesis, metastasis and other pro-tumorigenic processes (10).

A previous study has shown that the crosstalk between cholesterol metabolism and the TME contributes to tumorigenesis and progression (11). Moreover, oncogenic signaling pathways (12), ferroptosis (13), autophagy (14), epithelial-mesenchymal transition (EMT) (15) and the immune response (16) are modulated through cholesterol metabolism. Current evidence indicates that targeting cholesterol metabolism, either alone or in combination with other strategies, to enhance cancer treatment efficacy has proven to be a viable antitumor approach. Notably, interventions targeting cholesterol metabolism enzymes [such as HMG-CoA reductase (HMGCR) (17), sterol regulatory element binding proteins (SREBPs) (18), squalene epoxidase (SQLE) (19) and acetyl-CoA acetyltransferase 1 (ACAT1) (20)] or transporters [ATP-binding cassette transporter A1 (ABCA1) (21), ATP-binding cassette transporter G1 (ABCG1) (22) and low-density lipoprotein receptor (LDLR) (23)] have shown considerable anticancer potential.

However, the association between cholesterol and cancer progression is currently controversial. Several epidemiological studies have shown that hypercholesterolemia and high cholesterol diets are associated with an increased risk of developing hepatocellular carcinoma (HCC) (24), colorectal cancer (CRC) (25), prostate cancer (PC) (26) and other cancer types (27). Consistently, statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which effectively lower serum cholesterol levels by targeting cholesterol metabolism genes, have been found to suppress cancer progression in certain settings (28). By contrast, other large cohort studies report that serum total cholesterol (TC) levels are either inversely correlated with cancer risk or show no significant association (29,30). For instance, a large-scale prospective Korean cohort study demonstrated that higher TC levels were negatively associated with mortality rates in HCC and gastric cancer (GC) (31). The role of dietary cholesterol in carcinogenesis is similarly debated. While high-cholesterol diets have been shown to accelerate HCC and CRC development (32), a recent study showed a significant positive association between higher daily dietary cholesterol intake and ovarian cancer (OV) risk, whereas abnormal lipid levels were not associated with the risk of OV (33). These conflicting epidemiological data underscore the complexity of the role of cholesterol in cancer and highlight the need for further mechanistic and population-level studies to clarify the relationship between serum cholesterol levels and cancer risk.

In the present review, the latest progress in the interaction between cholesterol and cancer progression is summarized, focusing on the functional roles of cholesterol and its derivatives within cancer cells and their reciprocal regulation within the TME. The current therapeutic strategies targeting molecules such as HMGCR, SREBPs and SQLE are also discussed, offering new perspectives for anticancer drug development.

## 2. Cholesterol metabolism

Cholesterol is an essential lipid molecule and a critical component for maintaining normal functions in the human body (1,34). Cholesterol fulfills multiple vital roles, including maintaining membrane integrity, facilitating cell signaling cell membrane structure, mediating cell communication, enhancing immunity and serving as a precursor for synthesizing steroids, sex hormones, vitamin D, bile salts and oxysterols (35-37). Cholesterol metabolites also hold significant value. In the liver, cholesterol is converted into bile acids, which are essential for the emulsification and absorption of dietary lipids and represent the primary route for eliminating excess cholesterol from the body (38,39). Moreover, cholesterol serves as the precursor for all steroid hormones (such as cortisol, aldosterone, estrogen and testosterone). In the skin, under ultraviolet radiation, cholesterol is transformed into a vitamin D precursor, which is subsequently activated to regulate calcium and phosphate homeostasis (40-42). Thus, in healthy individuals, the homeostasis of cholesterol metabolism is indispensable for cellular activity, digestion function, endocrine regulation and skeletal health.

The body acquires cholesterol through two primary pathways: Endogenous synthesis (70-80%) and exogenous dietary intake (20-30%) (43). Dietary cholesterol is absorbed by Niemann-Pick-C1 like-1 protein (NPC1L1) on the intestinal epithelial cell membrane and subsequently esterified by ACAT1/2, enabling its uptake by the liver in the form of chylomicrons (44). The liver esterifies cholesterol synthesized internally and absorbed from food, assembling it with apolipoproteins and other components into very low-density lipoproteins (VLDLs), which are subsequently secreted into the bloodstream. These VLDLs are metabolized into low-density lipoproteins (LDLs), which are taken up by peripheral tissues via LDLRs. Excess cholesterol in peripheral tissues is delivered back to the liver via high-density lipoprotein cholesterol (HDL-C)-mediated reverse cholesterol transport, where it can be recycled or converted to bile acids for excretion (1,45). Intracellular cholesterol levels are regulated through receptor-mediated endocytosis of LDL-C and HDL-C, as well as through *de novo* synthesis in the endoplasmic reticulum (ER) via the mevalonate (MVA) pathway, which includes squalene biosynthesis and modification procedures (34). Key regulatory enzymes in this pathway are HMGCR and SQLE, which catalyze the conversion of HMG-CoA to MVA and squalene to 2,3-epoxysqualene, respectively. Subsequent steps involve enzymes such as farnesyl diphosphate synthase (FDPS) and geranylgeranyl pyrophosphate synthase (GGPPs), which are crucial for the biosynthesis of farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). Under the action of squalene synthase and squalene epoxidase, FPP is converted to squalene and eventually to cholesterol (46).

Cholesterol homeostasis is transcriptionally regulated by SREBPs. When intracellular cholesterol levels are high, SREBPs are retained in the ER through interaction with the SREBP cleavage-activating protein/insulin-induced gene-1 (INSIG-1) complex. When the cholesterol level of the endoplasmic membrane decreases, SREBPs are transported to the Golgi apparatus. Following proteolytic processing, their transcriptionally active N-terminal domains are released (47). Excess intracellular cholesterol is either esterified by ACAT1 and stored in lipid droplets or refluxed from cells via transporters such as ABCA1 and ABCG1 (48). The dysregulation of cholesterol metabolic enzymes is implicated in various pathologies, including familial hypercholesterolemia (49),

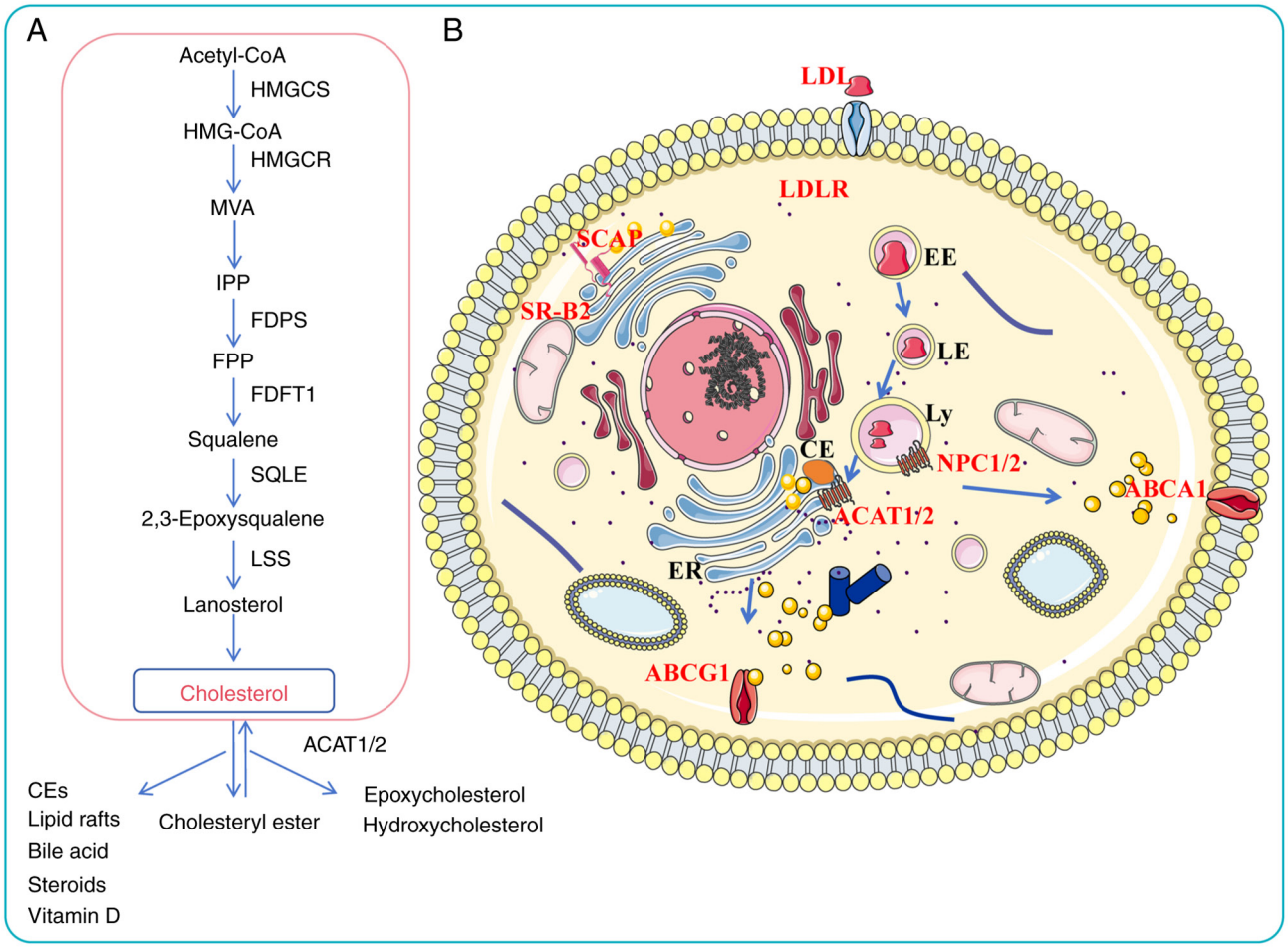


Figure 1. Cholesterol metabolism and cancer. The major pathways involved in intracellular cholesterol metabolism include biosynthesis, uptake, efflux, esterification and conversion. Intracellular cholesterol levels are precisely regulated through these pathways and cholesterol transport. (A) *De novo* biosynthesis converts acetyl-CoA to cholesterol through ~30 enzymatic steps, with HMGCR and SQLE serving as key rate-limiting enzymes. HMGCR, a glycoprotein localized to the ER, reduces HMG-CoA to MVA. SQLE, another rate-limiting enzyme downstream of HMGCR in cholesterol biosynthesis, converts the non-sterol intermediate squalene into 2,3-oxysqualene. (B) Besides synthesis, cells acquire cholesterol via LDLR-mediated endocytosis of LDL particles. LDL-derived cholesterol is transported via endosomes and lysosomes, with the assistance of NPC1/2 and sterol transfer proteins, to the plasma membrane and ER. Cholesterol can be converted into CE by ACAT1 and stored in lipid droplets; it can also be transformed into hydroxycholesterol, epoxycholesterol, vitamin D and steroid hormones. Excess cholesterol in the cell is secreted extracellularly via ABCA1/ABCG1. HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGCS, HMG-CoA synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; SQLE, squalene epoxidase; MVA, mevalonate; IPP, isoprene unit isopentenyl diphosphate; FDPS, farnesyl diphosphate synthase; FPP, farnesyl pyrophosphate; FDFT1, farnesyl-diphosphate farnesyltransferase 1; LSS, lanosterol synthase; LDL, low-density lipoprotein; LDLR, LDL receptor; SCAP, sterol regulatory element binding protein cleavage-activating protein; SR-B2, scavenger receptor class B protein; CE, cholesterol ester; EE, early late endosome; LE, late endosome; Ly, lysosome; ER, endoplasmic reticulum; ACAT1/2, acetyl-CoA acetyltransferase 1/2; NPC1/2, Niemann-Pick C1-like protein 1/2; ABCA1, ATP binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1.

atherosclerosis (35) and Alzheimer's disease (50). In summary, cholesterol levels in normal cells are tightly controlled through a balance of synthesis, uptake, efflux, transport and esterification. A thorough understanding of these regulatory mechanisms is essential for elucidating the pathophysiology of cholesterol-related disorders (Fig. 1).

## 3. Cholesterol and cancer progression

*Cholesterol metabolism in cancer cells*. During growth and invasion, cancer cells require a continuous supply of cholesterol to sustain biosynthetic processes and cellular functions. Consequently, abnormal activation of cholesterol metabolism genes is commonly observed across multiple types of cancer (51). Cholesterol metabolism-related genes are upregulated, cholesterol influx is increased and cholesterol efflux is decreased. HMGCR is the primary rate-limiting enzyme in cholesterol biosynthesis, and its high expression in malignant tumors promotes tumor progression. For instance, HMGCR induces immunosuppression in OV by activating X-box binding protein 1 and programmed death-ligand 1 (PD-L1), correlating with poor prognosis (52). In PC, stromal HMGCR upregulation induced by coculture with malignant cells promotes tumor growth (53). HCC is an aggressive human cancer with increasing incidence worldwide (54). Research has revealed that HMGCR promotes tumor growth in a mouse model of primary liver cancer by enhancing cholesterol synthesis and activating the PDZ-binding motif/TEA domain transcription factors 2/anillin/kinesin family member 23 pathway (55). Additionally, HMGCR overexpression augments the growth and migration of GC cells (56), breast cancer (BC) cells (57) and glioblastoma (GBM) cells (58).

SREBPs, as key regulators of cholesterol metabolism (59), contribute to establishing energy and lipid reserves in tumor cells, playing a crucial role in tumor proliferation, stemness and drug resistance (60). In GBM cells, SREBP1 promotes lipid droplet autophagy by regulating key autophagy genes (such as autophagy-related protein 9B, autophagy-associated gene 4A and light chain 3B), leading to cholesterol ester hydrolysis and the release of cholesterol into lysosomes, ultimately promoting tumor growth (61). Patients with HCC have a poor prognosis and are prone to drug resistance (62). The liver is the primary organ for cholesterol metabolism, and abnormal cholesterol levels are closely associated with the progression of HCC. A previous study has revealed that SREBP1 enhances monounsaturated fatty acid synthesis by upregulating stearoyl-CoA desaturase 1, thereby suppressing ferroptosis in HCC cells and promoting xenograft tumor invasion and sorafenib resistance in mice (63). Notably, Su and Koeberle (64) conducted a systematic review on the role of SREBP1 in HCC progression, metastasis and drug resistance. The review mainly summarized that SREBP1 is an independent prognostic indicator for overall survival (OS) and disease-free survival in patients with HCC. SREBP1 can also regulate signaling pathways in tumor cells, including the PI3K-AKT-mTOR axis, protein kinase A (PKA), c-Myc and Janus kinase (JAK). Moreover, SREBPs have been shown to be upregulated in the tissues of patients with PC (65), BC (66) and OV (67).

SQLE, as the second rate-limiting enzyme downstream of HMGCR, is considered an oncogene that promotes carcinogenic signaling (68). It has been reported that SQLE could enhance the PI3K/AKT signaling pathway to promote distant metastasis in head and neck squamous cell carcinoma (69). In CRC, SQLE induces EMT by triggering the Wnt/β-catenin pathway, thereby promoting tumor metastasis (70). Moreover, SQLE, which is abnormally expressed in liver cancer models, induces immune suppression by promoting cholesterol accumulation in the TME and inhibiting $CD8^+$ T cell function (71). Research has also shown that SQLE contributes to the resistance of BC cells to apoptosis by enhancing glycolysis (72). SQLE expression is specifically elevated in HCC and is strongly associated with poor clinical outcomes (73). SQLE significantly augments HCC growth in both *in vitro* and *in vivo models*, linked to the activation of serine-threonine kinase receptor associated protein-dependent transforming growth factor-β (TGF-β)/SMAD signaling pathways (74).

Farnesyl-diphosphate farnesyltransferase (FDFT1), another key enzyme in the cholesterol pathway, is dysregulated in various tumor types and represents a potential biomarker and therapeutic target (75). FDFT1 is highly expressed in HCC tissues and is correlated with poor patient prognosis (76,77). In HCC, FDFT1 suppressed fructose-1,6-bisphosphate aldolase B expression, thereby releasing its inhibitory control over the AKT signaling pathway and activating the PI3K/AKT pathway, ultimately promoting tumor growth and metastasis (76). Prognosis analysis showed that FDFT1, as a potential prognostic marker, was associated with shorter survival in patients with CRC and may partially contribute to the formation of a suppressive immune microenvironment (78). This indicates that the tumor-promoting effect of FDFT1 is dependent on the TME (79). Notably, another study has revealed a unique role of FDFT1 in CRC. This study found that under fasting conditions, SREBP2 upregulates FDFT1 expression, while elevated FDFT1 expression negatively regulates the AKT/mTOR/hypoxia-inducible factor-1α (HIF-1α) signaling pathway, thereby inhibiting glycolysis and proliferation in CRC cells (80). This suggests that FDFT1 may exert tumor-suppressive effects under specific metabolic conditions, such as fasting, indicating the complexity of its functional role.

ACAT1 is a multifunctional metabolic enzyme that plays a complex and sometimes seemingly contradictory role in various cancer types; it can suppress tumors under specific conditions while simultaneously promoting tumor progression through different mechanisms (81). In HCC, ACAT1-mediated acetylation of glycerophosphate *O*-acyltransferase (GNPAT) can stabilize GNPAT protein levels by antagonizing tripartite motif containing 21-catalyzed ubiquitination, ultimately promoting xenograft tumor growth (82). In bladder cancer (BLCA), ACAT1 promotes BLCA cell proliferation and invasion by activating the AKT/GSK3β/c-Myc signaling pathway (83). Additionally, a recent study has identified ACAT1 as a key factor in reducing the sensitivity of GBM to ferroptosis, with its mechanism of action dependent on the regulation of the iron efflux protein, solute carrier family 40 member 1 (84). However, under the influence of exogenous proinflammatory factors interleukin (IL)-12 and IL-18 proteins, ACAT1 is phosphorylated at the S60 site and translocates from mitochondria to the nucleus. Within the nucleus, it exerts its acetyltransferase activity, specifically acetylated the K146 site of the NF-κB family protein p50, thereby releasing its transcriptional repression on multiple immunochemical genes and natural killer (NK) cell activation ligands, thereby powerfully recruiting and activating NK cells. This enhances their tumor-killing capacity and inhibits tumor growth (85).

NPC1L1 is the primary protein responsible for the absorption of exogenous cholesterol. NPC1L1 is highly expressed in CRC and serves as an independent prognostic factor that is significantly correlated with pathological staging (86,87). An *in vitro* study revealed that targeting NPC1L1 with ezetimibe blocks the AKT/mTOR signaling pathway in HCC and suppresses cancer cell activity (88).

Collectively, these findings underscore that cholesterol metabolism is notably reprogrammed in cancer cells, with multiple enzymes in the biosynthetic pathway actively contributing to tumor development and progression.

*Cholesterol and molecular regulation*. Numerous studies have demonstrated that aberrantly activated genes or signaling pathways can promote cancer cell proliferation and suppress apoptosis through the regulation of cholesterol metabolism-related genes (89-93). For instance, the tumor suppressor p53 can inhibit the MVA pathway, and its deficiency or mutation releases multiple constraints on tumor growth (94). The p53 protein directly suppresses the transcription of SQLE and SREBP genes by binding to their promoters, thereby downregulating the MVA pathway in CRC, HCC, OV and BC (95). By contrast, upregulated or unmutated p53 transcriptionally induces ABCA1 gene expression to block SREBP2 activation and inhibit the MVA pathway (96,97). In recent years, the function of the tumor suppressor phosphatase and tensin homolog protein (PTEN) in metabolic regulation has attracted significant attention (98). As a phosphatase, PTEN

dephosphorylates phosphatidylinositol-3,4,5-trisphosphate, thereby directly inhibiting the oncogenic PI3K/AKT/mTOR signaling pathway (99). PTEN suppression in endocrine therapy-resistant BC cells leads to increased SQLE expression and a corresponding sensitization to the inhibition of cholesterol synthesis (100). In pancreatic ductal adenocarcinoma (PDAC), PTEN deficiency enhances the protein stability of SQLE by activating the PI3K/AKT/GSK3β-mediated proteasome pathway (101). Activated AKT phosphorylates the cytoplasmic phosphorylating rate-limiting enzyme phosphoenolpyruvate carboxy kinase 1, which is translocated to the ER and acts as a protein kinase that phosphorylates the INSIG protein and disrupts the interaction between the INSIG protein and the SREBP shear-activating proteins, which in turn activates the transcription of SREBPs as well as downstream genes related to lipid synthesis and uptake and promotes the progression of HCC (102). AKT regulates SREBP activation by activating mTOR1; it promotes the protein expression of nuclear SREBP2 through a dual mechanism: First, by phosphorylating and inhibiting its nuclear translocation inhibitor, lipin1; second, by regulating cholesterol transport from lysosomes to the ER (103). Furthermore, suppression of ciliary function activates the Wnt/β-catenin pathway, which synergistically promotes transcription of MVA pathway genes by directly interacting with SREBP2 (104).

Liver X receptors (LXRs) are nuclear receptors and members of the nuclear receptor family that regulate intracellular lipid homeostasis. Activated by high intracellular cholesterol, LXRs function as cholesterol sensors (105). c-Fos promotes alterations in cholesterol metabolism by suppressing the transcriptional activity of LXRα, leading to the accumulation of toxic sterols and bile acids, thereby promoting hepatocellular carcinogenesis (106). High expression of anoctamin-1 contributes to *in vivo* metastasis of primary esophageal squamous cell carcinoma by inhibiting LXR signaling, leading to cholesterol accumulation and decreased cholesterol hydroxylation via downregulation of the expression of the cholesterol hydroxylase cytochrome P450 family 27 subfamily A member 1 (107).

LDLR is the key molecule that maintains cholesterol balance in the body, releasing cholesterol into cells for utilization while simultaneously lowering cholesterol levels in the blood (108). LDLR-mediated cholesterol uptake plays a contributory role in cancer (109). A recent study has demonstrated that leukocyte immunoglobulin-like receptor B1 directly binds to the LDLR protein to form a complex, thereby enhancing LDLR-mediated cholesterol uptake and conferring resistance to ferroptosis in multiple myeloma (MM) cells (110).

Apolipoprotein B (APOB) is an essential structural component of VLDL and LDL; its C-terminal region contains an LDLR-binding domain that specifically recognizes LDLRs on hepatocyte surfaces, mediating LDL uptake and clearance to maintain plasma cholesterol homeostasis (111). APOB is classified into two primary subtypes: i) ApoB-100, which is synthesized in the liver and serves as the major structural protein of VLDL, intermediate-density lipoprotein (IDL), and LDL; and ii) ApoB-48, which is synthesized in the small intestine, constitutes the core component of chylomicrons and is primarily responsible for transporting dietary lipids (112). APOB is closely associated with metastasis in CRC and liver cancer. Compared with the control group, silencing of APOB in HCC cells has been shown to increase the relative rate of cell proliferation (113). A recent nested case-control study revealed that genetically predicted APOB levels are associated with a 31% reduction in HCC risk [95% confidence interval (CI), 19-42%] and each 0.1 g/l increase in circulating APOB levels was linked to an 11% decrease in HCC risk (95% CI, 8-14%) (114). Another prospective cohort study from Sweden also found that elevated circulating levels of APOB increased the risk of developing CRC (115).

PCSK9 is a key regulator of LDLR protein levels, binding to LDLRs on the cell surface and directing them to lysosomes for degradation (116). In the TME, tumor cell-derived PCSK9 disrupts T-cell receptor signaling by binding to LDLR on the membrane of $CD8^+$ T cells and directing LDLR to lysosomal degradation. This impaired $CD8^+$ T cell activation, proliferation and effector function, ultimately leads to lymphoma metastasis in mice (117). In lung adenocarcinoma (LUAD), the long non-coding RNA EMX2OS competitively binds to microRNA-1185-5p to regulate the LDLR, thereby promoting lung cancer cell proliferation and invasion (118). In addition, MEK/ERK signaling increases intracellular cholesterol uptake by upregulating LDLR expression, leading to HCC metastasis (119).

Similarly, dysregulation of cholesterol metabolism can activate gene expression. Poly (ADP-ribose) polymerase 1 (PARP1) is a multifunctional human ADP-ribosyl transferase (120). In addition to maintaining genomic integrity, PARP1 participates in transcriptional regulation (121). A recent study revealed that long-term high cholesterol promotes OV progression by activating focal adhesion kinase (FAK)/collagen type V alpha 1 chain (COL5A1) signaling through the upregulation of PARP1 expression (122). Several cholesterol derivatives and metabolites, including 7-ketocholesterol (123), 15α-hydroxycholesterol (124), 25-hydroxycholesterol (25-HC) (125), 17-β-estradiol (126) and vitamin D (127), have been shown to induce PARP1 expression.

Cholesterol is a key structural component of LRs. In PC cells, elevated serum cholesterol levels can increase cholesterol content within tumor cell liposomes, thereby activating the LR-mediated Src/PI3K/AKT signaling pathway (128,129). Mitochondrial cholesterol also exhibits physiological activity and promotes tumor cell proliferation and metastasis. For instance, a recent study revealed that the interaction between cytotoxin-associated protein A and cytochrome P450scc (CYP11A1) promotes mitochondrial cholesterol accumulation. This accumulated cholesterol then activates autophagy, thereby enhancing GC cell proliferation and suppressing apoptosis (130). The c-Myc proto-oncogene encodes a family of transcription factors and is one of the most commonly activated oncogenes in human tumors (131). Yang *et al* (132) found that c-Myc protein directly promotes SQLE transcription, thereby increasing cholesterol production and promoting tumor cell growth. Similarly, activated c-Myc protein has also been observed to enhance HMGCR transcriptional expression in T-cell acute lymphoblastic leukemia (133). Notably, upregulated SREBP1 protein directly interacts with SREBP1 binding elements in the c-Myc promoter region in PC to induce c-Myc activation to drive tumor stemness and metastasis (134). These studies illustrate a reciprocal regulatory relationship between

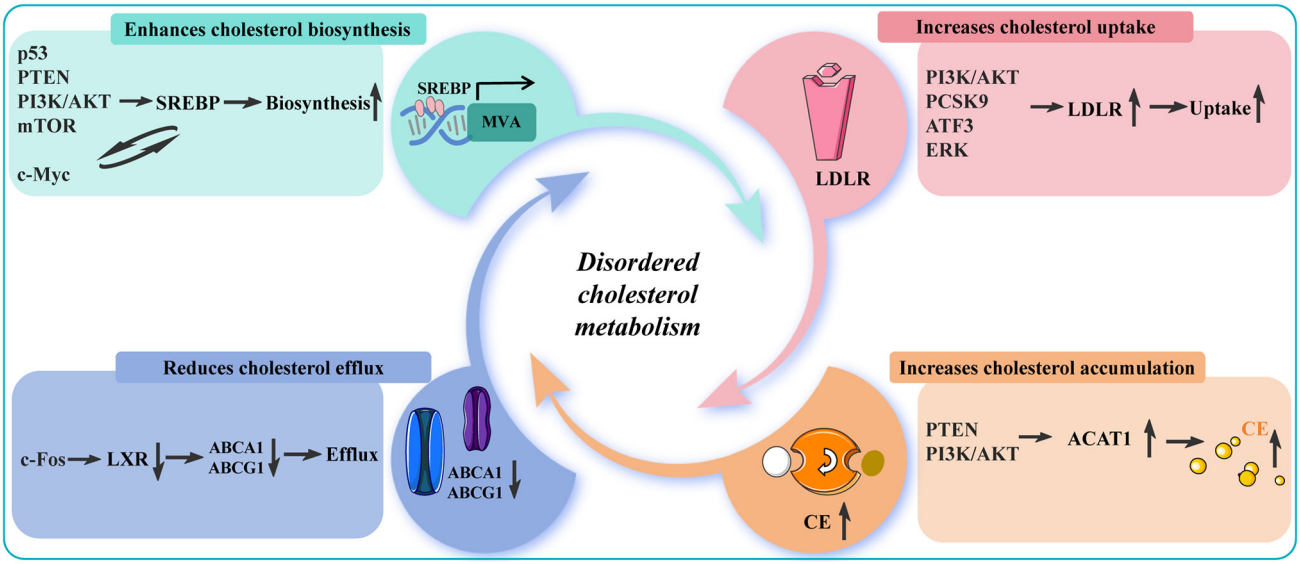


Figure 2. Genes and cholesterol metabolism. Schematic representation of the mechanism by which genes regulate cholesterol biosynthesis, uptake, efflux and esterification. PTEN, mutations in the phosphatase and tensin homolog; PI3K, phosphatidylinositol 3-kinase; SREBP, sterol regulatory binding protein; mTOR, mechanistic target of rapamycin; MVA, mevalonate; PCSK9, proprotein convertase subtilisin kexin/type 9; ATF3, activating transcription factor 3; ERK, extracellular-signal-regulated kinase; LDLR, low-density lipoprotein receptor; LXR, liver X receptor; ABCA1, ATP binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; CE, cholesterol ester; ACAT1, acetyl-CoA acetyltransferase 1.

cholesterol metabolism and genes, highlighting their critical roles in tumor cell proliferation and invasion (Fig. 2).

*Targeting cholesterol metabolism in cancer cells*. A large body of preclinical evidence has underscored the critical and multifaceted roles of cholesterol metabolism in cancer progression (135-138). Targeting key nodes of this pathway, such as inhibition of the MVA pathway, has emerged as a promising antitumor strategy (1,139). At present, statins, which act as inhibitors of HMGCR, and PCSK9 inhibitors have emerged as the predominant agents targeting cholesterol metabolism, extensively employed in both basic and clinical research (140,141). The anticancer function of statins has attracted significant attention. Existing evidence indicates that statins can promote tumor cell proliferation, differentiation and apoptosis (76,142,143). A clinical study demonstrated that initiating statin therapy within 1 year of diagnosis results in a 58% relative improvement in BC-specific survival and a 30% relative improvement in OS (144). Similarly, simvastatin (SIM) blocks the isoprenylation of Rab5 GTPase and its mediated endosomal maturation in antigen-presenting cells by depleting GGPP through inhibition of the MVA pathway, ultimately enhancing antitumor immunity by boosting antigen presentation and T cell activation (145). Bisphosphonates (BPs) are another widely studied inhibitor of the MVA pathway, which inhibits FDPS activity and prevents the conversion of isopentenyl pyrophosphate (IPP) to FPP (47,146,147). Bisphosphonate therapy has been reported to improve the prognosis of patients with bona fide MM, PC and BC (148). Moreover, BPs can reduce bone and visceral metastases in women with BC (149,150). Previous studies suggest that SQLE upregulation is closely associated with tumor progression. For instance, upregulated SQLE promotes HCC cell invasion by activating ERK (151) or AKT/mTOR signaling (152). However, targeting SQLE with terbinafine can delay tumor progression in endometrial cancer (ECa) (153), PC (154), CRC (155), HCC (156) and BC (157). Ezetimibe is an FDA-approved drug that acts on NPC1L1 to inhibit the progression of CRC (86), BC (158) and PC (159) by inhibiting intestinal cholesterol absorption. Intracellular cholesterol accumulation triggers LXRs and excess cholesterol is excreted via ABCA1 or ABCG1 (160). The LXR agonists RGX-104 (161), LXR 623 (162) and T0901317 (163) increase ABCA1 expression in a variety of tumor cells, decrease intracellular cholesterol levels and effectively inhibit the growth of mouse xenograft tumors. Additionally, T0901317 can reduce myeloid-derived suppressor cell infiltration through the LXR/APOE pathway, thereby lifting immune suppression, enhancing T cell function and ultimately improving overall immune therapy response (164).

Notably, statins also enhance the efficacy of conventional antitumor drugs (165). Retrospective studies have shown that statin therapy prolongs survival in patients with BC (166), HCC (167), CRC (168) and metastatic PC (169) treated with a combination of first-line chemotherapeutic agents. Results from a phase II clinical trial demonstrated that combining SIM with the epidermal growth factor receptor (EGFR) inhibitor, gefitinib, yielded superior antitumor effects compared with gefitinib alone in non-small cell lung cancer (NSCLC).

The NPC1 protein, which regulates endolysosomal cholesterol transport, has recently emerged as a therapeutic target. NPC1 represents a convergence point for cholesterol derived from LDL, HDL and VLDL, allowing simultaneous targeting of multiple cholesterol sources (170). A previous study has shown that targeted inhibition of NPC1 downregulates mTORC1 signaling and reduces autophagy and tumor growth (171). Moreover, lowering NPC1 expression enhances the therapeutic efficacy of cisplatin or trastuzumab in NSCLC (172), GC (173) and PC (174), leading to improved patient prognosis. These findings highlight the clinical potential of combining cholesterol metabolism inhibitors with existing anticancer agents

Table I. Anticancer therapies that target cholesterol metabolism.

| Reagent | Target | Mechanism | Phenotype/effect | Cancer type |
|---|---|---|---|---|
| Statins | HMGCR | Decreases serum total cholesterol level | Decreases cancer mortality and prolongs survival | BC (276), HNSCC (277), CRC (278) and PC (279) |
| Statins | NPC1 | Suppresses NPC1 signaling | Inhibits tumor growth | TNBC (280) |
| Statins | ERα | Decreases ERα expression and activity and promotes apoptosis | Reduces the size and weight of xenograft tumors | ACC (281) |
| Terbinafine | SQLE | Decreases cholesterol levels and increases chemotherapy sensitivity | Improves patient prognosis | HCC (156) and CRC (70) |
| Terbinafine | SQLE | Suppresses AKT/mTOR signaling | Inhibits tumor growth | HCC (151) |
| RGX-104 | LXR | Activates the LXR/ApoE signaling axis and increases radiosensitivity | Myeloid-derived suppressor cell depletion and increased T-cell activation | NSCLC (161,282) |
| LXR623/ GW3965 | LXR | Activates ATF4-dependent pro-apoptotic protein Noxa expression | Promotes tumor cell apoptosis | CRC (283) and GBM (284) |
| Fatostatin | SREBPs | Inhibits AKT/mTORC1/ GPX4 signaling | Promotes tumor cell apoptosis | GBM (285) and ECa (286) |
| Avasimibe | ACAT1 | Inhibits Wnt/β-catenin signaling | Blocks tumor metastasis | PC (287) |
| Itraconazole | NPC1 | Activates AMPK signaling | Inhibits tumor angiogenesis | CRC (288) and NSCLC (289) |

HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HNSCC, head and neck cutaneous squamous cell carcinoma; BC, breast cancer; CRC, colorectal cancer; PC, prostate cancer; TNBC, triple negative BC; ACC, adrenocortical carcinoma; ERα, estrogen receptor α; NPC1, Niemann-Pick disease Type C; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; GBM, glioblastoma; ECa, endometrial cancer; LXR, liver X receptor; ACAT1, acyltransferase/sterol O-acyltransferase 1; SREBPs, sterol regulator element binding proteins.

to overcome therapy resistance. Cancer therapies targeting cholesterol metabolism are summarized in Table I.

*Cholesterol and ferroptosis*. Ferroptosis, a regulated form of cell death driven by iron-dependent lipid peroxidation, represents a promising therapeutic avenue in oncology due to its involvement in tumor progression and treatment resistance (175). Glutathione peroxidase 4 (GPX4) and solute carrier family 7 member 11 are central to regulating ferroptosis (176). Elevated cholesterol levels in cancer cells have been shown to suppress ferroptosis and impair immune responses (177). Recent studies have shown that 7-dehydrocholesterol (7-DHC) and B-ring sterols act as free-radical-trapping antioxidants to protect mitochondrial membranes from phospholipid autoxidation, thereby resisting ferroptosis (178,179). While most cancer cells succumb under stress, surviving populations often accumulate high cholesterol levels to evade ferroptosis death (84,180,181). Chronic exposure to 27-hydroxycholesterol (27-HC), an abundant metabolite of circulating cholesterol, causes sustained expression of GPX4 and significantly increases the tumorigenic and metastatic capacity of BC cells (13). These findings highlight that aberrant cholesterol metabolism can influence cancer pathogenesis by activating ferroptosis. In cancer cells, increased uptake via the upregulation of lipoprotein receptors and increased synthesis rates through the hyperactive MVA pathway results in cholesterol accumulation, fostering cellular proliferation, tumor metastasis and immune suppression (182-184). Studies have revealed that GPX4 relies on the output of the MVA pathway to hinder lipid peroxidation production and ferroptosis sensitivity in HCC cells (185,186). Exogenous cholesterol supplementation activates the B7H3-mediated AKT/SREBP2 signaling pathway to promote ferroptosis resistance in CRC cells as well as xenograft tumor formation in mice (187).

Elevated cholesterol levels reduce membrane fluidity and promote LR formation, thereby inhibiting the diffusion of lipid peroxidation substrates and suppressing ferroptosis (188-190). A novel nanozyme composed of an iron metal-organic framework (Fe-MOF) and nanoparticles loaded with cholesterol oxidase and PEGylation (CP) for integrated ferroptosis and immunotherapy, depletes cholesterol and disrupts LR integrity, downregulates GPX4 and ferroptosis suppressor protein 1 (FSP1) and further promotes ferroptosis. Concurrently, Fe-MOF/CP augments immunogenic cell death,

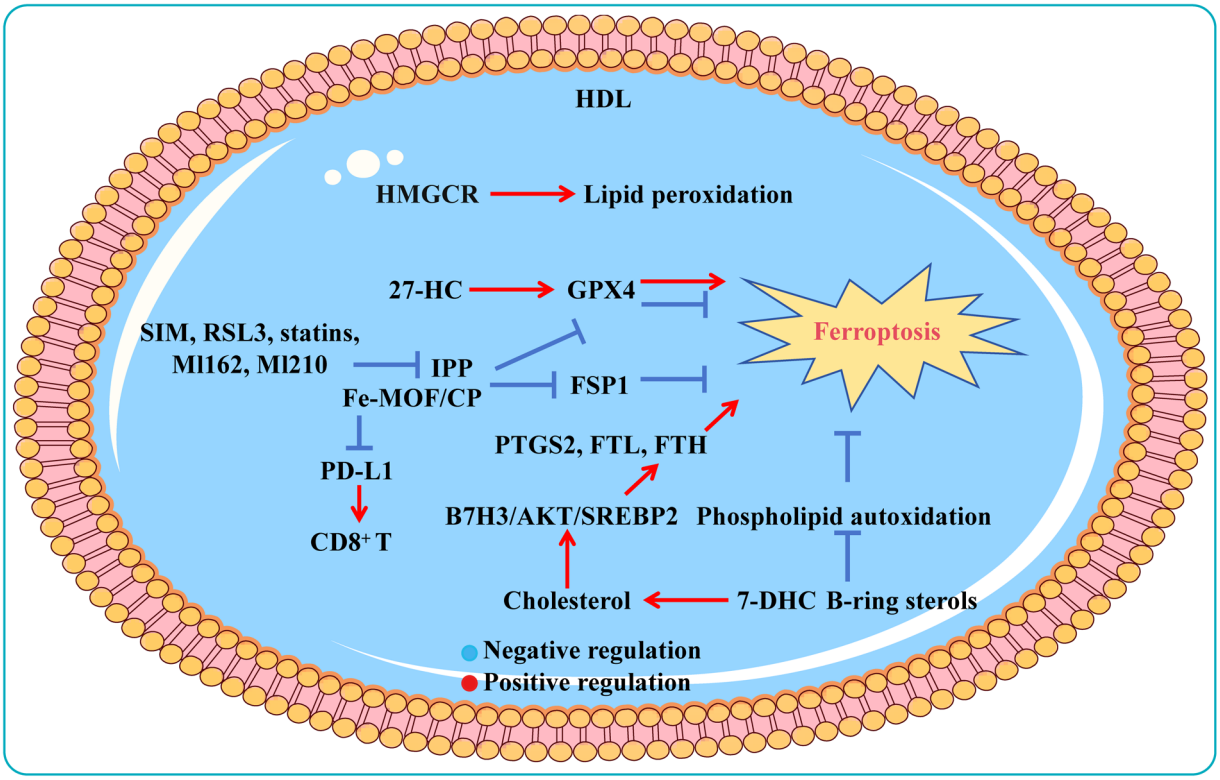


Figure 3. Regulation of ferroptosis by the cholesterol biosynthesis pathway. 7-DHC, 27-HC and B-ring sterols activate the ferroptosis process by upregulating GPX4, FSP1, PTGS2, FT1 and FTH expression. Inhibition of key enzymes of cholesterol metabolism such as HMGCR and IPP are expected as promising approaches to induce ferroptosis in cancer cells. HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HDL, high-density lipoprotein; 27-HC, 27-hydroxycholesterol; GPX4, glutathione peroxidase 4; SIM, simvastatin; RSL3, ras-selective lethal 3; IPP, isoprene unit isopentenyl diphosphate; Fe-MOF/CP, iron metal-organic framework/cholesterol oxidase and PEGylation; FSP1, Ferroptosis suppressor protein 1; PD-L1, programmed death ligand 1; SREBP2, sterol regulatory binding protein 2; 7-DHC, 7-dehydrocholesterol.

reduces programmed death-ligand 1 expression and revitalizes exhausted $CD8^+$ T cells (191). Similarly, in cholesterol-addicted lymphoma cells, targeting SCARB1 via HDL nanoparticles to reduce cholesterol uptake not only eliminates GPX4 expression but also triggers a compensatory response that enhances cholesterol biosynthesis, ultimately leading to ferroptosis (189). GPX4, a core regulator of ferroptosis, is modulated by IPP, a product of the MVA pathway and an intermediate in cholesterol synthesis. Thus, regulating the upstream synthesis pathways of IPP using inhibitors (such as FIN56, RSL3, statins, ML162 and ML210) induces ferroptosis by suppressing GPX4 (a protein responsible for preventing lipid peroxide formation); whereas FIN56 and withaferin can trigger GPX4 degradation (192). Squalene and HMGCR are thought to exert anti-ferroptosis effects on cancer cells (180,193). For example, SIM can inhibit the expression of HMGCR to downregulate the MVA pathway, GPX4 and FSP1, thereby inducing triple-negative BC cell ferroptosis (194,195). Conversely, SQLE exerts anti-ferroptosis effects, whereas exogenous cholesterol hydroperoxide induces dose-dependent cell death (196,197). These findings highlight the therapeutic potential of targeting cholesterol biosynthesis to sensitize cancer cells to ferroptosis (Fig. 3).

*Cholesterol and autophagy*. In cancer, autophagy exhibits a context-dependent dual role, capable of both suppressing and promoting tumorigenesis (198). During the early stages, autophagy prevents tumor initiation by eliminating oncogenic proteins, toxic misfolded aggregates and damaged organelles (199). However, in the later stages of tumorigenesis, autophagy functions as a dynamic degradation and recycling system that can enhance cancer invasiveness by promoting metastasis, thereby sustaining tumor survival and growth (200). Autophagy involves a variety of signaling pathways, such as the mitogen-activated protein kinase (MAPK), mTOR, AKT, HIF-1α and p53 pathways (201). Lysosomal cholesterol activates mTORC1 through the SLC38A9/NPC1 signaling axis, inducing autophagy that promotes tumor metastasis and invasion (202). Similarly, another study revealed that cholesterol also induces autophagy in HCC cells by activating mTORC1 via the SNHG6/FAF2/mTOR axis, increasing the incidence of HCC driven by a high cholesterol diet (203). In MM, researchers have reported that cholesterol accumulation mediates autophagy activation via the PI3K/AKT pathway (204). Conversely, phosphorylated AKT levels as well as rapamycin signaling are markedly suppressed after the use of statins by lowering intracellular cholesterol levels (205). The mTOR, AKT and p53 pathways also modulate SREBP activity, which in turn regulates cholesterol synthesis (96,206). Among these, the AKT and mTOR pathways are the most frequently studied *de novo* cholesterol synthesis pathways in cancer cells (207). mTOR serves as the core molecule mediating the regulatory function of AKT over SREBPs. mTOR operates through a dual mechanism: on the one hand, it is activated by AKT (206); on the other, it drives cholesterol biosynthesis by enhancing SREBP2 activity and inhibiting its degradation (208). Whether cholesterol-induced

autophagy initiates positive feedback regulation of these pathways warrants further investigation.

Emerging evidence indicates that cholesterol enrichment within organelles facilitates the recruitment of autophagy-initiation proteins and enhances autophagosome formation, contributing to chemoresistance (209,210). The cholesterol transporter protein GRAM domain containing 1B can coordinate cellular processes by mediating cholesterol distribution between organelles, thereby inhibiting autophagosome formation and reducing mitochondrial bioenergetic metabolism (211). Furthermore, cholesterol-rich membrane microstructure domain (CEMM)-mediated sequestration of the vesicle-associated membrane protein 3/syntaxin-6 complex inhibits autophagosome fusion. Conversely, CEMM deficiency promotes autophagosome formation and confers doxorubicin resistance in BC (212). Similarly, cholesterol inhibits the autophagic degradation of receptor tyrosine kinase in a Golgi membrane protein 1-dependent manner to promote HCC metastasis (213). Cholesterol accumulation in lysosomes induces autophagy initiation and enhances carboplatin resistance in OV cells by activating the NOTCH/DNA-binding protein recombination signal binding protein-Jκ signaling pathway (214). These results emphasize that cholesterol is an important regulator of signaling pathways in cancer.

Cholesterol metabolites also play a key role in activating autophagy. High 25-HC levels promote Kras-driven PDAC progression. Mechanistically, 25-HC promotes autophagy, leading to the downregulation of MHC-I and a reduction in $CD8^+$ T-cell infiltration into tumors (215). BC is one of the most common female cancer types in the world, with estrogen receptor-positive BC being the most common subtype (216). The accumulation of cholesterol-5,6-epoxide (5,6-EC) metabolites enhances resistance to tamoxifen through the activation of autophagy to potentiate antiestrogen binding site activity (217,218). Unraveling the molecular interactions within the regulatory networks of cholesterol metabolism and autophagy provides core guidance for identifying novel anti-cancer targets and formulating targeted strategies (Fig. 4).

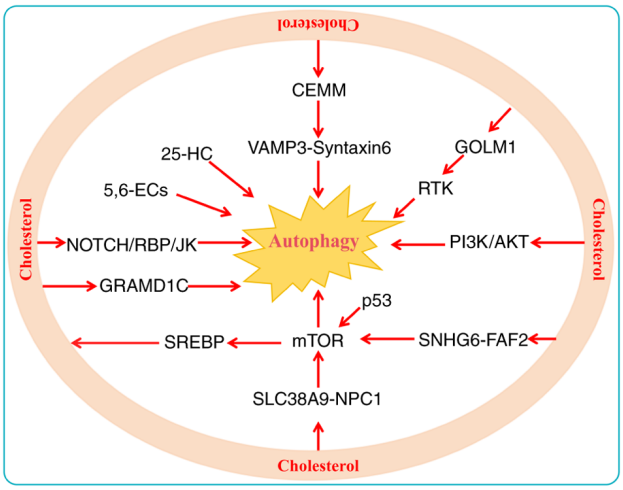


Figure 4. Cholesterol-induced activation of autophagy. Exogenous cholesterol supplementation and elevated endogenous cholesterol activate mTORC1-dependent autophagy through multiple pathways, including those involving p53, AKT and NPC1. Additionally, cholesterol derivatives such as 25-HC and 5,6-EC also stimulate autophagy in tumor cells. CEMM, cholesterol-enriched membrane micro-domains; 25-HC, 25-hydroxycholesterol; RBP-JK, DNA-binding protein recombination signal binding protein-Jκ; VAMP3, vesicle-associated membrane protein; GOLM1, Golgi membrane protein 1; RTK, receptor tyrosine kinase; PI3K, phosphatidylinositol 3-kinase; SREBP, sterol regulatory binding protein; mTOR, mechanistic target of rapamycin; SNHG6, small nucleolar RNA host gene 6; FAF2, Fas-associated factor family member 2; SLC38A9, solute carrier family 38 member 9; NPC1, Niemann-Pick C1.

*Cholesterol and EMT.* EMT is a key driver of tumor growth and metastasis, promoting a malignant phenotype by conferring enhanced metastatic capacity and resistance to therapeutic interventions. Tumor EMT states have also been found to exhibit high plasticity during transitions between epithelial and mesenchymal phenotypes (219). The progression of EMT is governed by the precise coordination of a core set of transcription factors, such as Snail1/2, zinc finger enhancer-binding protein 1 and Twist1, whose expression levels directly determine the degree of EMT activation and the transformation of cellular phenotypes (220). Cholesterol increases the risk of EMT in cancer. A high-cholesterol diet promotes lung metastasis of HCC in mice by activating sterol *O*-acyltransferase 1 (SOAT1)-mediated EMT. Mechanistically, SOAT1 increases cholesterol accumulation and esterification, thereby driving EMT and HCC progression (93). Treatment with 20 $\mu$mol/l cholesterol was found to promote *in vivo* graft tumor growth and distal metastasis in CRC by inducing EMT (19). Cholesterol has been demonstrated to regulate several classical signaling pathways that activate EMT. Cholesterol (10 $\mu$mol/l) induces adipocyte membrane-associated protein binding to EGFR substrate 15-associated protein, activates ERK1/2 and facilitates the EMT process in PC cells (221). The integrity of LRs is essential for the formation of the TGF-β receptor (TβR) I/TβRII/TGF-β1 complex, and LR disruption impedes canonical TGF-β signaling. Cholesterol within LRs promotes EMT, migration and invasion in BC cells via TGF-β-mediated MAPK activation (222). High cholesterol also promotes proliferation and migration in BC and PDAC cells through activation of Wnt/β-catenin signaling (223,224), and similarly induces EMT in melanoma via the MAPK pathway (225). Notably, our latest study revealed that long-term treatment of OV cells with high cholesterol concentrations (>20 $\mu$mol/l) significantly induces the expression of cellular EMT transcription factors and mesenchymal cell marker proteins. Mechanistically, cholesterol promotes invasion of orthotopic ovarian tumors into the liver and kidney in mice through activation of the PARP1/COL5A1/FAK/EMT axis (122). These studies collectively indicated that cholesterol plays a key role in promoting EMT.

Cholesterol-related genes also have key roles in EMT-induced metastasis and drug resistance. Upregulation of ABCA1 in CRC facilitates EMT induction and enhances the migratory and invasive abilities by modulating caveolin-1 stability (226). High ABCG1 expression enhances cisplatin resistance in LUAD by activating Slug-mediated EMT (227). Dysregulation of cholesterol metabolism not only promotes the development of HCC but also drives tumors to exhibit highly invasive characteristics, including intrahepatic spread and early extrahepatic metastasis (76,228,229). A recent study has shown that high expression of 7-DHC reductase is correlated with poor

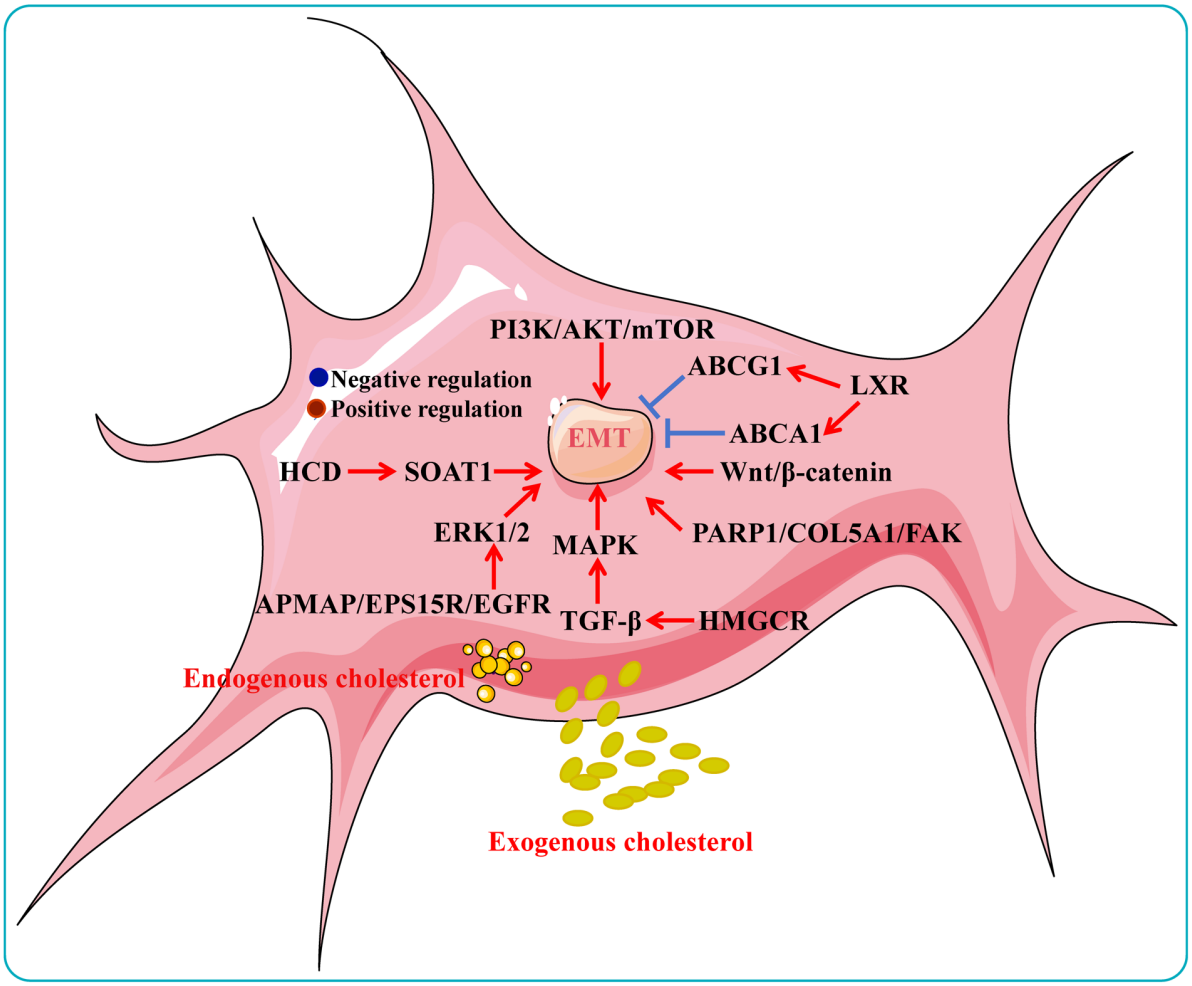


Figure 5. Cholesterol promotes EMT progression. High cholesterol levels facilitate EMT by activating signaling pathways including TGF-β/MAPK, Wnt/β-catenin, PI3K/AKT/mTOR, PARP1/COL5A1/FAK and APMAP/EPS15R/EGFR. Conversely, LXR-induced upregulation of ABCA1 and ABCG1 suppresses EMT in tumor cells. EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor β; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; mTOR, mechanistic target of rapamycin; PARP1, Poly (ADP-ribose) polymerase 1; COL5A1, collagen type V α1 chain; FAK, focal adhesion kinase; APMAP, adipocyte plasma membrane associated protein; EGFR, epidermal growth factor receptor; EPS15R, EGFR-substrate 15-related protein; LXR, liver X receptor; ABCA1, ATP binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; HCD, high cholesterol diet; SOAT1, sterol *O*-acyltransferases 1; ERK1/2, extracellular signal-related kinases 1 and 2.

prognosis in patients with BLCA and promotes metastasis in mice via PI3K/AKT/mTOR-mediated EMT activation (230). 27-HC, the most abundant oxysterol, increases the risk of BC progression by promoting EMT and oncogenic transformation of BC stem cells through LXR activation (15). Accumulation of apolipoprotein E leads to cholesterol enrichment in HCC cells, stimulating PI3K/AKT signaling, inducing EMT and increasing sorafenib resistance and invasiveness (231). Aberrant HMGCR expression enhances statin resistance in therapy-resistant PC cells and augments TGF-β-induced EMT in lung and ovarian epithelial carcinomas (232-234). Additionally, HMGCR augments TGF/β-induced EMT progression in epithelial cell carcinomas (lung and ovarian) (235). Collectively, this scientific evidence highlights the important role played by cholesterol in promoting EMT, providing a new means of targeting cholesterol metabolism to combat tumor progression (Fig. 5). Cholesterol-activated EMT markers and transcription factors in different cancer types are summarized in Table II.

## 4. Cholesterol and immunity

Recent studies have demonstrated that modulation of systemic cholesterol metabolism could improve responses to immunotherapy (16,136,236). Cholesterol depletion is a key metabolic basis for tumor-associated macrophages (TAMs) acquiring an immunosuppressive phenotype (6). In patients with CRC, cholesterol metabolism promotes macrophage polarization towards a pro-tumor phenotype and is associated with poorer prognosis (237). Notably, replenishing cholesterol or adding 7-DHC to mouse macrophages was shown to inhibit interferon-β production (238). In a murine melanoma model, cholesterol accumulation in the TME induced functional exhaustion of $CD8^+$ T cells (239). Cholesterol metabolism exhibits different effects on different T cell subsets. Cholesterol enhances receptor signaling and immune synapse formation in $CD8^+$ T cells by binding to T cell receptor β (240). Another *in vivo* study demonstrated that inhibition of ACAT1 by knockdown or pharmacological inhibition can inhibit intracellular cholesterol esterification

Table II. EMT markers or TFs activated by cholesterol in different cancer types.

| Cancer types | EMT markers or TFs | Phenotype/effect | Limitations of the mechanism validation |
|---|---|---|---|
| HCC (93,231,290) | E-cadherin, Vimentin, Twist1, N-cadherin, Snail1 and Slug | Proliferation and invasion | Absence of transcriptional regulation validation |
| GBM (285) | N-cadherin, Snail1 and Vimentin | Migration and invasion | Absence of gene interference validation |
| TNBC (291,292) | E-cadherin, N-cadherin Vimentin, ZEB1 and Snail2 | Migration and invasion | Absence of *in vivo* experiments |
| PC (221) | N-cadherin and Vimentin | Liver metastasis | Unvalidated in multiple tumor cell lines |
| OV (122) | E-cadherin, N-cadherin, Snail, Twist1 and Vimentin | Tumor invasion | Absence of transcriptional regulation validation |
| BLCA (230) | E-cadherin, N-cadherin, MMP-9 and Vimentin | Migration and invasion | Absence of gene interference validation |
| LUAD (293) | E-cadherin, N-cadherin and Vimentin | Tumor growth | Absence of transcriptional regulation validation |
| CCA (294) | N-cadherin, Vimentin, ZEB1 and Snail | Tumor growth | Unvalidated in multiple tumor cell lines |
| ECa (295) | N-cadherin, Vimentin and Snail2 | Migration and invasion | Absence of *in vivo* experiments |
| EC (296) | E-cadherin, Vimentin, Slug and Snail2 | Lung metastasis | Absence of transcriptional regulation validation |
| CRC (297) | N-cadherin, Vimentin and Snail | Lymph node and liver metastases | Absence of gene interference validation |

HCC, hepatocellular carcinoma; GBM, glioblastoma multiforme; TNBC, triple negative breast cancer; PC, prostatic cancer; OV, ovarian cancer; BLCA, bladder cancer; LUAD, lung adenocarcinoma; CCA, cholangiocarcinoma; ECa, endometrial cancer; EC, esophageal cancer; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; TFs, transcription factors.

in T cells and enhance the proliferative and effector capacity of $CD8^+$ T cells, whereas $CD4^+$ T cells are unaffected (241). In C57BL/6J mice, genes involved in cholesterol esterification (ACAT1/2, lecithin cholesterol acyltransferase and cholesterol ester transfer protein) and utilization (CYP11A1, CYP17A1 and CYP7A1) are upregulated in γδ T cells compared with αβ T cells (242). Moreover, cholesterol depletion using methyl-β-cyclodextrin reduces the activation phenotype of γδ T cells (243). However, the impact of hypercholesterolemia or lipid-lowering treatments on T cell signaling in human patients remains unclear.

Cholesterol has also been identified as a key immunomodulatory factor, whose accumulation promotes tumor immune escape. In the TME, cholesterol attenuates the efficacy of PD-L1 blockade by activating the signal transducer and activator of transcription 3/nuclear factor κB pathway, driving macrophages toward an M2-like phenotype that accelerates CRC progression (244). Additionally, cholesterol upregulates PD-L1 expression on cancer cells, facilitating immune evasion (245,246). Hyaluronic acid oligomers secreted by tumor cells increase cholesterol efflux from TAMs, promoting M2 polarization and tumor progression (6). Although IL-9-secreting $CD8^+$ T cells (Tc9 cells) exhibit potent antitumor activity, cholesterol suppresses IL-9 expression and impairs Tc9 cell function through LXR activation (247). In microsatellite-stable CRC, tumor cells secrete distal cholesterol precursors that polarize T cells into Th17 cells, promoting tumor growth (248).

Cholesterol derivatives similarly modulate immune responses. 27-HC promotes the development of the BC pre-metastatic microenvironment by attracting polymorphonuclear neutrophils and γδ-T cells at metastatic sites and depleting $CD8^+$ T cells (249). Furthermore, 27-HC induces T cell cholesterol deficiency by inhibiting SREBP2 and activating LXR, leading to autophagy-mediated T cell apoptosis (14). In HCC, oxidized sterols activate LXRα in dendritic cells (DCs), downregulating CC chemokine receptor 7 expression and impairing DC migration to lymphoid organs, thereby suppressing antitumor immunity (250).

In summary, the conflicting results of cholesterol in modulating immunotherapy suggest that a deeper understanding of the regulatory mechanisms of cholesterol metabolism in the interactions between tumor cells and immune cells in the TME will contribute to the development of new cancer immunotherapy strategies (Fig. 6). Targeting cholesterol metabolism in the tumor immune microenvironment represents a promising approach to enhance antitumor immunity.

## 5. Epidemiologic relationship between cholesterol and tumors

Although extensive basic and preclinical studies have demonstrated the involvement of cholesterol in cancer

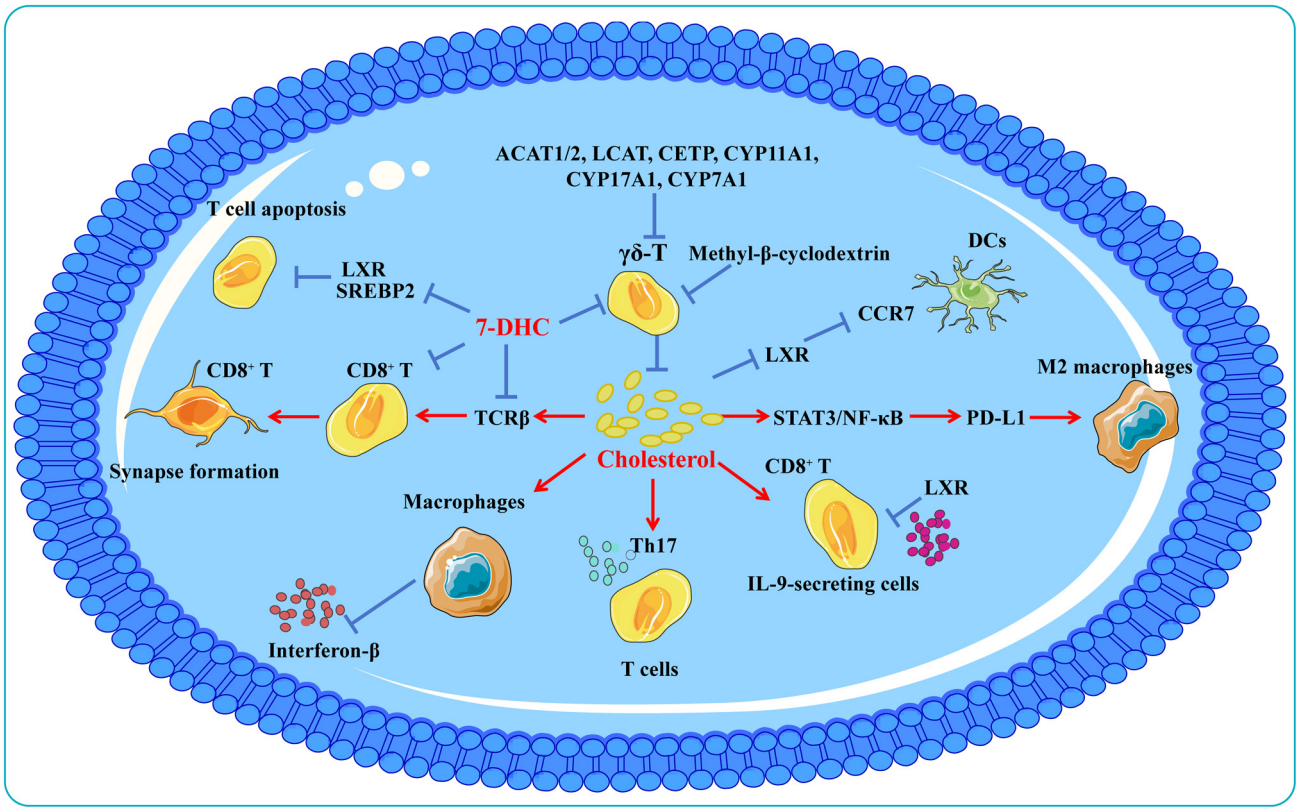


Figure 6. Impact of cholesterol and derivatives on the adaptive immune system. Cholesterol regulates T cell function through direct binding to the TCR or through indirect mechanisms, influencing immune synapse formation. Excessive cholesterol impairs T cell activity; it also promotes M2 macrophage polarization via the STAT3/NF-κB/PD-L1 axis. The oxysterol 27-HC induces T cell apoptosis through SREBP inhibition and LXR activation. Genes involved in cholesterol transport and metabolism (such as ACAT1/2, LCAT, CETP, CYP11A1, CYP17A1 and CYP7A1) modulate cholesterol levels in γδ T cells. Cholesterol enhances IL-9 secretion in macrophages but inhibits CCR7 in DCs; it also promotes Th17 cell differentiation and suppresses IFN-γ production in macrophages. TCR, T-cell receptor; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor κB; PD-L1, programmed death-1; 27-HC, 27-hydroxycholesterol; SREBP, sterol regulatory binding protein; LXR, liver X receptor; ACAT1/2, acetyl-CoA acetyltransferase 1/2; LCAT, lecithin cholesterol acyltransferase; CETP, cholesteryl ester transfer protein; CYP11A1, enzyme cytochrome P450 family 11 subfamily A member 1; CYP17A1, enzyme cytochrome P450 family 17 subfamily A member 1; CYP7A1, cholesterol 7α-hydroxylase; IL-9, interleukin-9; CCR7, chemokine receptor 7; DCs, dendritic cells; IFN-γ, interferon-γ; Th17, intestinal IL-17-producing T helper; 7-DHC, 7-dehydrocholesterol.

development and the potential of targeting its metabolism, the relationship between serum cholesterol levels and tumor risk remains controversial, with epidemiological studies reporting conflicting findings (3). Several large-scale studies have indicated a positive association between elevated serum cholesterol and cancer risk. For example, two prospective cohort studies provided evidence that higher cholesterol levels were positively associated with the risk of high-grade PC (251,252). Another study revealed an association between the use of statins to lower serum cholesterol levels and the risk of developing or dying from 13 tumor types, including HCC, MM, BC, ECa and CRC (253). A 10 mg/dl increase in cholesterol was correlated with a 9% increase in PC recurrence (128). In OV, elevated preoperative LDL-C was significantly associated with a poorer OS, whereas high HDL-C was correlated with improved progression-free survival (254). Patients with advanced-stage OV are typically accompanied by the presence of malignant ascites (MAs) and high cholesterol levels in these MAs (255). Moreover, high cholesterol levels promote drug resistance in OV cells by increasing the expression of multidrug resistance protein 1 (256). Dietary cholesterol and tumor risk also deserve attention. According to population-based cohort studies, tumorigenesis is closely related to dietary structure (257), and changes in dietary structure effectively prevent tumorigenesis and progression (258,259). Increased dietary cholesterol intake is positively associated with the risk of BC (260). Dietary cholesterol is a risk factor for the development of ECa, with a 35% increased risk of tumor development for every 150 mg/kcal of cholesterol consumed (261). Esophageal cancer (EC) ranks as the ninth most common cancer worldwide, with genetic factors, dietary factors and environmental risk factors potentially influencing its progression (262). A meta-analysis that investigated the association between high-cholesterol diets and EC revealed that dietary cholesterol intake may increase the risk of EC (summarized odds ratio, 1.424; 95% CI, 1.191-1.704) (263). Pancreatic cancer (PCa) risk is associated with elevated serum cholesterol levels, which are partially influenced by diet (264). A study involving 258 patients with PCa and 551 controls demonstrated that a plant-based cholesterol-lowering diet is associated with a reduced risk of PCa (265). In addition, higher cumulative dietary cholesterol intake is positively associated with the risk of GC (266), HCC (267) and OV (267). The incidence of OV is significantly lower by 40% in individuals consuming a low-cholesterol diet than those on a conventional diet (268).

Table III. Epidemiological evidence of cholesterol-cancer associations.

| HCD or serum TC level | Phenotype/effect | Relationship | Cancer types |
|---|---|---|---|
| HCD | Lung metastasis | Positive | HCC (298) |
| HCD | Cancer risk | Positive | ECa (299) |
| HCD | Associated with a longer overall survival | Positive | BC (300,301) |
| HCD | Cancer risk | Positive | GC (302) |
| HCD | Cancer risk | Unrelated | OV (267,303) |
| HCD | Cancer risk | Positive | PCa (265) |
| HCD | Cancer risk | Unrelated | LC (269) |
| HCD | Cancer risk | Positive | EC (263) |
| High serum TC | Associated with lymph node metastasis | Positive | PNENs (304) |
| Low serum TC | Associated with more advanced tumor grading | Positive | RCC (305) |
| High serum TC | Cancer risk | Unrelated | MM (306) |
| High serum TC | Associated with the diagnosis of high-grade PC | Positive | PC (26) |
| High serum TC | Associated with CRC incidence rate | Positive | CRC (307,308) |
| High serum TC | Associated with longer overall survival | Positive | NSCLC (309) |
| High serum TC | Cancer risk | Unrelated | BC (310) |
| High serum TC | Associated with longer overall survival | Positive | CCA (311) |
| High serum TC | 5-year survival rate reduced | Negative | HGG (312) |
| High serum TC | Cancer risk | Negative | GC (31) |
| High serum TC | Cancer recurrence | Positive | NB (313) |
| High serum TC | Cancer risk | Positive | PCOS (314) |
| High serum TC | Rate of prevalence | Positive | OSCC (315) |
| High serum TC | Total mortality rate | Negative | OS (316) |
| High serum TC | Cancer risk | Unrelated | OV (33) |

HCC, hepatocellular carcinoma; PNENs, pancreatic neuroendocrine neoplasms; RCC, renal cell carcinoma; MM, multiple myeloma; PC, prostate cancer; CRC, colorectal cancer; CCA, cholangiocarcinoma; HGG, high-grade glioma; PCa, pancreatic cancer; GC, gastric cancer; NB, neuroblastoma; PCOS, polycystic ovary syndrome; OSCC, oral squamous cell carcinoma; OS, osteosarcoma; OV, ovarian cancer; EC, esophageal cancer; TC, total cholesterol; HCD, high cholesterol diet; LC, lung cancer; ECa, endometrial cancer; BC, breast cancer; NSCLC, non-small cell lung cancer.

However, studies on dietary cholesterol and lung cancer risk have consistently shown no correlation (115,269,270).

Conversely, other epidemiological studies reported no clear association or even an inverse relationship between cholesterol and cancer. For instance, a large prospective cohort study from South Korea found that the association between serum TC levels and cancer was dependent on the cancer type (251). Further comparison across cancer types revealed that elevated serum TC levels showed a significant positive association with the risk of PC and CRC in men, as well as BC in women. Conversely, there was a significant negative association with the overall risk of HCC and GC in the general population. Moreover, a population-based cohort study has suggested that serum TC levels may be negatively associated with the risk of OV and that circulating lipid levels are not strongly correlated with the risk of OV (271). These studies showed that the positive correlation and negative correlation coexisted, indicating that the association was cancer type specific. Similarly, our latest study showed that higher daily dietary cholesterol intake was significantly positively associated with the risk of OV, whereas abnormal lipid levels were not associated with the risk of OV (33).

These conflicting epidemiological results suggest that the role of cholesterol in cancer development remains uncertain, warranting further investigation into its underlying mechanisms. Key issues include the reliability of dietary study data, the limitations of animal models in simulating human disease states and the potentially opposing effects of serum cholesterol across different tumor stages. The current epidemiological evidence regarding cholesterol and cancer risk is indeed contradictory, stemming from multiple confounding factors and methodological challenges. The primary concern is reverse causality: Actively growing tumors consume large amounts of cholesterol to build membrane structures and synthesize signaling molecules, potentially leading to reduced serum cholesterol levels. Thus, observed low cholesterol levels may result from undetected tumors rather than cause them. This is particularly notable in studies of malignancies such as liver and stomach cancer, potentially completely reversing the apparent 'protective association' (272,273). Cancer type specificity further complicates this relationship as metabolic dependencies vary significantly across tumor types: Hormone-sensitive cancers such as PC and OV may rely more heavily on cholesterol as

a steroid hormone precursor, showing positive correlations; whereas other tumor types may exhibit no clear association or even negative correlations (274,275). Methodological limitations also warrant attention: Dietary cholesterol studies rely on self-reporting, introducing recall bias; single serum cholesterol measurements may fail to reflect long-term exposure levels; and statin use confounds the association between serum cholesterol and cancer risk. Most critically, correlation does not imply causation. Observational studies reveal statistical associations but cannot establish biological mechanisms. These conflicting findings suggest systemic cholesterol levels may be unreliable cancer risk indicators, while targeted interventions affecting intracellular cholesterol metabolism may hold greater therapeutic promise than systemic cholesterol reduction. Recently, we suggested that low levels of cholesterol promote tumor progression, that high cholesterol may inhibit tumor cell growth and that chronically high levels of cholesterol ultimately screen for more proliferative and invasive tumor cells (122). Evidence from these studies suggests that the dysregulation of cholesterol homeostasis is an important factor in cancer development, but its true link to tumor progression remains unclear. Studies are needed to link population epidemiological data, molecular mechanisms and clinical data more broadly to more effectively unravel the processes by which cholesterol affects cancer. The associations of serum cholesterol and dietary cholesterol with the risk of cancer development are summarized in Table III.

## 6. Conclusions and perspectives

The present review describes the role of cholesterol in cancer progression from a multidimensional perspective. First, how cholesterol activates oncogenes and oncogenic signals was discussed. Then, the molecular mechanisms regulated by cholesterol in cancer were summarized. Finally, the ongoing controversies regarding cholesterol levels and cancer risk within epidemiological studies were addressed. Although substantial evidence supports a definitive role for cholesterol metabolism in tumorigenesis and progression, several critical questions remain unresolved. For example, whether the specific roles of cholesterol metabolites or derivatives are consistent, what the causal relationship is between abnormal cholesterol metabolism and tumorigenesis and how cholesterol metabolism influences other metabolic processes such as glucose metabolism. Notably, studies on the heterogeneity of cholesterol metabolism (such single-cell metabolomics) and comparative analyses across cancer types (such as BC vs. liver cancer) are fewer and deserve focused attention. This complexity suggests that not only do we need to modulate from a single cholesterol metabolic pathway but also interfere with the activation of oncogenes or oncogenic signals and that a combination of different drugs or inhibitors may be a more effective antitumor regimen.

In conclusion, dysregulation of cholesterol metabolism is increasingly recognized as a critical facilitator of cancer development. While population-based epidemiological findings have been inconsistent, both basic and clinical studies indicate that targeting cholesterol metabolism can significantly inhibit tumor progression. These insights provide a robust foundation for the development of cholesterol-focused therapeutics and offer promising new strategies for cancer prevention and treatment.

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## Availability of data and materials

Not applicable.

## Authors' contributions

ZH was responsible for conceptualization, writing the original draft and visualization. LZ and SG helped to revise the manuscript and collect literature. GX and XY were responsible for supervision, writing, reviewing and editing. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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