

Review

Cholesterol metabolism in tumor microenvironment: cancer hallmarks and therapeutic opportunities

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Abstract

Cholesterol is crucial for cell survival and growth, and dysregulation of cholesterol homeostasis has been linked to the development of cancer. The tumor microenvironment (TME) facilitates tumor cell survival and growth, and crosstalk between cholesterol metabolism and the TME contributes to tumorigenesis and tumor progression. Targeting cholesterol metabolism has demonstrated significant antitumor effects in preclinical and clinical studies. In this review, we discuss the regulatory mechanisms of cholesterol homeostasis and the impact of its dysregulation on the hallmarks of cancer. We also describe how cholesterol metabolism reprograms the TME across seven specialized microenvironments. Furthermore, we discuss the potential of targeting cholesterol metabolism as a therapeutic strategy for tumors. This approach not only exerts antitumor effects in monotherapy and combination therapy but also mitigates the adverse effects associated with conventional tumor therapy. Finally, we outline the unresolved questions and suggest potential avenues for future investigations on cholesterol metabolism in relation to cancer.

Keywords: antitumor immunity, cholesterol homeostasis, drug repurposing, metastasis, statin, tumor microenvironment

Introduction

The hallmarks of cancer are the acquired capabilities of cells during the transition from normal to neoplastic growth, facilitating the formation of malignant tumors. Six hallmarks of cancer were originally identified [1], but this number has since increased to fourteen. These include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative mortality, inducing or accessing vasculature, activating invasion and metastasis, deregulating cellular metabolism, avoiding immune destruction, genome instability and mutation, tumor-promoting inflammation, unlocking phenotypic plasticity, nonmutational epigenetic reprogramming, polymorphic microbiomes, and senescent cells [2]. The tumor microenvironment (TME) contributes to the acquisition and maintenance of these hallmarks to varying degrees. The TME refers to a micro-ecosystem comprising non-cancerous cells and tumor components that provide nutritional

support and growth-stimulating signals to tumor cells [3]. The evolving understanding of TME has resulted in a shift in the focus of cancer therapy from a tumor-centric approach to a TME-centric approach. However, specialized microenvironments provide more precise targets for tumor treatment than the whole TME. The complex TME was previously divided into six specialized microenvironments [4]. Recently, this classification has been expanded to include seven specialized microenvironments: hypoxic niche, immune microenvironment, metabolism microenvironment, acidic niche, innervated niche, mechanical microenvironment, and microbial microenvironment [2, 5]. These specialized microenvironments interact with each other to form a dynamic tumor ecosystem.

Cholesterol is an essential constituent of the cell membrane and plays a vital role in cell survival and proliferation. In addition, cholesterol serves as a

precursor for bile acids, steroid hormones, and oxysterol, which are crucial for maintaining various physiological processes [6]. Therefore, the maintenance of cholesterol homeostasis is critical for physiological functions. Dysregulation of cholesterol homeostasis not only leads to cardiovascular diseases, but also involved in tumorigenesis and progression of cancer [7]. The involvement of cholesterol in cancer has received increasing attention, with evidence of a dysregulated cholesterol balance in tumors. This imbalance in cholesterol homeostasis affects tumor hallmarks, promoting tumorigenesis, metastasis, and treatment resistance by reprogramming multiple microenvironments.

This review provides an overview of the regulatory mechanisms of cholesterol homeostasis and the effects of dysregulated cholesterol homeostasis on tumor hallmarks and interactions with various microenvironments. Finally, this paper provides a summary and discussion of the recent advances in the use of cholesterol metabolism as a target for cancer treatment.

Brief overview of cholesterol homeostasis

Cholesterol biosynthesis occurs in most mammalian cells, with hepatic cholesterol biosynthesis and dietary cholesterol being the primary sources of human cholesterol (Figure 1) [8]. Generally, cholesterol homeostasis is dynamically maintained through various cellular processes, including biosynthesis, uptake, esterification, efflux, and processing (Figure 2). Cholesterol biosynthesis is accomplished through the mevalonate pathway, which not only provides a metabolic route of cholesterol synthesis, but also provides various metabolites with significant biological functions. The mevalonate pathway involves the conversion of acetyl-CoA, the end product of glycolysis, to 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA), which is further metabolized through a series of enzymatic reactions to produce mevalonate, isopentenyl pyrophosphate (IPP), geranyl pyrophosphate (GPP), farnesyl pyrophosphate (FPP), squalene, lanosterol, and finally cholesterol [6]. Cholesterol homeostasis is regulated by transcription factors, such as sterol regulatory element-binding protein 2 (SREBP2) and liver X receptor (LXR). SREBP2 monitors cholesterol levels in the endoplasmic reticulum (ER) and remains inactive until intracellular cholesterol levels decrease [9]. Low cholesterol levels result in the release of the SREBP cleavage-activating protein (SCAP)-SREBP2 complex from the insulin-induced gene (INSIG) protein in the ER. This complex is then transported to the Golgi apparatus via COPII-coated vesicles, where SREBP2 undergoes

proteolytic cleavage by site-1 (S1P) and site-2 (S2P) proteases [10]. Upon cleavage, the N-terminus of SREBP2 enters the nucleus and activates the transcription of target genes, such as HMG-CoA reductase (HMGCR), low-density lipoprotein (LDL) receptor (LDLR), and Niemann-Pick type C1-like 1 (NPC1L1). This results in elevated cholesterol biosynthesis and uptake [6, 10, 11]. Elevated intracellular cholesterol levels result in an interaction between SCAP and INSIG proteins, preventing SCAP from binding to COPII and retaining the SCAP-SREBP2 complex within the ER, thereby impeding cholesterol biosynthesis. Furthermore, ER retention of the SCAP-SREBP2 complex modulates cholesterol uptake by reducing the expression of LDLR and NPC1L1 [6]. In addition to biosynthesis, diet and subsequent uptake of cholesterol from the circulation play a significant role in maintaining cholesterol homeostasis. Cells typically acquire cholesterol from circulation via LDLR-mediated endocytosis. LDLR binds to LDL in the bloodstream, and the resulting LDL-LDLR complex is transported to lysosomes for degradation. This process releases free cholesterol via Niemann-Pick C1 (NPC1) and C2 (NPC2) proteins [12]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to LDLR and promotes its cellular uptake. Finally, the LDLR-PCSK9 complex undergoes lysosomal degradation [13]. Dietary cholesterol is a major source of cholesterol in humans, and its uptake by enterocytes is mediated by the NPC1L1 protein [14]. Following a series of processes, free cholesterol absorbed by NPC1L1 is esterified and transported as chylomicrons into circulation, ultimately being assimilated by the liver [14, 15]. The human NPC1L1 gene comprises two sterol regulatory elements (SRE), the sterol-sensing structural domain, and is activated by SREBP2. A high-cholesterol diet was found to suppress NPC1L1 expression, suggesting negative feedback regulation between cholesterol content and its absorption pathway [16].

Maintaining cholesterol homeostasis requires ensuring sufficient cholesterol biosynthesis and uptake for cell growth and function, while also preventing the overabundance of intracellular cholesterol through esterification, efflux, and processing. When intracellular cholesterol levels exceed demand, excess cholesterol can be esterified to cholesterol esters (CEs) by acyl-CoA: cholesterol acyltransferase (ACAT) and stored in the cytoplasm as lipid droplets (LDs) [17]. In addition, cholesterol can be further metabolized into bile acids or steroid hormones secreted extracellularly [18, 19]. Cholesterol serves as a vital precursor for oxysterols. Excess cholesterol can be converted into oxysterols, which

are more polar and have distinct physiological functions [20]. Activation of LXR by specific oxysterols increases the expression of cholesterol efflux-related genes, such as ATP-binding cassette (ABC) subfamily A member 1 (ABCA1), ABC subfamily G member 1 (ABCG1), ABCG5, and ABCG8 [21]. Excess cholesterol is exported into circulation via ABCA1 and ABCG1 and transported back to the liver as high-density lipoprotein (HDL) complexes [22, 23]. ABCG5 and ABCG8 are expressed on the apical surface of hepatocytes and enterocytes, where they function as heterodimers to transport excess cholesterol to the bile duct and intestinal lumen [6].

The overview reveals that cholesterol homeostasis involves a complex regulatory network comprising various pathways and components, including cholesterol biosynthesis (HMGCR, SREBP2, SCAP, INSIG, S1P, and S2P), uptake (LDLR, PCSK9, and NPC1L1), esterification (ACAT), efflux (LXR, ABCA1, ABCG1, ABCG5, and ABCG8), and processing (bile acids, steroid hormones, and oxysterols). The complexity and accuracy of this

regulatory network ensure a dynamic balance in intracellular cholesterol levels.

Dysregulated cholesterol homeostasis as a contributor to the hallmarks of cancer

Dysregulation of cholesterol homeostasis is a characteristic feature of cancer cells. Cancer cells require higher cholesterol levels for membrane formation and signal transduction because of their rapid proliferation compared with normal cells [24, 25]. Lipid rafts, which contain cholesterol, are involved in diverse cellular processes [26]. Lipid rafts are abundant in many cancer cells, and their disruption can inhibit cancer cell growth [27]. Moreover, certain cholesterol precursors and derivatives have been found to affect cancer progression [28, 29]. Recent studies have shown that dysregulated cholesterol homeostasis affects tumor development, progression, metastasis, and therapeutic resistance through various regulatory mechanisms (Figure 3 and Table 1) [30-33].

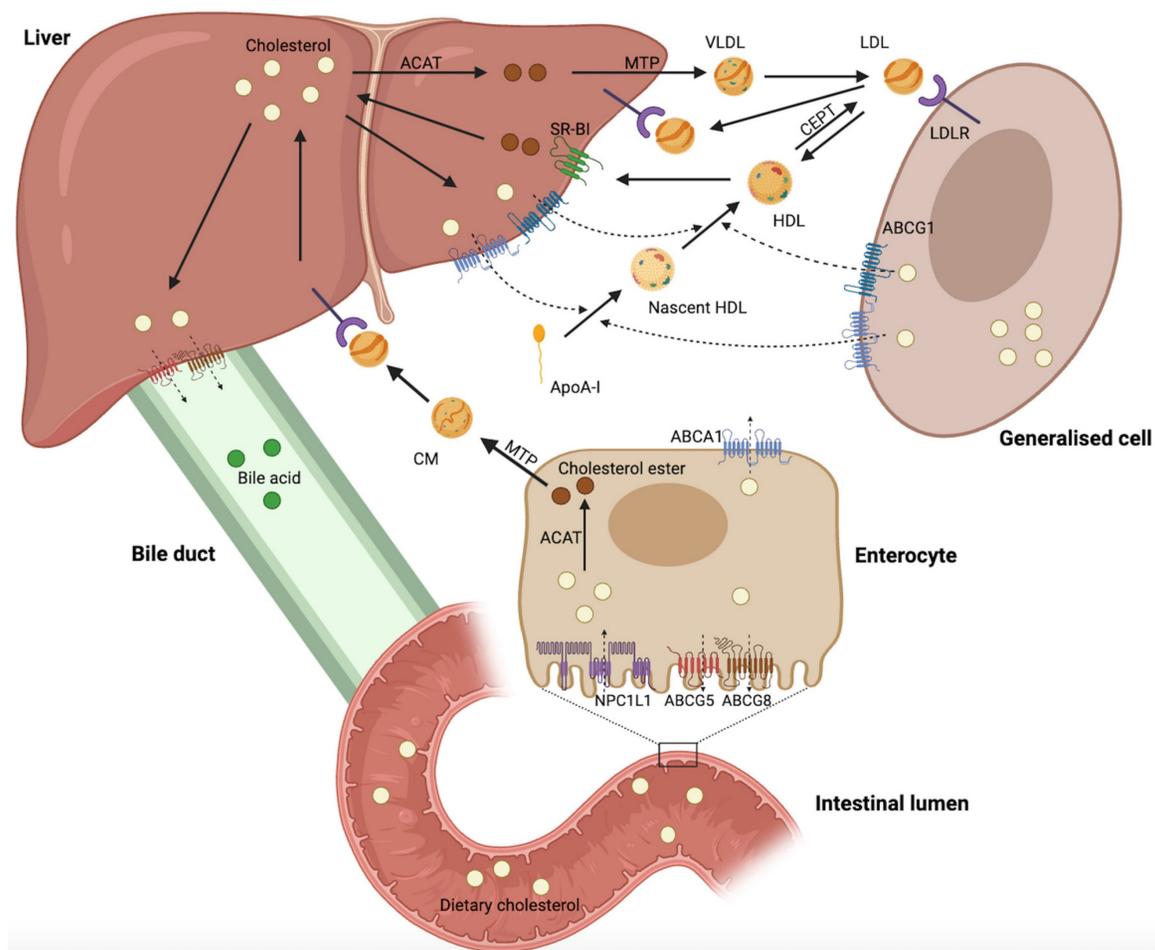


Figure 1. Regulation of mammalian cholesterol homeostasis. Hepatic cholesterol biosynthesis and dietary cholesterol primary sources of cholesterol in humans. Excess cholesterol in the liver is excreted into the bile and eventually into the intestinal lumen for fecal excretion. Cholesterol in the circulation can be excreted directly into the intestinal lumen via enterocytes. This figure was created using BioRender (<https://biorender.com/>).

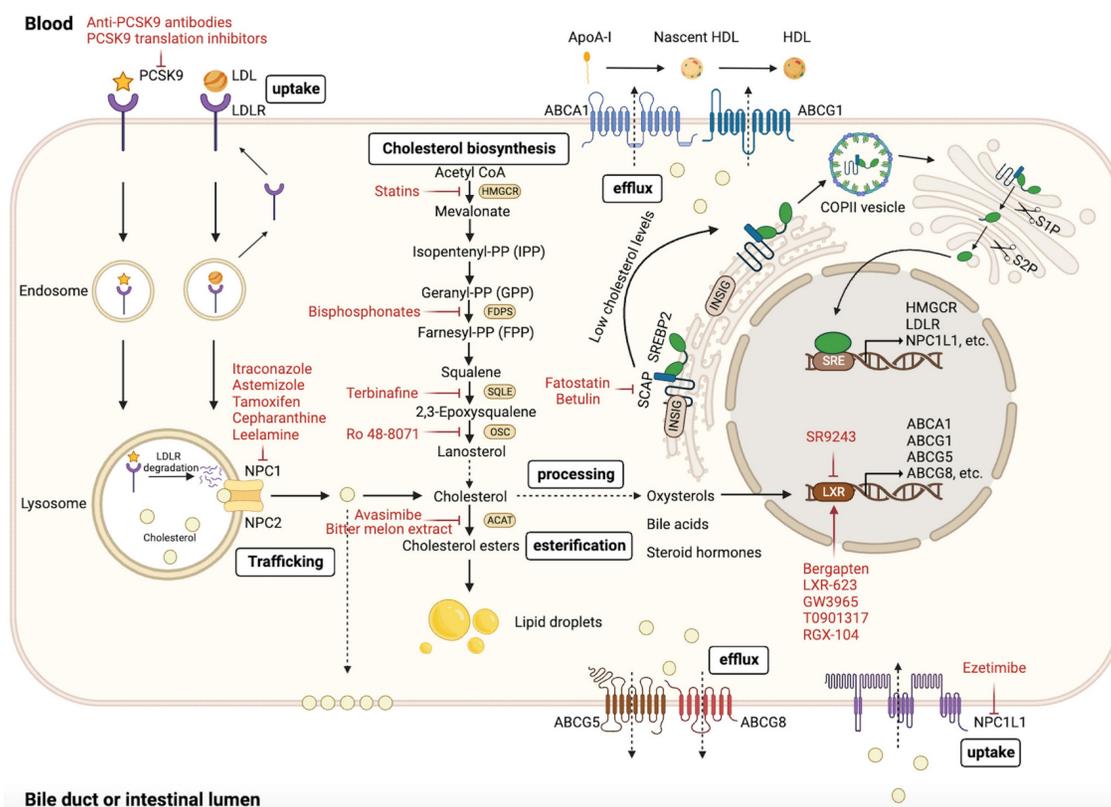


Figure 2. Regulation of cellular cholesterol homeostasis. The maintenance of cholesterol homeostasis is critical for physiological functions. Cellular cholesterol homeostasis is dynamically balanced through various processes, such as biosynthesis, uptake, esterification, efflux, and processing. Intracellular cholesterol levels are precisely regulated by these processes. This figure was created using BioRender (<https://biorender.com/>).

Dysregulation of cholesterol homeostasis in the development and progression of cancer

The association between cholesterol and tumorigenesis has been explored since the last century. Several prospective cohort studies have indicated a positive correlation between high dietary cholesterol intake and elevated plasma cholesterol levels with cancer incidence [34, 35]. Dysregulated cholesterol homeostasis is prevalent in many types of cancer and contributes to the onset and progression of the disease. Recent studies have reported various regulatory mechanisms by which dysregulation of cholesterol homeostasis affects cancer development and progression.

A recent report suggested that cholesterol and saturated fatty acids synergistically promote prostate cancer progression in mice [36]. Wu et al. found that cholesterol activates the PI3K/AKT pathway to promote colorectal cancer (CRC) progression [37]. In addition, PTEN loss and PI3K/AKT activation-induced cholesterol ester accumulation to promote prostate cancer progression [38]. Cancer cells are characterized by their resistance to ferroptosis, a process closely linked to cholesterol biosynthesis. Liu et al. found that dysregulated cholesterol homeostasis contributes to ferroptosis resistance, promoting cancer tumorigenicity [7]. *N*¹-methyladenosine methylation

in tRNA has been shown to drive liver tumorigenesis by inducing cholesterol biosynthesis, which activates Hedgehog signaling [39]. SREBP2, a key transcription factor involved in cholesterol biosynthesis, is frequently upregulated in various cancers. Copy number amplification of gene alpha-endosulfine (ENSA) promotes triple-negative breast cancer (TNBC) progression by increasing SREBP2 expression [32]. Gu et al. found that kinesin-like protein KIF11 promotes the progression of pancreatic ductal adenocarcinoma (PDAC) via SREBP2-dependent activation of mevalonate crosstalk [40]. Furthermore, Wei et al. found that unspliced X-box binding protein 1 (XBP1) colocalizes with SREBP2 and inhibits its degradation, promoting cholesterol biosynthesis and hepatocellular carcinoma (HCC) tumorigenesis [41]. Cellular senescence is associated with suppression of tumorigenesis [42-44], and tumor cells use various strategies to overcome senescence. A recent study found that transcription factor CP2 (TFCP2) interacts with SREBP2 to synergistically activate cholesterol biosynthesis and overcome cellular senescence in pancreatic cancer [45]. Oxysterols, being a derivative of cholesterol, have been extensively studied for their association with cancer due to their beneficial and detrimental effects on the disease [46, 47]. CYP27A1, a cytochrome P450 oxidase, catalyzes the conversion of

cholesterol to 27-hydroxycholesterol (27HC) [48]. CYP27A1 has demonstrated renal cell carcinoma (RCC)-inhibiting effects by increasing 27HC concentrations in the body [49]. Similarly, Liang et al. found that CYP27A1 activates LXRs/ABCA1 by upregulating 27HC, promoting intracellular cholesterol efflux, and eventually inhibiting proliferation and migration in clear cell renal cell carcinoma (ccRCC) [50]. Evidence suggests that 27HC may promote the onset and progression of tumors. Luo et al. found that the histone reader zinc finger MYND-type containing 8 (ZMYND8) activates LXR and promotes breast cancer initiation by inhibiting 27HC catabolism and cholesterol efflux [51]. Avena et al. reported that 27HC promotes the progression of estrogen receptor-negative breast cancer (ER-BC) by binding to G protein-coupled estrogen receptor (GPER) [52]. In addition, 22HC induces cell cycle arrest by activating LXR, thereby inhibiting the progression of prostate, breast, and liver cancers [53]. However, Yoon et al. found that 22HC contributes to the development and progression of cholangiocarcinoma by stimulating COX-2 expression via a p38 MAPK-dependent mechanism [54]. Other oxysterols, such as 24HC and 25HC, have been identified as

significant contributors to the development and progression of cancer [55-58]. PCSK9 promotes LDLR degradation, leading to increased circulating LDL levels. PCSK9 is a key regulator of cholesterol homeostasis and has been implicated in various aspects of cancer biology [59]. PCSK9 overexpression in CRC promotes cholesterol biosynthesis and accumulation of its intermediate geranylgeranyl diphosphate (GGPP) by inhibiting cholesterol uptake, ultimately inducing tumorigenesis [60]. In addition, squalene epoxidase (SQLE), the rate-limiting enzyme of cholesterol biosynthesis, has also been shown to promote the progression of p53-deficient castration-resistant prostate cancer (CRPC) [61], proliferation of p53 wild-type HCC cells, liver tumorigenesis in p53 knockout mice [62], and colorectal carcinogenesis by promoting gut dysbiosis [63]. Interestingly, Zhang et al. also found that dietary cholesterol drives the development of non-alcoholic fatty liver disease in HCC by altering gut microbiota and metabolites [64]. These findings establish a correlation between cholesterol homeostasis, gut microbiota, and tumorigenesis, providing a novel approach to exploring the involvement of cholesterol homeostasis in tumorigenesis.

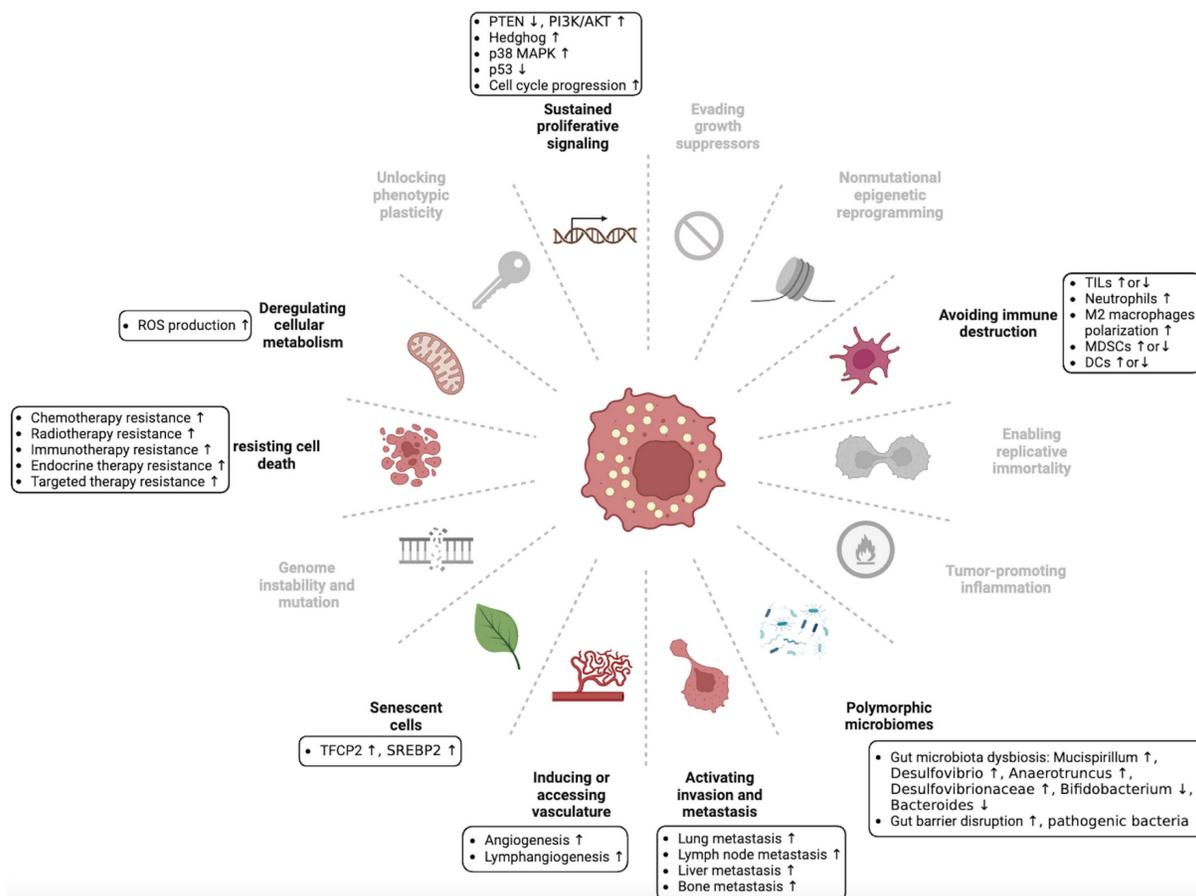


Figure 3. Dysregulation of cholesterol homeostasis and hallmarks of cancer. Hanahan and Weinberg originally proposed the concept of cancer hallmarks, which has since been expanded to encompass fourteen hallmarks. We summarize the association between dysregulated cholesterol homeostasis and some of these cancer hallmarks, although further exploration is necessary to fully understand this relationship. This figure was created using BioRender (<https://biorender.com/>).

Table I. Summary of the dysregulation of cholesterol homeostasis and its functions in different cancer types.

Cancer types	Mechanism	Phenotype/effect	References
Breast cancer	Activation of LXRs by inhibiting 27HC catabolism and cholesterol efflux	Tumorigenesis	[51]
	Copy number amplification of ENSA enhances cholesterol biosynthesis	Tumor progression	[32]
	Dysregulation of cholesterol homeostasis induces the resistance of metastatic cells to ferroptosis	Enhanced metastatic capacity	[7]
	Chemokine regulatory loop induces cholesterol biosynthesis	Enhanced metastatic capacity	[30]
	Enhanced cholesterol biosynthesis pathway	Enhanced metastatic capacity	[69]
	27HC activates LXR	Enhanced metastatic capacity	[77]
	27HC promotes an immunosuppressive microenvironment by interacting with immune cells at distal metastatic sites	Enhanced metastatic capacity	[78]
	SREBP2 regulates osteoclast formation and function	Enhanced metastatic capacity	[84]
	Enhanced cholesterol biosynthesis pathway	Therapeutic resistance	[105]
	Liver cancer	Enhanced cholesterol biosynthesis activates Hedgehog signaling	Tumorigenesis
Unspliced XBP1 enhances cholesterol biosynthesis by stabilizing SREBP2		Tumorigenesis	[41]
Dietary cholesterol induces alterations in gut microbiota and metabolites		Tumorigenesis	[64]
LDLR inhibition enhances cholesterol biosynthesis through the MEK/ERK signaling pathway		Enhanced metastatic capacity	[70]
SCAP regulates autophagy by influencing AMPK signaling		Therapeutic resistance	[110]
Caspase-3-induced SREBP2 activation enhances cholesterol biosynthesis		Therapeutic resistance	[111]
Prostate cancer		PTEN deletion and PI3K/AKT activation induce cholesterol ester accumulation	Tumor progression
	PTEN/p53 deficiency enhances cholesterol biosynthesis by upregulating SQLE expression	Tumor progression	[61]
	SREBP2 induces transcriptional activation of c-Myc	Enhanced metastatic capacity	[83]
	27HC enhances the transcriptional activity of androgen receptors and expression of prostate-specific antigens	Therapeutic resistance	[92]
	HMGCR overexpression	Therapeutic resistance	[107]
	Cholesterol-rich macrophages transfer cholesterol to tumor cells	Therapeutic resistance	[108]
Lung cancer	27HC enhances osteoclast differentiation	Enhanced metastatic capacity	[81]
	Cholesterol induces ABCG2 expression	Therapeutic resistance	[96]
	HOXB13 induces ABCG1 expression	Therapeutic resistance	[97]
	Cholesterol promotes ERRA re-expression through the EGFR/Src/Erk/SP1 signaling pathway	Therapeutic resistance	[31]
	High cholesterol levels in lipid rafts	Therapeutic resistance	[109]
Gastric cancer	PCSK9 promotes the MAPK signaling pathway by upregulating HSP70	Enhanced metastatic capacity	[73]
	25HC upregulates TLR2/NF- κ B-mediated MMP expression	Enhanced metastatic capacity	[76]
	SOAT1 enhances cholesterol biosynthesis by regulating the expression of SREBP1 and SREBP2	Enhanced metastatic capacity	[87]
Pancreatic cancer	KIF11 activates mevalonate crosstalk in a SREBP2-dependent manner	Tumor progression	[40]
	TFCP2 interacts with SREBP2 to synergistically activate cholesterol biosynthesis	Cellular senescence	[45]
Colorectal cancer	Cholesterol accumulation in lipid rafts	Therapeutic resistance	[91]
	Overexpression of PCSK9 promotes cholesterol biosynthesis and accumulation of its intermediate	Tumorigenesis	[60]
	GGPP by inhibiting cholesterol uptake		
	SQLE promotes gut dysbiosis	Tumorigenesis	[63]
Melanoma	Cholesterol activates the PI3K/AKT signaling pathway	Tumor progression	[37]
	Ahnak regulates PCSK9 expression	Enhanced metastatic capacity	[72]
Ovarian cancer	Cholesterol in malignant ascites activates LXRA/ β	Therapeutic resistance	[99]
Cholangiocarcinoma	22HC promotes COX-2 expression via a p38 MAPK-dependent mechanism	Tumorigenesis and tumor progression	[54]
Cervical cancer	Fatty acid synthase regulates cholesterol reprogramming and induces lymphangiogenesis	Enhanced metastatic capacity	[89]
Bladder cancer	Activation of the mevalonate pathway	Therapeutic resistance	[95]

Clinical and preclinical studies have demonstrated a strong link between cholesterol homeostasis and cancer. However, the mechanism by which dysregulated cholesterol homeostasis contributes to the onset and progression of cancer remains to be fully elucidated.

Dysregulation of cholesterol homeostasis in tumor metastasis

Cancer metastasis is a dynamic and multi-step process [65, 66]. The prognosis of patients with metastatic cancer is extremely poor, with over 90% of cancer-related deaths attributable to metastasis [67]. However, the regulatory mechanisms that underlie cancer metastasis remain unclear. The correlation between cholesterol homeostasis and the mechanism of cancer metastasis is currently under investigation.

A clinical study highlighted that pretreatment serum cholesterol levels were higher in patients with metastatic prostate cancer than those with nonmetastatic prostate cancer [68]. Additionally, Liu

et al. found that dysregulated cholesterol homeostasis in breast cancer promotes metastasis by inducing resistance to ferroptosis [7]. Han et al. revealed that regulation of the cholesterol synthesis pathway through a chemokine regulatory loop could promote metastatic growth of lung-colonizing TNBC cells [30]. Kim et al. reported that the cholesterol synthesis pathway increases tumor sphere formation and invasion in breast cancer cell metastasis [69]. Chen et al. found that the inhibition of LDLR expression in liver cancer stimulates intracellular cholesterol biosynthesis via the MEK/ERK signaling pathway, thereby promoting lung metastasis of HCC [70]. Interestingly, PCSK9, an inhibitor of LDLR, inhibits the lung metastasis of HCC [71], but stimulates lung metastasis of melanoma cells [72]. Xu et al. reported that PCSK9 could enhance lung and lymph node metastasis in gastric cancer (GC) by upregulating heat shock protein 70 levels and promoting the MAPK signaling pathways [73]. Sun et al. found that PCSK9 deficiency reduced liver metastasis in melanoma by

decreasing cholesterol levels [74]. Oxysterols have also been implicated in cancer metastasis. Ortiz et al. found that cholesterol 25-hydroxylase (CH25H) produces 25HC, which inhibits the uptake of tumor-derived extracellular vesicles by normal cells and restricts the development of premetastatic niches in melanoma [75]. 25HC promotes lung metastasis of gastric cancer by upregulating TLR2/NF- κ B mediated matrix metalloproteinase (MMP) expression [76]. Additionally, Nelson et al. found that 27HC promotes breast cancer lung metastasis by activating LXR [77]. Baek et al. reported that 27HC promotes the distant metastasis of breast cancer cells to the lungs by interacting with $\gamma\delta$ -T cells and polymorphonuclear neutrophils [78]. Recently, Deng et al. reported that anoctamin 1 (ANO1) interacts with JUN to suppress CYP27A1-LXR signaling, leading to intracellular cholesterol accumulation and TME reprogramming, thus enhancing esophageal squamous cell carcinoma metastasis [79]. Late-stage lung cancer is associated with a higher incidence of osteolytic bone metastases [80]. Zhang et al. found that 27HC promotes the colonization of lung adenocarcinoma cells in the bone by stimulating osteoclast differentiation and creating a favorable microenvironment for tumor growth [81]. In addition, elevated cholesterol levels have been observed in bone metastases from prostate cancer [82]. SREBP2 facilitates distant metastasis of prostate cancer to the bone, adrenal gland, and lungs by transcriptionally activating c-Myc [83] and promotes bone metastasis in breast cancer by regulating osteoclast formation and function [84]. When intracellular cholesterol levels are high, sterol O-acyltransferase 1 (SOAT1), also known as ACAT1, converts excess cholesterol to cholesteryl ester (CE) [9]. SOAT1 is overexpressed in cancer and associated with poor patient prognosis [47, 85, 86]. Studies have shown that SOAT1 promotes lymph node metastasis in GC by regulating the expression of SREBP1 and SREBP2 [87], and its inhibition significantly suppresses lymph node and liver metastasis of pancreatic cancer [88]. Furthermore, Du et al. revealed that fatty acid synthase promotes cervical cancer lymph node metastasis by regulating cholesterol reprogramming and inducing lymphangiogenesis in cervical cancer [89].

Therefore, dysregulation of cholesterol homeostasis can contribute to cancer metastasis through multiple mechanisms. Consequently, there has been extensive research on potential drugs that target cholesterol metabolism for cancer therapy. Statins, a well-studied class of repurposed drugs that target cholesterol biosynthesis, have emerged as promising anticancer agents because of their ability to inhibit cancer metastasis via multiple mechanisms

[90]. However, further investigation is required to understand the mechanism by which dysregulated cholesterol homeostasis promotes cancer metastasis, and to develop effective anticancer drugs targeting cholesterol metabolism.

Dysregulation of cholesterol homeostasis promotes cancer therapeutic resistance

Advancements in cancer research have led to significant progress in the exploration and implementation of various anticancer strategies. However, therapeutic resistance often results in treatment failure in most cancer patients. Studies have shown that dysregulated cholesterol homeostasis contributes significantly to resistance against cancer therapeutic strategies, including chemotherapy, radiotherapy, immunotherapy, endocrine therapy, and targeted therapy through multiple mechanisms.

Chemotherapy is a common treatment for cancer, and the dysregulation of cholesterol homeostasis has been linked to chemotherapy resistance in various studies. In pancreatic ductal adenocarcinoma, Yu et al. found that overexpression of cellular retinoic acid-binding protein II (CRABP-II) induces cholesterol accumulation in lipid rafts by upregulating the downstream SREBP-1c and eventually promoting resistance to gemcitabine [91]. Similarly, 27HC promotes the proliferation of prostate cancer cells and induces resistance to docetaxel via an androgen receptor (AR)-dependent mechanism [92]. Furthermore, Wang et al. demonstrated that 25HC promotes 5-fluorouracil (5-FU) resistance in human GC cells [76]. Autophagy plays an important role in cell growth and development and has a biphasic effect on cancer progression, with studies demonstrating its ability to both suppress and promote tumors at different stages [93]. Lipid raft deficiency has been linked to doxorubicin resistance in breast cancer by promoting autophagy [94], whereas activation of the mevalonate pathway has been associated with doxorubicin resistance in bladder cancer cells [95]. Cholesterol and HOXB13 have been found to induce resistance to platinum-based chemotherapy in lung adenocarcinoma by upregulating ABCG2 and ABCG1 expression, respectively [96, 97]. The SREBP2 pathway [98] and malignant ascites cholesterol have been found to contribute to cisplatin resistance in ovarian cancer cells. Malignant ascites cholesterol activates LXR α/β , which increases the resistance of ovarian cancer cells to cisplatin and paclitaxel [99]. Research indicates that inhibition of PCSK9 can protect prostate cancer cells from radiation-induced cell damage, suggesting that PCSK9 may be a promising therapeutic target for enhancing radiosensitivity in prostate cancer [100]. Programmed

death ligand 1 (PD-L1) is a therapeutic target in cancer immunotherapy, and PD-L1 inhibitors have been successfully used to treat cancer by restoring T-cell tumor-killing activity [101, 102]. However, tumor cell resistance to PD-L1 inhibitors is a significant concern. Studies have shown that statin treatment significantly lowers the expression of PD-L1, suggesting that cholesterol is closely related to PD-L1 [103]. Recently, Wang et al. found that the transmembrane domain of PD-L1 contains two cholesterol-recognition amino acid consensus (CRAC) motifs that can be recognized and bound by cholesterol, resulting in increased stability of PD-L1 in cancer cells and immune evasion [104]. Furthermore, although endocrine therapy has been proven beneficial for numerous patients, the emergence of resistance to endocrine therapy has become a growing concern in recent years. Research indicates that 25HC may induce resistance to estrogen deprivation in estrogen receptor-positive (ER+) breast cancer by mimicking hormones [105]. Recently, Palma et al. reported that cholesterol depletion sensitizes breast cancer cells to tamoxifen [106]. HMGCR is a crucial enzyme in cholesterol biosynthesis. Kong et al. found that HMGCR overexpression promoted resistance of CRPC to enzalutamide, and statins were effective in overcoming this resistance [107]. Furthermore, El-Kenawi et al. found that cholesterol-rich macrophages induce resistance to endocrine therapy in CRPC by transferring cholesterol to cancer cells [108].

Targeted therapy is a type of precision medicine that provides optimism for cancer treatment. The continuous emergence of targeted drugs has significantly improved the prognosis of cancer patients. However, drug resistance presents a significant challenge for cancer treatment. Therefore, exploring the resistance mechanisms of targeted drugs can offer insight into improving their therapeutic efficacy. Cholesterol induces resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in non-small cell lung cancer (NSCLC) via the EGFR/Src/Erk/SP1 signaling pathway [31], while elevated levels in lipid rafts induce gefitinib resistance [109]. SCAP and caspase-3 promote HCC resistance to sorafenib via AMPK-mediated autophagy [110] and SREBP2-induced sonic hedgehog signaling [111], respectively. Interestingly, statins can overcome sorafenib resistance in HCC [111] and delay GC resistance to Trastuzumab [112].

Cancer therapeutic resistance is a major concern that requires further investigation. Studies have demonstrated a correlation between cholesterol homeostasis and therapeutic resistance, with ongoing research aimed at understanding the underlying mechanisms of cholesterol-induced therapeutic

resistance. Fortunately, cholesterol biosynthesis-targeting drugs have shown significant efficacy in overcoming therapeutic resistance. In the future, the combination of cholesterol metabolism-targeting drugs with conventional anticancer drugs may serve as a promising novel cancer therapeutic strategy.

Cholesterol metabolism and the TME

Constant interaction between tumor cells and their microenvironment is a crucial factor in the development, progression, metastasis, and therapeutic outcomes of cancer. Cholesterol metabolism appears to contribute significantly to this interaction, tumor cells in the TME can adapt to the complex microenvironment by reprogramming cholesterol metabolism. Therefore, exploring the mechanisms of cholesterol metabolism in seven specialized microenvironments can provide insights into the crosstalk between tumor cells and the complex TME. This section summarizes the diverse effects of cholesterol metabolism on hypoxic niche, immune microenvironment, metabolism microenvironment, acidic niche, innervated niche, mechanical microenvironment, and microbial microenvironment (Figure 4).

Cholesterol metabolism and immune microenvironment

During all stages of tumor progression, there is a constant interplay between tumor cells and tumor-infiltrating immune cells (TIICs) in the tumor immune microenvironment (TIME). These TIICs comprise immune effector and immunosuppressive cells, including T lymphocytes, B lymphocytes, natural killer (NK) cells, neutrophils, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and dendritic cells (DCs), which perform diverse antitumor or protumor functions in the TME [113, 114]. Evidence suggests that cholesterol metabolism influences antitumor immunity by acting on various TIICs [115].

Tumor-infiltrating lymphocytes (TILs) recognize and kill tumor cells, and cytotoxic T lymphocytes (CTLs) play a central role in antitumor immunity. Cholesterol metabolic reprogramming occurs in the TME during the functional maturation and activation of TILs. Cholesterol is required for T cell proliferation and activation. SREBP-mediated upregulation of cholesterol biosynthesis plays an important role in the activation and proliferation of CD8⁺ T cells [116]. Research has demonstrated that inhibiting ACAT1 activity upregulates plasma membrane cholesterol levels in CD8⁺ T cells, which results in enhanced T cell receptor clustering and signal transduction, as well as more efficient immunological synapse formation and

antitumor response [117]. Wang et al. recently found that SOAT1-targeting compounds reprogrammed cholesterol metabolism in tumor cells and enhanced the antitumor response of CD8⁺ T cells against liver cancer [118]. Additionally, trogocytosis has been identified as an important process in immune regulation and other biological processes [119]. Trogocytosis refers to the extraction and transfer of biomolecules between adjacent cells, resulting in changes in both donor and acceptor cell functions [119, 120]. Trogocytosis between tumor cells and CTLs promotes the loss of antigens on target cells and destruction of CTLs, enabling tumor cells to evade the immune system [121]. Recent studies have shown that CH25H can enhance antitumor immunity by

inhibiting trogocytosis and stimulating CTL activity [122]. Furthermore, another study found that CH25H promotes major histocompatibility complex class I (MHC-I) presentation and increases CD8⁺ T cell infiltration into tumors, sensitizing PDAC cells to immune checkpoint inhibitors [123]. In contrast, 27HC promotes the development of the breast cancer premetastatic niche by attracting polymorphonuclear neutrophils and $\gamma\delta$ -T cells at metastatic sites while depleting CD8⁺ T cells [78]. Recently, Yan et al. found that 27HC induces cholesterol deficiency in T cells by inhibiting SREBP2 and activating LXR, subsequently leading to autophagy-mediated apoptosis of T cells [124].

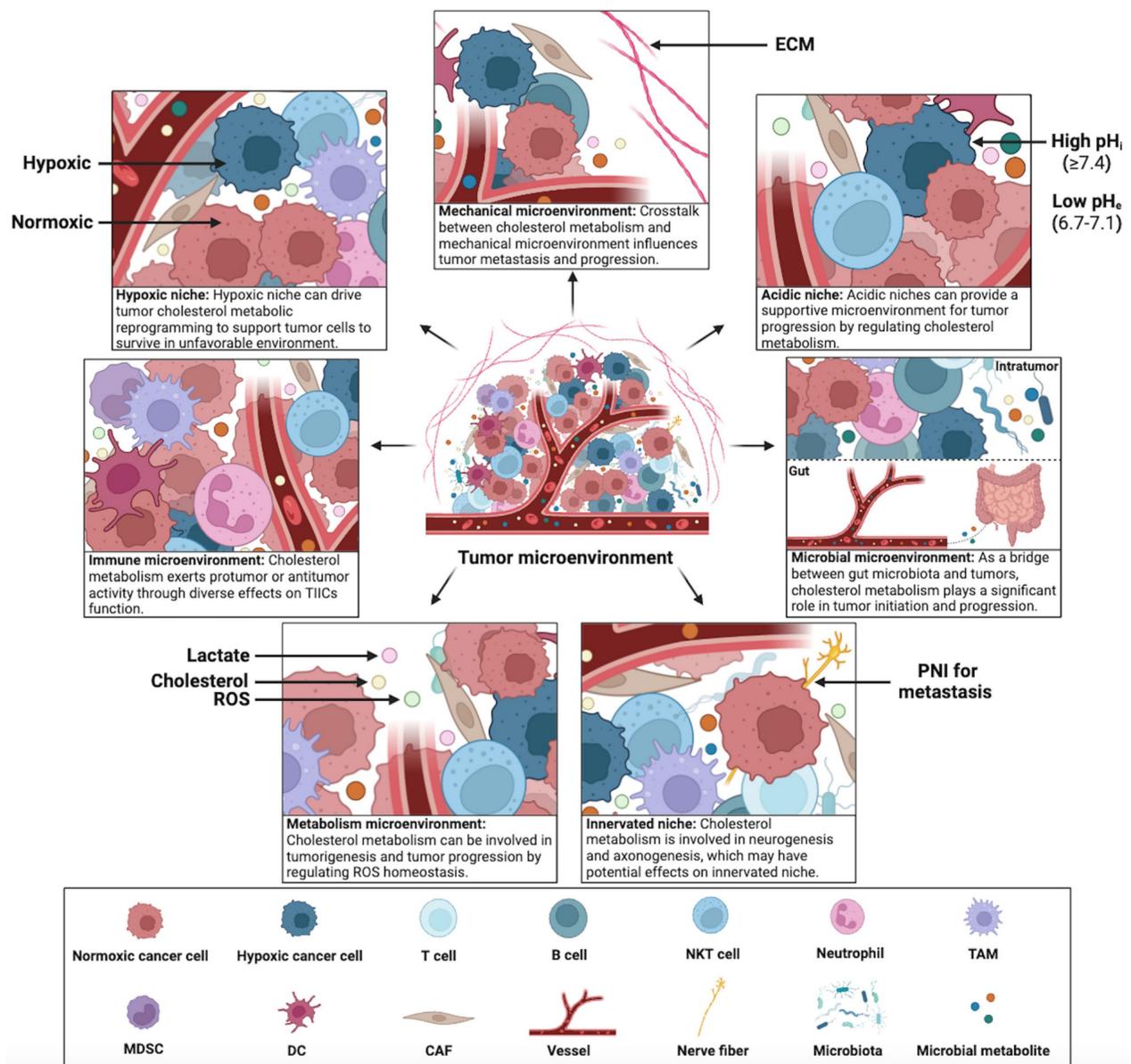


Figure 4. Crosstalk between cholesterol metabolism and the TME. The TME has been categorized into seven specialized microenvironments: hypoxic niche, immune microenvironment, metabolism microenvironment, acidic niche, innervated niche, mechanical microenvironment, and microbial microenvironment (including intratumoral and gut microbiota). Crosstalk between cholesterol metabolism and specialized microenvironments plays a significant role in tumorigenesis and tumor progression. This figure was created using BioRender (<https://biorender.com/>).

Interestingly, increasing cholesterol levels of chimeric antigen receptor (CAR)-T cells by blocking LXR can enhance antitumor activity, suggesting that improving CAR-T therapy by regulating cholesterol metabolism is a promising antitumor strategy [124]. Cytotoxic NK cells, which are crucial for antitumor immunity, are also affected by cholesterol metabolism. Qin et al. found that upregulating LDLR expression in NK cells improved their ability to combat HCC by elevating intracellular cholesterol levels, suggesting that increasing cholesterol uptake in NK cells could be a promising therapeutic strategy for HCC [125]. Yuan et al. found that the antitumor activity of CD8⁺ T cells is enhanced by LDLR via regulation of T-cell receptor (TCR) cycling and signaling through its interaction with the TCR complex [126] and inhibited by PCSK9 via inhibition of the recycling of LDLR and TCR to the CD8⁺ T cell plasma membrane [126]. Furthermore, Liu et al. revealed that PCSK9 binds to MHC-I in lysosomes and triggers its degradation, thereby preventing CTL infiltration and inhibiting antitumor immunity [127]. These findings suggest that PCSK9 inhibition could be a promising strategy for enhancing the immune response against tumors. However, the effect of cholesterol on T cell function is controversial, and high cholesterol levels in the TME have been linked to CD8⁺ T cell exhaustion by triggering immune checkpoint activation and ER stress [128]. Therefore, reducing cholesterol levels in the TME can effectively restore the antitumor activity of CD8⁺ T cells [128]. CD8⁺ T cell subset interleukin-9 (IL-9)-secreting (Tc9) cells have stronger antitumor activity than Tc1 cells, and IL-9 is indispensable for the antitumor activity of Tc9 cells. Cholesterol suppresses IL-9 expression by activating LXRs, thereby inhibiting the antitumor activity of Tc9 cells [129]. Recent studies have shown that colorectal cancer with microsatellite stability (MSS CRC) cells polarize T cells toward Th17 cells by secreting distal cholesterol precursors, thus promoting tumor progression [130]. SREBP2-mediated hepatic cholesterol accumulation suppresses natural killer T (NKT) cell cytotoxicity and antitumor immunosurveillance in liver cancer [131]. Wang et al. found that reducing serum cholesterol levels inhibited the mammalian target of rapamycin complex 2 (mTORC2) signaling in T lymphocytes and increased CD8⁺ T cell infiltration in prostate cancer [132]. These findings suggest that intrinsic and extrinsic cholesterol may exert differential effects on the function of TILs. Increasing intrinsic cholesterol biosynthesis and uptake of TILs may enhance their antitumor activity, whereas excessive extrinsic cholesterol in the TME may inhibit it. Moreover, B cells play a crucial role in the regulation of immune

responses to tumors. Recent research indicates that SREBP signaling is crucial for B cell maturation, suggesting the significance of cholesterol metabolism in B cell regulation [133]. Bibby et al. found that cholesterol metabolism promotes the production of IL-10 from regulatory B cells via GGPP, thus restraining the immune response [134].

In addition to TILs, other TIICs have also been shown to be regulated by cholesterol metabolism. In the TIME, neutrophils typically exhibit protumor activity, and cholesterol derivatives, oxysterols, have been reported to exert protumor activity by regulating neutrophils. Raccosta et al. found that tumor-derived 22HC can recruit neutrophils via CXC chemokine receptor 2 (CXCR2) and promote tumor growth by stimulating angiogenesis and immunosuppression [135]. Soncini et al. found that hypoxia-inducible factor-1 α (HIF-1 α) can enhance neoangiogenesis in pancreatic neuroendocrine tumors by attracting neutrophils via 24HC upregulation [55]. Furthermore, 27HC has been reported to promote breast cancer metastasis through the recruitment of polymorphonuclear neutrophils at metastatic sites [78]. Tumor-infiltrating myeloid cells, including TAMs, MDSCs, and DCs, are also important components of the TIME. Cholesterol metabolic reprogramming can shift these myeloid cells towards an antitumor or a protumor phenotype. TAMs exhibit distinct antitumor M1-like and protumor M2-like phenotypes. Studies have suggested that tumors can alter cholesterol metabolism to promote the protumor function of TAMs. For instance, ovarian cancer cells secrete hyaluronic acid to promote cholesterol efflux from TAM membranes and induce a protumor M2-like phenotype [136]. Moreover, glioblastoma multiforme (GBM)-derived 25HC can activate the recruitment of macrophages to tumors through the G-protein-coupled receptor 183 (GPR183) [137]. MDSCs, as immature myeloid cells, typically exhibit immunosuppressive properties in TIME. Recently, Yang et al. reported that the UPR component XBP1 stimulates cholesterol biosynthesis and secretion in tumor cells, activating MDSCs to exhibit immunosuppressive properties [138]. In contrast, Tavazoie et al. found that LXR β reduces the infiltration of protumor MDSCs into tumors, thus enhancing antitumor immunity [139]. However, Xie et al. recently found that chronic activation of LXR α can have an immunosuppressive effect by increasing the infiltration of MDSCs into tumors [140]. Therefore, future studies must elucidate the contradictory functions of LXRs in the immune response to cancer. The maturation of antigen-presenting DCs is essential for the activation and maintenance of the antitumor activity of TILs. Zhang et al. found that

cholesterol-modified antimicrobial peptide DP7 induces DCs maturation and enhances antigen presentation by transporting various antigen peptides into DCs [141]. Xia et al. found that inhibiting geranylgeranylation of Rab5 in DCs resulted in cell surface antigen retention, enhanced antigen presentation, and CD8⁺ T cell activation [142]. Villablanca et al. found that oxysterol in the TME inhibits CC chemokine receptor-7 (CCR7) expression on the surface of mature DCs by activating LXR α , thereby inhibiting DC migration to lymphoid organs and reducing antitumor immunity [143]. In contrast, another study showed that LXR inverse agonists facilitate DC migration to the lymph nodes and boost antitumor immunity [144]. These findings suggest that the inhibition of LXR expression may be a promising immunotherapeutic approach for tumors.

In summary, cholesterol metabolism is critical for regulating the crosstalk between tumor cells and TIME. Cholesterol metabolism affects TIICs in the TIME through multiple mechanisms, resulting in either protumor or antitumor effects on the function of TIICs. Therefore, a deeper understanding of the regulation of cholesterol metabolism in the interaction between tumor cells and TIME will facilitate the development of novel immunotherapeutic strategies for cancer treatment. Targeting cholesterol metabolism in TIME has the potential as an effective antitumor approach by augmenting immunity against tumors.

Cholesterol metabolism and metabolism microenvironment

Metabolic reprogramming is a fundamental characteristic of cancer cells. Aerobic glycolysis (Warburg effect) is an early indication of metabolic reprogramming in cancer, that is, cancer cells prefer glycolysis to oxidative phosphorylation even under normoxic conditions [145]. Aerobic glycolysis allows cancer cells to compete with surrounding normal cells for glucose uptake, thereby sustaining their growth [146]. Lactate, produced through aerobic glycolysis, has significant effects on TME and tumor-associated cells [147]. Aerobic glycolysis can mitigate excessive accumulation of reactive oxygen species (ROS) by avoiding oxidative phosphorylation [148]. ROS plays a dual role in tumorigenesis by promoting tumor onset and progression via activation of various redox reactions and signaling pathways while also causing tumor cell damage and eventual death through oxidative stress [149]. Tumor cells exhibit higher levels of ROS than normal cells, and continuous oxidative stress causes them to tolerate slight accumulation of ROS (known as ROS addiction) [149]. Increasing evidence suggests that ROS addiction

contributes to tumorigenesis and tumor progression. Cholesterol metabolism might play a role in this process by regulating ROS homeostasis.

Cholesterol accumulation in the tumor cell mitochondria triggers a cascade of chain reactions, leading to ROS production [150]. Interestingly, in ovarian cancer, increased mitochondrial ROS generation and activation of the AKT/mTOR signaling pathway upregulate SREBP2 expression, thereby promoting cholesterol biosynthesis [151]. Furthermore, increased cholesterol uptake protects against ROS-induced damage in ccRCC [152]. Shapira et al. found that cholesterol depletion decreased autophagic flux in an ROS- and JNK-dependent manner [153]. Wang et al. found that cholesterol promotes CRC progression by activating ROS and MAPK signaling pathway [154]. Liu et al. demonstrated that SQLE contributes to HCC tumorigenesis by silencing PTEN via ROS-induced DNA methyltransferase 3A (DNMT3A) expression [155]. In addition, the interaction between 27HC and ROS has been linked to both drug resistance and tumor progression. 27HC activates glucose-regulated protein 75 (GRP75) via elevated oxidative stress signaling in HCC, which regulates redox homeostasis by regulating ROS production and the antioxidant defense system, thereby inducing multidrug resistance [156]. Furthermore, evidence suggests that ROS contributes to 27HC-induced breast cancer cell invasion and angiogenesis by regulating reversion-inducing-cysteine-rich protein with Kazal motifs (RECK)/STAT-3 signaling via DNA methylation [157] and STAT-3/VEGF signaling [158], respectively.

Cholesterol metabolism and hypoxic niche

Tumors exhibit high adaptability, which enables them to thrive under adverse conditions. Intratumoral hypoxia is induced by rapid tumor growth and inadequate angiogenesis. Hypoxia-inducible factors (HIFs) are significant regulators of hypoxic response [159]. Hypoxia activates vascular endothelial cells, stimulates tumor angiogenesis, and promotes tumor growth and metastasis [160, 161]. More importantly, the hypoxic response triggers the “angiogenic switch” and promotes metabolic reprogramming in tumors [66, 162]. Evidence suggests that tumors can adapt to these hypoxic environments by reprogramming cholesterol metabolism to enhance tumor stemness and angiogenesis, which promotes their survival and growth. HIF-1 α facilitates SREBP maturation in the hypoxic niche by upregulating the Ephrin-A3/EphA2 axis expression, thus enhancing cancer stemness in HCC [163]. Hypoxia activates HIF-1 by inducing protein kinase B (PKB) phosphorylation, thereby upregulating SREBP expression in breast cancer cells

[164]. In addition, HIF-1 α upregulates 24HC to attract neutrophils to hypoxic areas and induce the occurrence of “angiogenic switch” in pancreatic neuroendocrine tumor [55].

In summary, the hypoxic niche drives cholesterol metabolic reprogramming in tumors and interacts with other specialized microenvironments, promoting the survival of tumor cells under unfavorable conditions.

Cholesterol metabolism and acidic niche

Cancer is characterized by dysregulated or reversed pH, with a higher intracellular pH ($\text{pH}_i \geq 7.4$) and a lower extracellular pH ($\text{pH}_e = 6.7-7.1$) [165]. Higher pH_i facilitates cancer cell proliferation, migration, metabolic adaptation, and anti-apoptosis, whereas lower pH_e facilitates cancer cell invasion and metastasis [165]. The acidic niche is closely linked to the hypoxic niche and metabolism microenvironment because the acidic niche is primarily caused by lactate secretion and CO_2 production from anaerobic glycolysis and the pentose phosphate pathway, respectively [166]. Evidence suggests that an acidic niche provides a supportive microenvironment for tumor progression by regulating cholesterol metabolism.

Acidic extracellular environments can promote cholesterol biosynthesis in tumor cells by activating SREBP2, thereby promoting tumor growth [167]. Importantly, acidic pH-regulated SREBP2 target genes are inversely correlated with the overall survival of cancer patients [167]. Fukamachi et al. found that reducing GGPP synthesis can inhibit the proliferation of synovial sarcoma cells in acidic environments [168]. Additionally, John et al. found that activation of the IRE1-sXBP1-SREBP2-ACSS2 response axis at low pH_e promotes cholesterol biosynthesis and cell membrane surface trafficking in astrocytic tumors, thereby enhancing cell membrane surface mechanical tenacity, preventing acid-mediated cell membrane hydrolysis, and supporting tumor cell survival [169]. In addition, Corbet et al. found that acidosis-induced TGF- β 2 activation facilitated LD accumulation, enhancing the distant metastatic potential of cancer cells [170].

Cholesterol metabolism and mechanical microenvironment

The mechanical microenvironment, which is comprised of intracellular components (neurofilaments, vimentin, and actin), extracellular components (fibrin and collagen), stromal cells (fibroblasts), and intercellular signaling (integrin and focal adhesion) has been shown to affect intracellular signal transduction and, consequently, the biological

behavior of tumor cells [171, 172]. Cholesterol metabolism appears to play a significant role in the mechanical microenvironment.

Cancer-associated fibroblasts (CAFs) are primary stromal cells in the mechanical microenvironment of tumors and can contribute to metastasis by secreting MMPs or activating yes-associated protein (YAP), leading to extracellular matrix (ECM) remodeling and epithelial-mesenchymal transition (EMT) [173-175]. Han et al. observed that TNBC-derived C-X-C motif chemokines 1/2/8 (CXCL1/2/8) stimulate CAFs and other lung-resident fibroblasts to secrete C-C motif chemokines 2/7 (CCL2/7), thereby activating cholesterol synthesis in TNBC cells to support metastatic tumor growth [30]. Moreover, 25HC was found to promote lung metastasis of GC by upregulating MMP expression [76]. Enhanced mevalonate pathway signaling by mutant p53 promotes the activity of YAP and PDZ-binding motif (TAZ) proto-oncogenes [176], whereas the oncogenic activity of YAP is dependent on ZMYND8-mediated cholesterol biosynthesis [177]. Cholesterol is essential for receptor signaling (e.g., integrin) by maintaining the stability of lipid rafts. Ramprasad et al. reported that depletion of cholesterol in the plasma membrane decreases α 5 β 1 integrin-mediated adhesion and motility of lung adenocarcinoma cells to fibronectin [178]. In addition, Hoque et al. found that LDL-cholesterol promotes the motility and spread of tumor cells by participating in integrin trafficking, focal adhesion assembly, and ECM secretion [179]. Recently, transcription factor EB (TFEB) was shown to facilitate integrin-mediated endothelial cell adhesion to the ECM by upregulating cholesterol synthesis-associated genes in response to integrin signaling [180]. Maja et al. found that cholesterol-enriched cell surface domains are involved in ECM degradation, which promotes breast cancer cell invasion [181]. In addition, Shen et al. found that 27HC increases MMP9 expression and EMT through STAT-3 activation, thus promoting breast cancer migration and invasion [182]. This effect has also been validated by Avena et al. and Torres et al., who demonstrated that 27HC promotes EMT and migration of breast cancer cells [52, 183]. High cholesterol-mediated upregulation of adipocyte plasma membrane-associated protein (APMAP) in cholesterol-induced lipid rafts inhibits EGFR degradation, thereby activating the extracellular-regulated protein kinase 1/2 (ERK1/2) pathway and inducing EMT in prostate cancer cells [184]. Therefore, crosstalk between cholesterol metabolism and the mechanical microenvironment influences tumor metastasis and progression.

Cholesterol metabolism and microbial microenvironment

The microbial microenvironment is an emerging specialized microenvironment that delineates a landscape composed of intratumor microbiota, intestinal microbiota, and their metabolites [5, 185]. Intestinal microbiota plays an indispensable role in cholesterol metabolism. In this section, we discuss the interplay between cholesterol metabolism and the microbiota in the initiation and progression of tumors.

Zhang et al. found that dietary cholesterol contributes to non-alcoholic fatty liver disease (NAFLD)-associated HCC formation by inducing gut microbial dysbiosis [64], which could be effectively prevented by statin treatment [64]. This suggests a potential association between changes in the gut microbiota and tumorigenesis. Additionally, Li et al. proposed that SQLE promotes CRC carcinogenesis by modulating the gut microbiota-metabolite axis [63]. Cholesterol is converted to primary bile acids in the liver and subsequently processed into secondary bile acids by the gut microbiota [186]. Accumulating evidence suggests that secondary bile acids can promote tumorigenesis [187-190]. Yamada et al. found that the accumulation of secondary bile acids produced by the gut microbiota can activate mTOR signaling pathways in hepatocytes, thus promoting HCC carcinogenesis [191]. Primary bile acids have a positive effect on antitumor immunity by increasing CXCL16 expression in liver sinusoidal endothelial cells, consequently promoting the accumulation of CXCR6⁺ hepatic NKT cells [192]. In contrast, gut microbiome-mediated secondary bile acids suppress antitumor immunity by inhibiting the accumulation of hepatic NKT cells [192]. This suggests that cholesterol metabolism plays a significant role in the microbial microenvironment-TIME crosstalk.

In summary, cholesterol metabolism serves as a bridge between the intestinal microbiota and tumors and plays a significant role in the initiation and progression of tumors by regulating intestinal homeostasis and the immune system.

Cholesterol metabolism and innervated niche

With increasing awareness of the interaction between neurology and cancer science, Monje et al. have proposed a new field of study, "cancer neuroscience," to explore bidirectional interactions between the nervous system and cancer [193]. We propose that the crosstalk between nerves and cancer is mediated by acellular components such as nerve-derived neurotransmitters or neuropeptides, resulting in a specialized microenvironment called "innervated niche" [4]. Some previous studies have

also used the terms "perineural niche," "neural regulation in TME," or "neural microenvironment" [194-196].

Currently, there is a lack of evidence to support the effect of cholesterol metabolism on innervated niches despite the significant role of cholesterol in the nervous system [197]. Cholesterol is a vital structural component of neuronal plasma membranes and is necessary for maintaining fluidity and proper functioning of neurons [198]. Myelin is the continuous extension of the neuronal plasma membranes, with a higher lipid content, including 25-30% cholesterol [199]. Cholesterol is also involved in synapse and dendrite formation [200], and axon elongation [201]. In addition, cholesterol is responsible for the bilayer curvature required for synaptic vesicle fusion and fission, which is the basis of neurotransmission [202]. Cholesterol plays a crucial role in the production and maintenance of many neurotransmitter receptors [203-205] and can specifically interact with these receptors, suggesting another mechanism for regulating neurotransmission [203, 206]. Neurogenesis and axonogenesis may be considered as novel hallmarks of cancer associated with cancer progression [207, 208], making them potential targets for tumor therapy. Notably, several studies have demonstrated a strong correlation between cholesterol metabolism and neurogenesis [209-212]. Furthermore, Petro et al. found that sequestering cholesterol-induced membrane raft disruption promotes axonogenesis in murine neuroblastoma cells [213].

In summary, cholesterol is abundant in neurons and contributes to the regulation of vital membrane-associated functions of the nervous system. Additionally, cholesterol metabolism is implicated in neurogenesis and axonogenesis, suggesting its potential effects on the innervated niche. However, currently there is no direct evidence to elucidate the correlation between cholesterol metabolism and the innervated niche. Further research is required to address this gap in the field.

Targeting cholesterol metabolism as a promising antitumor strategy

Ample evidence suggests that cholesterol metabolism is critical for tumor progression. Several preclinical and clinical studies have demonstrated that certain drugs can target cholesterol metabolism and exhibit antitumor effects. Ongoing research continues to explore new drugs that can target cholesterol metabolism in the treatment of cancer (Figure 1 and Table 2).

Table 2. Summary of antitumor drugs that target cholesterol metabolism.

	Target	Drugs	Stage of clinical development	Mechanism	Cancer types	References		
Targeting cholesterol biosynthesis	HMGR	Statins	Clinical trial	Atorvastatin inhibits breast cancer proliferation by influencing the expression of cyclin D1 and p27	Breast cancer	[222]		
	SREBP	Fatostatin	Clinical trial	Fluvastatin promotes tumor cell apoptosis	Prostate cancer	[223]		
			Preclinical study	Blocking SREBP-regulated metabolic pathways and androgen receptor signaling networks	Prostate cancer	[233]		
			Preclinical study	Induces tumor cell apoptosis	Endometrial cancer	[234]		
	FDPS	Betulin	Preclinical study	Induces tumor cell apoptosis	Breast cancer	[342]		
		Bisphosphonates	Preclinical study	Suppress tumor angiogenesis through the HIF-1 α /VEGF signaling pathway	Breast cancer	[343]		
SQLE	Terbinafine	Preclinical study	Inhibits cancer cell proliferation and angiogenesis	Oral cancer	[248]			
OSC	Ro 48-8071	Preclinical study	Suppresses tumor angiogenesis and metastasis	Colorectal cancer, pancreatic cancer	[249]			
Targeting cholesterol uptake and efflux	LXR	Bergapten (LXR agonist)	Preclinical study	Inhibits HCC carcinogenesis and progression by regulating the LXR/PI3K/Akt and LXR/IDOL/LDLR pathways and reducing LDLR expression in a dose-dependent manner	Liver cancer	[254]		
		LXR-623 (LXR agonist)	Preclinical study	Promotes LDLR degradation and induces ABCA1 expression	Glioblastoma	[252]		
			Preclinical study	Upregulates ABCA1 expression and downregulates LDLR expression	Kidney cancer	[259]		
		GW3965 (LXR agonist)	Preclinical study	Promotes LDLR degradation and induces ABCA1 expression	Glioblastoma	[255]		
		T0901317 (LXR agonist)	Preclinical study	GW3965 induces ApoE expression	Melanoma	[256]		
		RGX-104 (LXR agonist)	Preclinical study	Upregulates ABCG1 expression	Prostate cancer	[257]		
		SR9243 (LXR inverse agonist)	Preclinical study	Induces MDSCs depletion and increases CTLs activation by upregulating ApoE expression	Multiple cancer types	[139]		
			Preclinical study	Induces tumor cell apoptosis by inhibiting the Warburg effect and lipogenesis	Multiple cancer types	[258]		
		NPC1L1	Ezetimibe	Preclinical study	Inhibits intracellular lipogenesis	Kidney cancer	[259]	
				Preclinical study	Suppresses tumor angiogenesis	Prostate cancer	[268]	
Targeting intracellular cholesterol trafficking	NPC1	Itraconazole	Preclinical study	Enhances antitumor immunity in a CD8 ⁺ T cell-dependent manner by inhibiting mTORC2 signaling	Multiple cancer types	[132]		
			Preclinical study	Blocks dietary cholesterol absorption	Liver cancer	[270]		
			Preclinical study	Suppresses tumor angiogenesis	Liver cancer	[269]		
			Preclinical study	Inhibits angiogenesis and tumor growth	Lung cancer	[275]		
		Astemizole	Preclinical study	Inhibits tumor cell proliferation	Cervical cancer	[344]		
			Preclinical study	Inhibits tumor angiogenesis by blocking intracellular cholesterol trafficking	Breast cancer	[279]		
		Cepharanthine	Preclinical study	Inhibits tumor angiogenesis	Multiple cancer types	[280]		
			Preclinical study	Inhibits the signaling cascades that drive tumor cell survival by blocking intracellular cholesterol trafficking	Melanoma	[281]		
		Targeting cholesterol esterification	ACAT1	Avasimibe	Preclinical study	Inhibits tumor cell proliferation	Liver cancer	[86]
					Preclinical study	Promotes tumor cell apoptosis by inhibiting cholesterol esterification	Pancreatic cancer	[88]
Preclinical study	Induces tumor cell apoptosis				Glioblastoma	[283]		
Preclinical study	Impairs the Wnt/ β -catenin pathway				Prostate cancer	[284]		
Preclinical study	Enhances antitumor immunity mediated by CD8 ⁺ T cells				Melanoma	[117]		
Preclinical study	Enhances antitumor immunity by increasing CD8 ⁺ T cell tumor infiltration				Lung cancer	[286]		
Preclinical study	Enhances chimeric antigen receptor-modified T cell-mediated antitumor immunity				Leukemia	[287]		
Preclinical study	Inhibits tumor cell growth				Breast cancer	[285]		
Combination therapy	Chemotherapy + HMGR	Bitter melon extract	Preclinical study	Inhibits tumor cell growth	Breast cancer	[285]		
		Doxorubicin + simvastatin	Preclinical study	Synergistically promote cancer cell apoptosis	Breast cancer	[288]		
		Anthracycline + statins	Observational clinical cohort study	Associated with a lower incidence of heart failure	Breast cancer	[332]		
		Irinotecan + simvastatin	Preclinical study	Simvastatin enhances irinotecan-induced growth inhibition and apoptosis of cancer cells	Prostate cancer	[289]		
		Gemcitabine + pitavastatin	Preclinical study	Synergistically suppress tumor growth	Pancreatic cancer	[291]		
Dacarbazine +	Preclinical study	Synergistically promote autophagy and	Melanoma	[293]				

Target	Drugs	Stage of clinical development	Mechanism	Cancer types	References
	pitavastatin		apoptosis in tumor cells		
	Cisplatin + lovastatin	Preclinical study	Lovastatin sensitizes cancer cells to cisplatin	Gallbladder cancer	[294]
	Cisplatin + atorvastatin	Clinical trial	Atorvastatin significantly reduces the incidence of cisplatin-induced hearing loss without reducing the efficacy of cisplatin	Head and neck cancer	[326]
	5-FU + pravastatin	Clinical trial	Prolongs the survival of patients with advanced HCC	Liver cancer	[221]
	5-FU + atorvastatin	Preclinical study	Atorvastatin effectively prevents leukopenia secondary to experimental 5-FU chemotherapy	Not reported	[320]
Radiotherapy + HMGR	Radiotherapy + atorvastatin	Preclinical study	Atorvastatin enhances the radiosensitivity of prostate cancer cells by inhibiting hypoxia-induced HIF-1 α protein expression	Prostate cancer	[290]
SREBP + HMGR	Dipyridamole + statins (Atorvastatin, simvastatin, and rosuvastatin)	Preclinical study	Dipyridamole enhances the antitumor activity of statins and prevents their resistance	Breast cancer	[226]
	Dipyridamole + fluvastatin	Preclinical study	Dipyridamole enhances apoptosis in statin-insensitive tumor cells	Prostate cancer	[229]
Targeted therapy + HMGR	Erlotinib + pitavastatin	Preclinical study	Synergistically enhances cytotoxicity and overcome erlotinib resistance	Lung cancer	[292]
	Gefitinib + simvastatin	Clinical trial	Increases PFS in patients	Lung cancer	[307]
	Trastuzumab+ statins (Atorvastatin, simvastatin, rosuvastatin, and pravastatin)	Randomized Controlled Trial	Statins effectively reduce trastuzumab-induced cardiotoxicity	Breast cancer	[331]
Immunotherapy + HMGR	PD-1 inhibitors+ statins (Atorvastatin, simvastatin, rosuvastatin, and others)	Clinical trial	High-intensity statins can enhance the clinical activity of PD-1 inhibitors	Lung cancer	[308]
FDPS + HMGR	Zoledronic acid + statins (Atorvastatin, simvastatin, and rosuvastatin)	Preclinical study	Synergistically exert antitumor effects	Breast cancer	[295]
Chemotherapy + FDPS	Paclitaxel + Zoledronic acid	Preclinical study	Synergistically promote tumor cell apoptosis	Breast cancer	[296]
	Epirubicin + docetaxel + bisphosphonates	Clinical trial	Significantly enhances the clearance of disseminated tumor cells in patients with locally advanced breast cancer compared with chemotherapy alone	Breast cancer	[313]
Targeted therapy + LXR	Afatinib + GW3965	Preclinical study	Synergistically inhibit tumor progression	Prostate cancer	[297]
	Gefitinib + GW3965	Preclinical study	GW3965 enhances the sensitivity of NSCLC cells to gefitinib by inhibiting activation of the Akt-NF- κ B signaling pathway	Lung cancer	[298]
	Gefitinib + GW3965	Preclinical study	GW3965 reverses gefitinib resistance in NSCLC by inhibiting vimentin expression	Lung cancer	[299]
	Gefitinib + T0901317	Preclinical study	Suppresses the migration and invasion of tumor cells by inhibiting the ERK/MAPK signaling	Lung cancer	[300]
Immunotherapy + PCSK9	PD-1 inhibitors + PCSK9 antibodies	Preclinical study	PCSK9 antibodies synergistically inhibit tumor growth with PD-1 inhibitors by promoting the intratumoral infiltration of cytotoxic T cells	Multiple cancer types	[127]
Chemotherapy + NPC1	5-FU + itraconazole	Preclinical study	Synergistically inhibit tumor cell growth	Gastric cancer	[302]
	Pemetrexed + itraconazole	Clinical trial	Improved OS in patients with advanced lung cancer compared with pemetrexed alone	Lung cancer	[319]
	5-FU + cepharanthine	Preclinical study	Synergistically inhibit the growth of colorectal cancer cells containing p53 mutations	Colorectal cancer	[303]
Chemotherapy + ACAT1	Gemcitabine + avasimibe	Preclinical study	Synergistically exert antitumor effects	Pancreatic cancer	[304]
Chemoimmunotherapy + ACAT1	Paclitaxel + immunoadjuvant α GC + avasimibe	Preclinical study	Avasimibe enhances the antitumor activity of chemo-immunotherapy by relieving CD8 ⁺ T cell suppression	Melanoma	[305]
Anticancer vaccines + ACAT1	CSCs-DC vaccine + avasimibe	Preclinical study	Synergistically inhibit tumor cell growth	Head and neck cancer	[306]

Targeting cholesterol biosynthesis

Evidence suggests that dysregulation of the mevalonate pathway drives oncogenic lesions, and targeting the mevalonate pathway to block cholesterol biosynthesis is a feasible antitumor strategy [214, 215]. Statins (HMGR inhibitors) have been extensively studied as repurposed drugs for their antitumor activity. Interestingly, lipophilic statins exhibit higher antitumor activity than hydrophilic statins, indicating

their potential superiority in antitumor therapy [216-218]. Many epidemiological and clinical studies have shown that statins can reduce the incidence and mortality of tumors [219, 220]. We previously summarized that statins can exert antitumor properties in vivo and in vitro through multiple mechanisms [90], and have emerged as promising antitumor agents in various clinical trials [221-223]. A randomized controlled trial has shown that

fluvastatin suppresses proliferation and increases apoptosis in high grade breast cancer [224]. Interestingly, in addition to having direct effects on tumor cells, statins have also been demonstrated to enhance antitumor immunity. Recent studies have shown that simvastatin suppresses lncRNA SNHG29-mediated YAP activation and inhibits PD-L1 expression in CRC [225]. Furthermore, statins may maximize efficacy and overcome the shortcomings of conventional cancer therapy [90]. However, statin-induced inhibition of the mevalonate pathway drives SREBP activation and the mevalonate pathway-related gene transcription, thereby restoring the mevalonate pathway activity [226, 227]. This mechanism may contribute to resistance to statins, potentially accounting for the lack of response to statin therapy in certain patients with cancer [226, 227]. Therefore, targeting SREBP is a viable strategy to improve the anticancer effects of statins and overcome drug resistance. Combining statin therapy with SREBP targeting can optimize the antitumor activity. Dipyrindamole, which inhibits SREBP cleavage, has been found to enhance the antitumor effects of statins and prevent their resistance by blocking the restorative feedback response of the mevalonate pathway [226, 228-232]. Fatostatin and betulina, which are SCAP inhibitors that specifically target SREBP activation, have also been shown to exhibit high antitumor activity [233-238]. Furthermore, inhibiting PCSK9 can also inhibit the expression of SREBP. Studies have shown that PCSK9 inhibitors (anti-PCSK9 antibodies and PCSK9 translation inhibitors) combined with simvastatin exert a synergistic antitumor effect in APC/KRAS-mutant CRC [60]. Further well-designed clinical trials are required to evaluate the efficacy of combining statins and SREBP inhibitors in cancer therapy.

Other enzymes in the cholesterol biosynthesis pathway may serve as viable targets for pharmacological intervention. Bisphosphonates are inhibitors of the cholesterol biosynthesis pathway that target farnesyl diphosphate synthase (FDPS) to block the production of FPP [239]. Preclinical and clinical studies have reported the direct antitumor effects of bisphosphonates [240-243]. Furthermore, alendronate, a bisphosphonate used to treat osteoporosis, has been reported to suppress glioblastoma spheres maintenance and activate necrosis-related pathways by inhibiting FDPS [244]. SQLE is an oncogene that is frequently overexpressed in various tumors [245]. Accumulating evidence indicates that SQLE promotes tumor progression through multiple mechanisms; therefore it is a promising antitumor target [63, 155, 246]. Terbinafine, a US Food and Drug Administration (FDA)-approved antifungal drug, has

also been investigated for its potential as an antitumor drug by targeting SQLE in multiple studies [62, 155, 247, 248]. In addition, Ro 48-8071 can suppress cancer cell proliferation and metastasis by targeting oxidosqualene cyclase (OSC) and preventing the conversion of 2,3-oxidosqualene to lanosterol [249].

Targeting cholesterol uptake and efflux

LXR is a key transcriptional regulator that maintains cholesterol homeostasis by regulating the function of target genes involved in cholesterol uptake and efflux [250]. Several studies have evaluated the potential of targeting cholesterol uptake and efflux as an antitumor strategy, yielding promising outcomes.

Tumor cells upregulate LDLR expression to acquire extrinsic cholesterol and reduce energy consumption during cholesterol biosynthesis [251-253]. Bergapten, an LXR agonist, impedes the onset and progression of HCC by regulating the LXR/PI3K/Akt and LXR/IDOL/LDLR pathways and decreasing LDLR expression in a dose-dependent manner [254]. Additionally, other LXR agonists, such as LXR-623 and GW3965, induce tumor cell death in GBM via LDLR degradation and ABCA1 cholesterol efflux transporter upregulation [252, 255]. Furthermore, GW3965 inhibits melanoma invasion, angiogenesis, and metastasis by inducing apolipoprotein-E (ApoE) expression transcriptionally [256]. The LXR agonist T0901317 has shown promise in prostate cancer treatment by inducing apoptosis through ABCG1 expression-mediated cholesterol efflux and subsequent lipid raft disruption [257]. In addition to the effects on cancer cells, LXR agonists exert regulatory effects on immune cells. RGX-104, an LXR agonist, has been reported to enhance antitumor immunity by inducing depletion of MDSCs and upregulating ApoE expression, leading to increased activation of CTLs [139]. This finding was validated in a phase I clinical trial [139]. Interestingly, in addition to LXR activation, LXR repression also affects tumor progression. SR9243, an LXR inverse agonist, induces tumor cell apoptosis by inhibiting the Warburg effect and lipogenesis without causing toxic effects on non-malignant cells [258]. Furthermore, in ccRCC, Wu et al. found that both LXR agonist LXR-623 and LXR inverse agonist SR9243 could inhibit tumor cell growth [259]. Mechanistically, LXR-623 and SR9243 induce tumor cell apoptosis through distinct mechanisms. LXR-623 reduces intracellular cholesterol levels by upregulating ABCA1 expression and downregulating LDLR expression, whereas SR9243 inhibits intracellular lipogenesis [259]. These findings suggest that both LXR activation and repression can influence tumor progression.

PCSK9 regulates cholesterol homeostasis by facilitating LDLR degradation. Recent studies have demonstrated a close association between PCSK9 expression and tumor progression. Clinical evidence suggests that higher PCSK9 expression levels in tumors are negatively correlated with clinical prognosis [260-262], although contradictory findings have been reported [263]. PCSK9 has been found to promote tumor progression through multiple mechanisms [59, 72, 73], while also exerting antitumor effects [71, 263]. Recently, PCSK9 inhibitors (anti-PCSK9 antibodies and PCSK9 translation inhibitors) have been reported to suppress the growth of APC/KRAS-mutant CRC and exert synergistic antitumor effects with simvastatin [60]. Liu et al. reported that PCSK9 inhibition showed promising synergistic antitumor effects in combination with immune checkpoint therapy for tumors [127]. Consequently, PCSK9-targeting agents, such as anti-PCSK9 antibodies, vaccines, antisense RNAi, and some drugs (acRoots, lupin peptides, and pseurotin A) have been developed to target the regulation of PCSK9 for potential cancer treatment strategies. [264, 265]. Preclinical and clinical investigations are required to evaluate the efficacy and safety of PCSK9 inhibition as a potential tumor therapy. NPC1L1, a cholesterol uptake mediator on the apical surface of enterocytes, facilitates dietary cholesterol absorption [6] and has been linked to colitis-associated tumorigenesis [266]. The FDA-approved drug ezetimibe, which inhibits intestinal cholesterol absorption, has demonstrated significant antitumor effects by targeting NPC1L1. Multi-omics analysis revealed that NPC1L1 is an effective therapeutic target for the treatment of PDAC, and ezetimibe inhibits tumor growth without affecting the cytotoxicity of gemcitabine [267]. Furthermore, Ezetimibe inhibits tumor angiogenesis in prostate cancer [268], suppresses HCC progression [269], blocks dietary cholesterol absorption in nonalcoholic steatohepatitis (NASH)-driven HCC [270], and enhances antitumor immunity by inhibiting mTORC2 signaling in a CD8⁺ T cell-dependent manner [132]. Therefore, targeting intestinal cholesterol absorption is another promising strategy for treating tumors.

Targeting intracellular cholesterol trafficking

Cholesterol homeostasis depends on intracellular cholesterol trafficking. Studies have shown that inhibition of lysosomal cholesterol release can exert significant antitumor effects. Certain azoles, such as itraconazole, function as intracellular inhibitors of cholesterol trafficking and induce lysosomal cholesterol accumulation by targeting NPC1 and blocking its function [271-274]. Thus, itraconazole

suppresses tumor growth and angiogenesis by downregulating mTORC1 signaling [273-276]. Importantly, the antitumor properties of itraconazole have been further validated in clinical trials [271, 272, 277]. Furthermore, astemizole has also been reported to exert antitumor activity by blocking intracellular cholesterol trafficking [278].

In addition to itraconazole and astemizole, other repurposed drugs have demonstrated antineoplastic effects by targeting intracellular cholesterol trafficking, such as selective estrogen receptor (ER) modulators (SERMs), cepharanthine, and leelamine. Tamoxifen, an estrogen receptor modulator, inhibits tumor angiogenesis by blocking intracellular cholesterol trafficking [279]. Additionally, cepharanthine, an anti-inflammatory drug, targets NPC1 to inhibit angiogenesis and tumor growth [280]. Furthermore, leelamine, a lipophilic diterpene amine, inhibits the tumor cell survival signaling cascade by blocking intracellular cholesterol trafficking [281]. More well-designed clinical trials are required to validate the efficacy of these repurposed drugs in cancer treatment.

Targeting cholesterol esterification

Tumor cells typically exhibit elevated CE levels, suggesting a correlation between cholesterol esterification and tumor progression [282]. Evidence suggests that targeting cholesterol esterification is a viable approach for tumor therapy. Avasimibe, a well-studied inhibitor of cholesterol esterification, has been found to effectively suppress tumor cell proliferation by targeting ACAT1 (SOAT1) to inhibit CE production. ACAT1 overexpression in HCC is associated with a poor prognosis [86]. Avasimibe has been reported to effectively suppress pancreatic cancer cell proliferation and metastasis by inhibiting cholesterol esterification [88]. Bemlih et al. found that avasimibe targets ACAT1 to inhibit tumor cell growth and induce apoptosis in glioblastoma [283], as well as depleting CEs in prostate cancer and impairing the Wnt/ β -catenin pathway, which inhibits metastasis [284]. Bitter melon extract has been reported to inhibit tumor cell growth in TNBC by downregulating ACAT1 expression [285].

In addition to having direct effects on tumor cells, cholesterol esterification inhibition has also been demonstrated to exert antitumor activity by affecting immune cells. Yang et al. found that avasimibe improves CD8⁺ T cell receptor clustering and immune synapse formation in melanoma by targeting ACAT1, which increases CD8⁺ T cell plasma membrane cholesterol levels, thereby enhancing CD8⁺ T cell-mediated antitumor immunity [117]. Avasimibe has also been reported to increase CD8⁺ T cell

infiltration in lung cancer [286] and CAR-T cell-mediated antitumor immunity by inhibiting cholesterol esterification [287]. Therefore, targeting cholesterol esterification can directly inhibit tumor cells and enhance antitumor immunity, suggesting that targeting cholesterol esterification may be a promising avenue for developing novel therapeutic approaches against cancer.

Combination therapy

Previously, we provided a summary of the evidence supporting the effectiveness of targeting cholesterol metabolism as monotherapy for tumors. However, in the context of precision medicine, the investigation of drug combination strategies is a crucial area of research. Accumulating evidence suggests that combining a cholesterol metabolism-targeting strategy with other antitumor therapies improves the effectiveness of tumor therapy. This review article explores the potential of such combination strategies targeting cholesterol metabolism for tumor therapy and highlights the advantages of such strategies in alleviating the adverse effects associated with conventional tumor therapy.

Targeting cholesterol metabolism in preclinical studies has demonstrated significant advantages in combination therapies and potential synergies with conventional tumor therapy. Statins, which target cholesterol biosynthesis, have been reported to act synergistically with conventional tumor therapy. For instance, simvastatin has been shown to enhance doxorubicin-induced apoptosis in breast cancer cells [288] and irinotecan-induced growth inhibition and apoptosis in prostate cancer cells [289]. Furthermore, atorvastatin increases the radiosensitivity of prostate cancer cells by inhibiting hypoxia-induced HIF-1 α protein expression [290]. Chen et al. reported that pitavastatin and gemcitabine synergistically inhibited pancreatic cancer cell proliferation by inducing cell cycle arrest, leading to the effective inhibition of tumor growth in nude mouse xenograft models [291]. Pitavastatin has been found to increase cytotoxicity and overcome erlotinib resistance in non-small cell lung cancer (NSCLC) when used in combination with erlotinib [292], as well as enhance melanoma cell autophagy and apoptosis when combined with dacarbazine [293]. Additionally, Zhang et al. found that lovastatin sensitized gallbladder cancer cells to cisplatin and significantly prolonged the survival of subcutaneous xenograft mice [294]. However, statins inhibit the mevalonate pathway, leading to the activation of SREBP and affecting the expression of mevalonate pathway-related genes. This feedback response is a contributing factor to statin resistance [227]. Dipyrindamole effectively targets SREBP to

prevent statin resistance and enhance statin-mediated antitumor activity [226, 228-232]. Bisphosphonates (FDPS inhibitors) have also been demonstrated to enhance antitumor effects in combination with statins [295]. Jagdev et al. found that the combined use of bisphosphonates and paclitaxel induces apoptosis in breast cancer cells [296]. In addition, targeting cholesterol uptake and efflux has shown synergistic effects with conventional antitumor drugs. Chen et al. found that a combination of the LXR agonist GW3965 and EGFR inhibitor afatinib effectively suppressed prostate cancer progression [297]. Further research has revealed that GW3965 can increase the sensitivity of NSCLC cells to gefitinib, primarily by inhibiting activation of the Akt-nuclear factor (NF)- κ B signaling pathway [298]. Additionally, Hu et al. observed that GW3965 could reverse gefitinib resistance in NSCLC by inhibiting vimentin expression [299]. Furthermore, the combination of T0901317, an LXR agonist, and gefitinib reduced the migration and invasion of lung cancer cells by inhibiting ERK/MAPK signaling [300]. PCSK9 antibodies have been reported to synergistically inhibit tumor growth with programmed cell death protein 1 (PD-1) inhibitors by promoting intratumoral infiltration of cytotoxic T cells, suggesting that PCSK9 inhibition is a feasible strategy for enhancing immune checkpoint therapy [127]. In addition, inhibiting drug efflux is also a feasible antitumor strategy. Nelfinavir exhibits synergistic antitumor effects with ezetimibe in multiple myeloma by inhibiting drug efflux transporter ABC subfamily B member 1 (ABCB1) [301]. Combining itraconazole, a cholesterol trafficking inhibitor, with 5-FU has shown a synergistic effect in inhibiting the growth of gastric cancer cells [302]. Cepharanthine, another cholesterol trafficking inhibitor, has been reported to act synergistically with 5-FU to suppress p53 mutated colorectal cancer cell growth [303]. In addition, targeting cholesterol esterification in combination with conventional tumor therapy is a promising strategy. Avasimibe, an ACAT1 inhibitor, exhibits synergistic antitumor effects when used together with gemcitabine in pancreatic cancer [304], enhances the efficacy of chemo-immunotherapy by relieving CD8⁺ T cell suppression [305], and potentially improves anticancer vaccine responses. Avasimibe has been reported to synergize with the KRAS vaccine to enhance antitumor immunity [286]. In particular, its combination with a cancer stem cell (CSC)-DC vaccine synergistically inhibited head and neck cancer growth in nude mouse xenograft models [306].

Clinical studies have demonstrated the potential of targeting cholesterol metabolism as adjuvant tumor therapy. In a randomized phase II study, combining simvastatin with gefitinib resulted in increased

progression-free survival (PFS) in patients with gefitinib-resistant NSCLC [307]. Furthermore, Cantini et al. found that high-intensity statins combined with PD-1 inhibitors improved the prognosis of patients with malignant pleural mesothelioma and advanced NSCLC [308]. A randomized controlled trial revealed that pravastatin combined with 5-FU prolonged the survival of patients with advanced HCC, suggesting its potential as an adjuvant therapy for tumors [221]. Another randomized controlled trial revealed that atorvastatin is associated with decreased adrenal androgens in the serum and possibly in the prostate, suggesting that atorvastatin may improve the efficacy of androgen deprivation therapy [309]. In a randomized, double-blind, placebo-controlled trial, simvastatin improved sensitivity to fluorouracil, adriamycin, and cyclophosphamide therapy in HER2 overexpression locally advanced breast cancer patients [310]. Additionally, a cohort study demonstrated that administering statins to lung cancer patients undergoing EGFR-TKI treatment is linked to increased survival rates and has a synergistic effect on antitumor activity [311]. Bisphosphonates have shown potential in combination strategies. Epidemiological data indicate that combining bisphosphonates with statins significantly improves survival in patients with cancer [312]. A phase 2 clinical trial revealed that combining bisphosphonates with neoadjuvant chemotherapy eliminates disseminated tumor cells more effectively than chemotherapy alone in patients with locally advanced breast cancer [313]. Furthermore, the combination of bisphosphonate and chemotherapy significantly reduces the residual invasive tumor size in patients with breast cancer undergoing surgery [314]. Additionally, adjuvant bisphosphonates can improve disease-free survival (DFS) in postmenopausal patients with early-stage breast cancer [315]. Targeting intracellular cholesterol trafficking in combination with conventional tumor therapy is a promising strategy. Itraconazole combined with conventional tumor therapy has been found to significantly improve the clinical prognosis of cancer patients [316, 317]. A retrospective study has shown that the administration of itraconazole in combination with chemotherapy prolongs PFS and overall survival (OS) in patients with refractory ovarian cancer compared to chemotherapy alone [318]. In a phase 2 clinical study, itraconazole combined with pemetrexed improved OS in patients with advanced lung cancer compared with pemetrexed alone [319]. Therefore, numerous preclinical and clinical studies suggest that cholesterol metabolism-targeting in combination with other standard treatment modalities is a promising

antitumor strategy. These evidences may provide a reference for the inclusion of targeting cholesterol metabolism in future tumor therapies.

Importantly, targeting cholesterol metabolism improves the efficacy and mitigates the adverse effects of conventional tumor therapy. Leukopenia is a significant adverse effect of chemotherapy. Atorvastatin was found to be effective in preventing 5-FU chemotherapy-induced leukopenia in an experimental model [320]. Cisplatin is widely used in the treatment of various malignant tumors. Despite its therapeutic advantages, this drug has a high level of ototoxicity, causing permanent hearing loss in over 50% of the treated patients [321-325]. A combined retrospective and prospective observational study reported that atorvastatin significantly reduced the incidence of cisplatin-induced hearing loss, while maintaining the efficacy of cisplatin [326]. Anthracyclines and trastuzumab are frequently used for breast cancer treatment. However, cardiotoxicity associated with these drugs increases the risk of heart failure [327, 328]. Based on the findings of multiple clinical studies, statins are considered promising candidates for attenuating anthracycline- and trastuzumab-induced cardiac injury [329-333]. These evidences validate the potential of statins in preventing chemotherapy-induced cardiac injury and warrants further clinical trials to investigate their efficacy in preventing cardiotoxicity. Tamoxifen is the primary treatment for ER-positive breast cancers. However, prolonged use of tamoxifen can result in NAFLD [334]. When used in combination with tamoxifen, fatostatin, a SREBP inhibitor, has been reported to reduce tamoxifen-induced hepatic lipid accumulation [335]. Further research into the molecular mechanisms that target cholesterol metabolism is required to prevent these adverse effects. This could provide a basis for rational combination strategies involving cholesterol metabolism-targeting and antitumor drugs to optimize tumor therapy. In summary, in addition to improving the survival rate of cancer patients, mitigating the adverse effects of conventional tumor therapy is imperative for improving the quality of life of cancer patients.

Conclusions and perspectives

The role of cholesterol metabolism in tumors has received increasing attention. Therefore, this article provides a summary of the molecular mechanisms by which the dysregulation of cholesterol homeostasis contributes to the hallmarks of cancer. In addition, cholesterol metabolism plays a significant role in the constant communication between tumor cells and their microenvironment. Therefore, this study

highlights the diverse effects of cholesterol metabolism on seven specialized microenvironments as well as its involvement in tumor cell-to-TME communication via distinct molecular pathways. Targeting cholesterol metabolism is emerging as a promising antitumor strategy, with drugs capable of exerting antitumor effects by targeting this metabolic pathway. The evidence supporting the use of various antitumor strategies, including targeting cholesterol biosynthesis, uptake and efflux, intracellular trafficking, and esterification, is summarized. Numerous preclinical and clinical studies have suggested that combining conventional tumor therapy with cholesterol-targeting therapies can exert synergistic antitumor effects. Of note, targeting cholesterol enhances the efficacy of conventional tumor therapy and mitigates its adverse effects. These findings suggest that targeting cholesterol metabolism could enhance both the survival and quality of life of patients with cancer.

Despite the initiation of clinical trials for various repurposed drugs that target cholesterol metabolism, certain issues remain unresolved. First, given the low specificity of targeting cholesterol metabolism, which affects both tumor cells and immune cells, improving the specificity of targeting cholesterol metabolism to enhance both direct antitumor effects and antitumor immunity is an urgent problem to be solved. Cholesterol is required for the proliferation and activation of cancer and immune cells [32, 116]. In this context, it is particularly important to improve the specificity of targeting cholesterol metabolism. The advancements in nanotechnology enable controlled release of drugs at target sites [336]. Targeting cholesterol metabolism combined with nanoparticles may be a potential solution. Second, assessing the suitability of these repurposed cholesterol-targeting drugs in patients with different tumor types. A meta-analysis has shown that statin use reduces mortality in breast cancer patients [218]. However, a prospective population-based cohort study suggests that statin use is not associated with prostate cancer recurrence or progression [337]. Therefore, further well-designed clinical trials are required to assess the suitability of these repurposed cholesterol-targeting drugs in patients with different tumor types. Third, elucidating the potential adverse effects of these repurposed drugs in cancer patients. For instance, high doses of statins can lead to some adverse effects, with the most common ones being hepatic dysfunction and statin-associated muscle symptoms (SAMS) [338, 339]. Nevertheless, statins are generally well tolerated, and adverse effects vary depending on the exact statin used, as well as the dosage and combination with other drugs [340]. Therefore, when

using repurposed drugs targeting cholesterol metabolism for cancer treatment, adverse effects and other drug interactions should be fully understood, drug dosages should be controlled, and adverse reactions should be monitored. Fourth, evaluating the optimal combination strategy for patients with different tumor types. In a preclinical study, the LXR agonist GW3965 has been reported to increase the sensitivity of NSCLC cells to gefitinib [298]. Furthermore, a clinical trial reported that simvastatin improved the efficacy of gefitinib in patients with gefitinib-resistant NSCLC [307]. Similarly, several studies have reported that avasimibe and pitavastatin combined with gemcitabine have synergistic antitumor effects in pancreatic cancer [291, 304]. A clinical trial reported that pravastatin prolongs survival in patients with advanced HCC treated with 5-FU after catheter arterial embolization [221]. However, another clinical trial reported that pravastatin did not improve survival in advanced HCC patients treated with sorafenib [341]. Therefore, the optimal combination strategy for patients with different tumor types requires further detailed evaluation. Further well-designed preclinical studies and clinical trials are required to address these unresolved issues.

Abbreviations

ANO1: Anoctamin 1
TME: Tumor microenvironment
HMG-CoA: 3-hydroxy-3-methyl-glutaryl-CoA
IPP: Isopentenyl pyrophosphate
GPP: Geranyl pyrophosphate
FPP: Farnesyl pyrophosphate
SREBP2: Sterol regulatory element-binding protein 2
LXR: Liver X receptor
ER: Endoplasmic reticulum
SCAP: SREBP cleavage-activating protein
INSIG: Insulin-induced gene
S1P: Site-1 protease
S2P: Site-2 protease
HMGCR: HMG-CoA reductase
LDL: Low-density lipoprotein
LDLR: Low-density lipoprotein receptor
NPC1L1: Niemann-Pick type C1-like 1
NPC: Niemann-Pick C
PCSK9: Proprotein convertase subtilisin/kexin type 9
SRE: Sterol regulatory elements
CEs: Cholesterol esters
ACAT: Acyl-CoA: cholesteryl acyltransferase
LDs: Lipid droplets
ABC: ATP-binding cassette
ABCA: ATP-binding cassette subfamily A member
ABCB: ATP-binding cassette subfamily B member
ABCG: ABC subfamily G member
HDL: High-density lipoprotein
CRC: Colorectal cancer
ENSA: Gene alpha-endosulfine

TNBC: Triple-negative breast cancer
 PDAC: Pancreatic ductal adenocarcinoma
 XBP1: X-box binding protein 1
 HCC: Hepatocellular carcinoma
 TFCEP2: Transcription factor CP2
 27HC: 27-hydroxycholesterol
 RCC: Renal cell carcinoma
 ccRCC: Clear cell renal cell carcinoma
 ZMYND8: Zinc finger MYND-type containing 8
 ER-BC: Estrogen receptor-negative breast cancer
 GPER: G protein-coupled estrogen receptor
 GGPP: Geranylgeranyl diphosphate
 SQLE: Squalene epoxidase
 CRPC: Castration-resistant prostate cancer
 GC: Gastric cancer
 CH25H: Cholesterol 25-hydroxylase
 MMP: Matrix metalloproteinase
 SOAT1: Sterol O-acyltransferase 1
 CRABP-II: Cellular retinoic acid-binding protein II
 AR: Androgen receptor
 5-FU: 5-fluorouracil
 PD-L1: Programmed death ligand 1
 CRAC: Cholesterol-recognition amino acid consensus
 ER+: Estrogen receptor-positive
 EGFR-TKIs: Epidermal growth factor receptor tyrosine kinase inhibitors
 NSCLC: Non-small cell lung cancer
 TIICs: Tumor-infiltrating immune cells
 TIME: Tumor immune microenvironment
 NK: Natural killer
 TAMs: Tumor-associated macrophages
 MDSCs: Myeloid-derived suppressor cells
 DCs: Dendritic cells
 TILs: Tumor-infiltrating lymphocytes
 CTLs: Cytotoxic T lymphocytes
 MHC-I: Major histocompatibility complex class I
 CAR: Chimeric antigen receptor
 TCR: T-cell receptor
 IL-9: Interleukin-9
 NKT: Natural killer T
 mTORC2: Mammalian target of rapamycin complex 2
 CXCR2: CXC chemokine receptor 2
 HIF-1 α : Hypoxia-inducible factor-1 α
 GBM: Glioblastoma multiforme
 GPR: G-protein-coupled receptor
 CCR7: CC chemokine receptor-7
 ROS: Reactive oxygen species
 DNMT3A: DNA methyltransferase 3A
 RECK: Reversion-inducing-cysteine-rich protein with Kazal motifs
 HIFs: Hypoxia-inducible factors
 PKB: Protein kinase B
 CAFs: Cancer-associated fibroblasts
 YAP: Yes-associated protein
 ECM: Extracellular matrix
 EMT: Epithelial-mesenchymal transition
 CXCL1/2/8: C-X-C motif chemokines 1/2/8
 CCL2/7: C-C motif chemokines 2/7
 TAZ: PDZ-binding motif
 TFEB: Transcription factor EB
 APMAP: Adipocyte plasma membrane-associated protein

ERK1/2: Extracellular-regulated protein kinase 1/2
 NAFLD: Non-alcoholic fatty liver disease
 FDPS: Farnesyl diphosphate synthase
 FDA: Food and Drug Administration
 OSC: Oxidosqualene cyclase
 ApoE: Apolipoprotein-E
 NASH: Nonalcoholic steatohepatitis
 SERMs: Selective estrogen receptor modulators
 NF: Nuclear factor
 PD-1: Programmed cell death protein 1
 CSC: Cancer stem cell
 PFS: Progression-free survival
 DFS: Disease-free survival
 OS: Overall survival
 SAMS: Statin-associated muscle symptoms

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WJ, WLJ and AMX conceptualized the study. WJ and WLJ collected the relevant literature. WJ wrote the original draft and prepared the figure and the tables. WJ, WLJ and AMX significantly edited the manuscript text, figure and tables and supervised the project. All authors reviewed and approved the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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