

Cholesterol metabolism implications for cancer and therapy

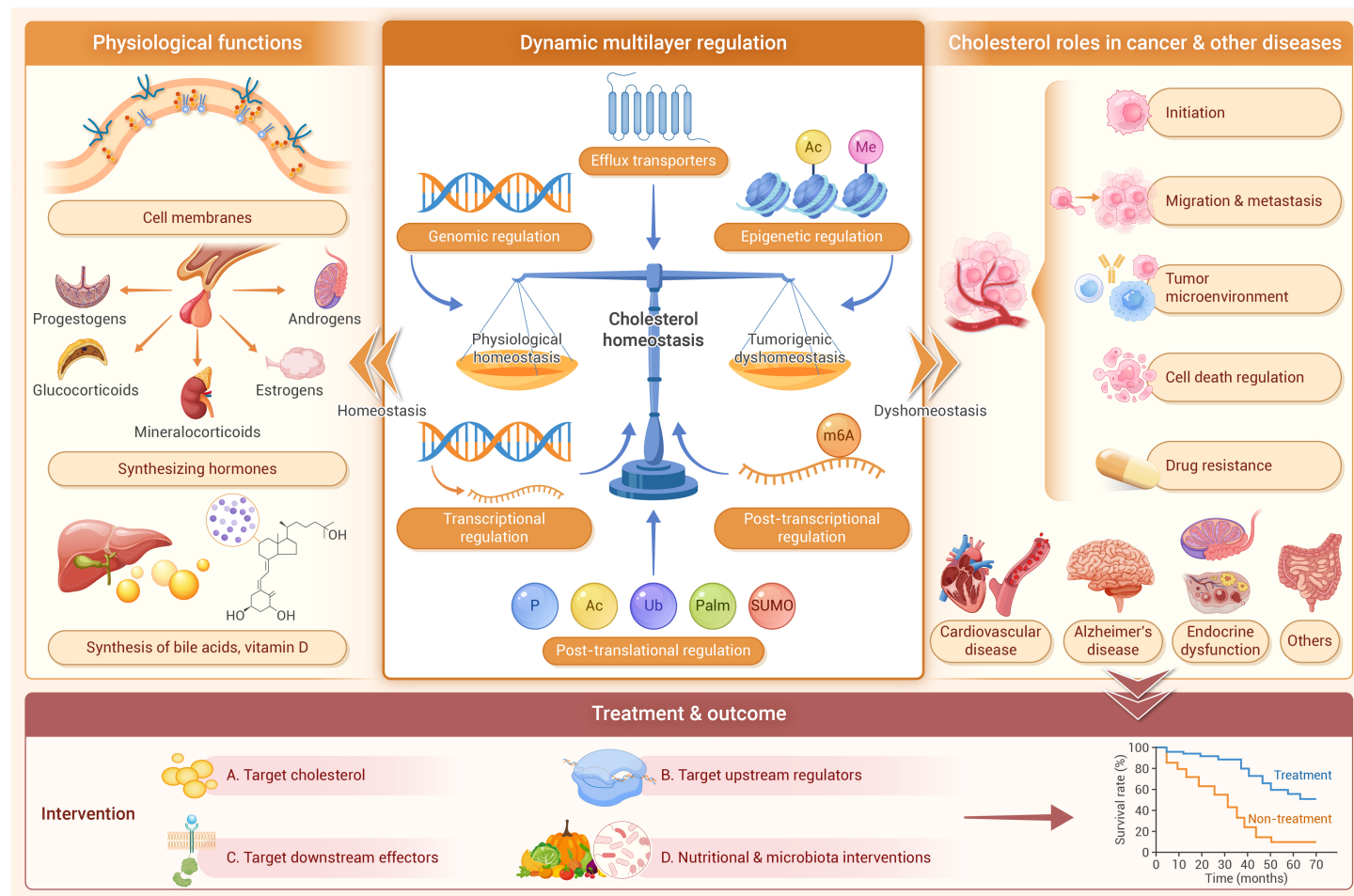
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Healthy cells use a precise multi-layered system to balance cholesterol production and clearance.
- Cancer cells hijack cholesterol production, uptake, and storage to fuel tumor growth and spread.
- Cholesterol imbalance in the tumor microenvironment (TME) rewires immune cells to suppress defenses.
- Blocking cholesterol synthesis or restoring its balance boosts immune attack and drug sensitivity.

Cholesterol metabolism implications for cancer and therapy

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Cholesterol constitutes an indispensable lipid metabolite for all eukaryotic cells and governs diverse core metabolic processes. Its homeostasis is precisely controlled by multilayered dynamic regulatory. Malignant cells subvert this homeostatic network to reprogram cholesterol synthesis, lipoprotein uptake and intracellular esterification, which collectively fuels tumorigenesis, metastasis and therapeutic resistance. Meanwhile, dysregulated cholesterol metabolism educates tumor microenvironment and induces immunosuppression especially by switching the polarization of tumor-associated macrophages. Therefore, targeting cholesterol metabolism has emerged as a highly promising anti-tumor strategy, in particular for the immunotherapy. This review focuses on the multi-layered regulatory mechanisms of cholesterol and its pathological roles in cancer, summarizes the latest advances in relevant targeted therapies, and elucidates the core value of cholesterol metabolism as a therapeutic vulnerability in cancer treatment.

INTRODUCTION

As an indispensable lipid metabolite ubiquitous in eukaryotic cells, cholesterol fulfills multifaceted biological roles: it maintains membrane structural integrity, serves as the universal precursor for steroid hormones and bile acids biosynthesis, and organizes lipid raft microdomains to govern membrane-associated signal transduction. To adapting to distinct cell identities, developmental stages and fluctuating extracellular stimuli, a sophisticated, multi-tiered regulatory network coordinates transcriptional regulation, post-translational modifications, and coordination of metabolic flux, ensuring cholesterol levels are precisely adjusted.¹ However, under the pressure of the tumor microenvironment (TME), this tightly balanced sterol homeostatic program undergoes thoroughly remodeling. Cancer cells drive malignant progression by hijacking core cholesterol synthesis, uptake and efflux pathways. Meanwhile, a spectrum of cholesterol-derived bioactive metabolites acts as intercellular signaling molecules to reshape the immune-suppressive landscape of the TME. Collectively, dysregulated cholesterol metabolism not only supports tumor proliferation, migration, and chemoresistance but also creates a unique metabolic vulnerability amenable to therapeutic targeting. Herein, we systematically bridge basic mechanisms with clinical translational progress, offering novel insights into cholesterol-centered metabolic intervention against human malignancies.

CHOLESTEROL METABOLISM

Cholesterol metabolism is a highly coordinated network that maintains cellular and systemic lipid homeostasis through the integration of endogenous synthesis, exogenous uptake, intercellular transport, intracellular trafficking, and catabolism. Cholesterol is obtained from both endogenous biosynthesis and exogenous dietary intake, and these two sources cooperate to maintain intracellular cholesterol homeostasis.

Dietary cholesterol is absorbed by intestinal epithelial cells via the Niemann–Pick type C1 (NPC1)-like 1 (NPC1L1) protein, followed by chylomicron formation and secretion.² The liver acquires cholesterol from chylomicron remnants via low-density lipoprotein receptor (LDLR). In addition to dietary cholesterol uptake, endogenous cholesterol biosynthesis provides the major source of cholesterol in most tissues. Endogenous cholesterol synthesis primarily occurs in the liver and small intestine, with the entire biosynthetic pathway spanning the cytoplasm and endoplasmic reticulum (ER) membrane.^{3–4} The biosynthetic pathway can be divided into three sequential stages, and its key regulatory steps are tightly controlled to adapt to cellular

cholesterol demands. The first stage involves mevalonate production. The pathway is initiated with acetyl-CoA, which is catalyzed and condensed by 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1) to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). HMG-CoA is then reduced by the key enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) to generate mevalonate.⁵ This step represents the rate-limiting step of cholesterol synthesis and serves as the primary target for clinical lipid-lowering drugs, such as statins. The resulting mevalonate subsequently undergoes a series of phosphorylation and decarboxylation reactions to generate the activated isoprenoid units, isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). These two molecules are condensed under the catalysis of farnesyl pyrophosphate synthase (FPPS) to produce farnesyl pyrophosphate (FPP).⁶ In the final stage of cholesterol biosynthesis, two molecules of FPP are condensed by squalene synthase (SQS) to form squalene. Squalene is then oxidized by the second rate-limiting enzyme, squalene monooxygenase (SQLE), to form 2,3-oxidosqualene. This intermediate subsequently undergoes a series of complex conversion steps to generate mature cholesterol (Figure 1).⁷

After synthesis and uptake, hepatic cholesterol is packaged into very low-density lipoprotein (VLDL) and secreted into the circulation, thereby distributing cholesterol to peripheral tissues.⁸ VLDL loses triglycerides via lipoprotein lipase (LPL) to form intermediate-density lipoprotein (IDL), which is subsequently converted into low-density lipoprotein (LDL).⁹ LDL serves as the major carrier of cholesterol in the circulation and is taken up by peripheral cells via LDLR-mediated endocytosis.¹⁰ This process is essential for maintaining tissue cholesterol supply, and defects in LDLR function led to hypercholesterolemia (Figure 1). Once internalized, cholesterol undergoes dynamic intracellular trafficking to maintain membrane integrity, support organelle function, and participate in cellular signaling.¹¹ To prevent intracellular cholesterol overload, cells promote cholesterol efflux through ATP-binding cassette (ABC) transporters. ABCA1 mediates cholesterol efflux to apolipoprotein A-I (ApoA-I), forming nascent high-density lipoprotein (HDL), while ABCG1 further transfers cholesterol to mature HDL.¹² The cholesterol-enriched HDL subsequently transports cholesterol back to the liver through reverse cholesterol transport (RCT). In hepatocytes, scavenger receptor class B type 1 (SR-B1) selectively mediates the uptake of cholesteryl esters from HDL, thereby completing the RCT process.¹³ Additionally, intestinal and hepatic ABCG5/ABCG8 facilitate biliary cholesterol efflux, thereby exerting direct control over whole-body cholesterol homeostasis. Intracellular surplus free cholesterol can also be esterified by acyl-coenzyme A: cholesterol acyltransferase (ACAT) to generate cholesteryl esters (CEs), which are subsequently stored in lipid droplets or secreted as components of VLDL.^{14–16} Beyond intracellular lipid storage, cholesterol can be irreversibly eliminated through conversion into bile acids in the liver. This process is initiated by cholesterol 7 α -hydroxylase (CYP7A1), the rate-limiting enzyme of the classical bile acid synthesis pathway (Figure 1).

ROLES OF CHOLESTEROL AND ITS ASSOCIATED METABOLITES

Cholesterol is an indispensable lipid molecule with a sophisticated and tightly regulated metabolic network. It serves as the essential precursor for the biosynthesis of bile acids, vitamin D, and all steroid hormones.¹⁷ Among these cholesterol metabolites, oxysterols are the most extensively characterized cholesterol derivatives and have emerged as critical signaling molecules linking cholesterol metabolism to human diseases. Oxysterols can be classified into two categories according to their biosynthetic mechanisms.¹⁸ The first category comprises enzymatically oxidized products, including 27-

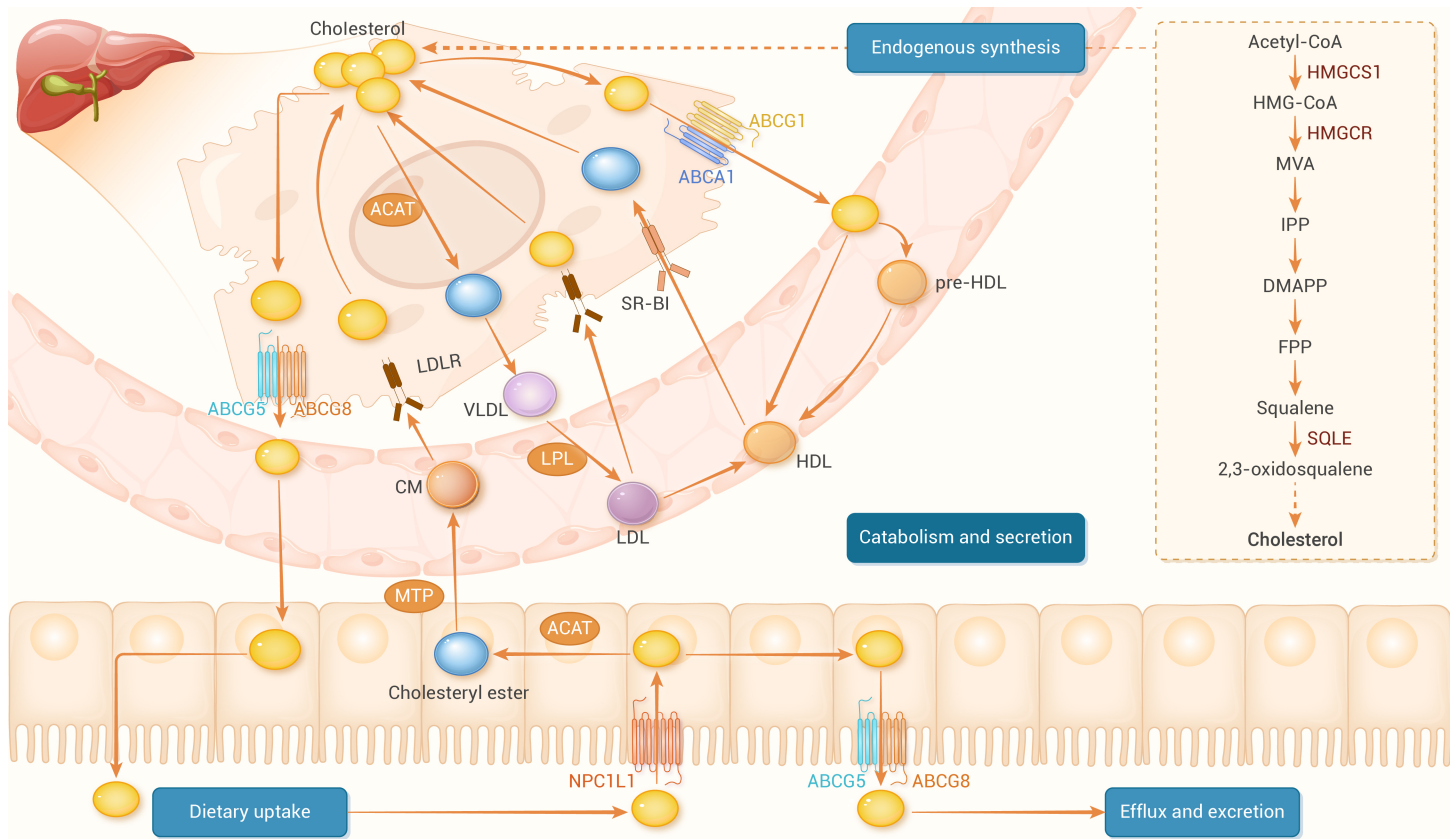


Figure 1. Core cholesterol metabolic pathways in normal physiology The core network of cholesterol metabolism. Exogenous cholesterol is uptake by intestinal epithelial cells via NPC1L1, then assembled into chylomicrons and secreted into the circulation. The liver captures chylomicron remnants via LDLR. Endogenous cholesterol is mainly synthesized in the liver, with acetyl-CoA as the initial substrate, and mature cholesterol is gradually generated through three consecutive stages. Among them, the MVA generation step mediated by HMGCR and the squalene oxidation step mediated by SQLE are key rate-limiting steps, and also serve as important therapeutic targets for lipid-lowering drugs. The liver integrates endogenous and exogenous cholesterol, packages it into VLDL and secretes it into the blood. VLDL is sequentially converted into LDL under the action of LPL, and peripheral cells take up LDL-bound cholesterol via LDLR. Excess intracellular cholesterol can be effluxed or excreted through ABC transporters (ABCA1, ABCG1, ABCG5/ABCG8), and can also be esterified into cholesterol esters by ACAT for intracellular storage or secretion. In the liver, cholesterol can be catabolized into bile acids via CYP7A1.

Hydroxycholesterol (27-HC), 25-Hydroxycholesterol (25-HC), 24(S)-Hydroxycholesterol (24S-HC), 7 α -Hydroxycholesterol (7 α -HC). The second category consists of non-enzymatically oxidized products, represented by 7-Ketcholesterol (7-KC), generated via reactive oxygen species (ROS)-mediated oxidation. As signaling molecules, oxysterols exert critical regulatory roles in metabolism, immunity, and tumor biology through acting on nuclear receptors, membrane receptors, or through direct interactions with enzymes or proteins.

Roles of major cholesterol metabolites in diseases

27-Hydroxycholesterol. 27-Hydroxycholesterol (27-HC) is the most abundant oxysterol in the circulation. It is primarily generated from cholesterol by the mitochondrial cytochrome P450 enzyme CYP27A1, and is subsequently metabolized into bile acids by oxysterol 7 α -hydroxylase (CYP7B1).¹⁹⁻²¹ As a ligand of liver X receptors (LXRs), 27-HC upregulates the expression of ABCA1/ABCG1, inhibits the translocation of sterol regulatory element-binding protein 2 (SREBP2) to the Golgi apparatus, and thereby reduces intracellular cholesterol levels.²²⁻²⁴

In addition to regulating cholesterol homeostasis, 27-HC also functions as the first identified endogenous selective estrogen receptor modulator (SERM). 27-HC binds to estrogen receptor α (ER α) and estrogen receptor β (ER β), thereby influencing multiple estrogen-dependent physiological and pathological processes.²⁵⁻²⁷ In atherosclerosis, macrophage-secreted 27-HC acts as a paracrine signaling molecule under hypercholesterolemic conditions. 27-HC impairs vasodilatory function via the 27-HC-ER α -endothelial nitric oxide synthase (eNOS)-nitric oxide (NO) axis, inhibits the proliferation and migration of endothelial cells, and disrupts endothelial barrier integrity.²⁸ These findings indicate that 27-HC contributes to endothelial dysfunction and accelerates the progression of atherosclerotic lesions. Clinical evidence further supports the pathogenic role of 27-HC in cardiovascular diseases. Compared with statin monotherapy, combination with statins and ezetimibe

significantly reduces plasma 27-HC levels, which is significantly and positively correlated with decreased coronary plaque burden.²⁹

Beyond cardiovascular diseases, accumulating evidence has demonstrated that 27-HC also contributes to tumorigenesis and tumor progression. 27-HC promotes epithelial-mesenchymal transition (EMT) and tumorigenesis through LXR activation.³⁰ In breast cancer, 27-HC exerts immunosuppressive effects on T cells via targeting the LXR-ABCA1/ABCG1 axis in macrophages.³¹ In estrogen receptor-positive (ER+) breast tumors, elevated 27-HC levels are correlated with decreased CYP7B1 expression, and are associated with poor survival outcomes in patients (Figure 2).³²

25-Hydroxycholesterol. 25-Hydroxycholesterol (25-HC) is an enzymatically generated oxysterol catalyzed and generated by cholesterol 25-hydroxylase (CH25H).³³ As an important regulator of cholesterol homeostasis, 25-HC exerts feedback inhibition on cholesterol biosynthesis while simultaneously promoting cholesterol storage. Specifically, 25-HC inhibits the activation and subsequent transcriptional activity of SREBP2, thereby suppressing cholesterol biosynthesis. In parallel, it facilitates cholesterol esterification by upregulating ACAT expression.³⁴⁻³⁷ These dual regulatory effects enable 25-HC to rapidly restrain intracellular cholesterol accumulation and maintain lipid homeostasis. Interestingly, a positive feedback regulatory loop exists between 25-HC and LXR signaling. In macrophages, 25-HC upregulates CH25H expression through an LXR-dependent pathway, suggesting that 25-HC not only functions as a metabolic regulator but also participates in the fine-tuning of immune and inflammatory responses.³⁸

Beyond lipid metabolism, 25-HC exhibits diverse biological functions in tumor immunity. In melanoma, 25-HC secreted by lymphatic endothelial cells into the TME antagonizes the immunosuppressive function of tumor cells.³⁹ These findings indicate that 25-HC may exert anti-tumor effects by reshaping the immune microenvironment. 25-HC has also emerged as an important mediator linking cholesterol metabolism to neuroinflammation and

Alzheimer's disease (AD). It amplifies pro-inflammatory signaling in microglia, thus promoting tau-mediated neurodegeneration.⁴⁰ Furthermore, 25-HC significantly enhances lipopolysaccharide (LPS)-induced production of the pro-inflammatory cytokine interleukin-1 β (IL-1 β) in microglia, and this effect is apolipoprotein E (ApoE) isoform-dependent.⁴¹ Consistently, following peripheral LPS challenge, *Ch25h*-KO mice exhibit markedly reduced levels of cerebral pro-inflammatory cytokines and decreased leukocyte infiltration into the brain parenchyma.⁴² Conversely, accumulating amyloid- β (A β) upregulates CH25H expression in microglia, and in turn the elevated 25-HC directly impairs the migration and phagocytic ability of microglia.⁴³ These findings suggest the existence of a feed-forward inflammatory loop involving A β , CH25H, and 25-HC that contributes to AD progression (Figure 2).

24(S)-Hydroxycholesterol. 24(S)-Hydroxycholesterol (24S-HC), also known as cerebrosterol, is predominantly generated in the brain and plays a central role in cerebral cholesterol homeostasis. 24S-HC is produced from cholesterol by the cytochrome P450 enzyme CYP46A1.⁴⁴ As cholesterol itself cannot efficiently cross the blood-brain barrier (BBB), neurons rely on CYP46A1-mediated conversion cholesterol into 24S-HC with higher polarity, which can readily diffuse across the BBB.⁴⁵

In addition to maintaining cholesterol turnover in the central nervous system, 24S-HC exerts concentration-dependent biphasic effects on neuronal survival and function. At physiological levels, 24S-HC activates LXRs in astrocytes, upregulates ABCA1/ABCG1 expression, and facilitates cholesterol trafficking to neurons, thus exerting neuroprotective effects.⁴⁶ At high concentrations, 24S-HC triggers necroptosis in neuroblastoma SH-SY5Y cells.⁴⁷⁻⁴⁸ The dual biological properties of 24S-HC are also reflected in AD. Circulating and cerebrospinal fluid levels of 24S-HC levels are significantly increased during early stage of AD, but decrease markedly in advanced disease, which may partly result from enhanced BBB permeability and the ability of 24(S)-HC to readily diffuse into the circulation.⁴⁹⁻⁵³ Mechanistically, 24S-HC suppresses A β production by retaining immature amyloid precursor protein (APP) in the ER, whereas it amplifies A β -induced neurotoxicity via promoting ROS generation.⁵⁴⁻⁵⁵ Furthermore, exogenous 24S-HC administration effectively inhibits tau hyperphosphorylation and oligomerization in mouse neurons.⁵¹ However, elevated plasma 24S-HC levels in ApoE4-positive individuals are associated with an increased risk of AD onset.⁵⁶ It highlights the context-dependent and stage-dependent effects of 24S-HC in neurodegeneration (Figure 2).

7 α -Hydroxycholesterol. 7 α -Hydroxycholesterol (7 α -HC) not only participates in hepatic cholesterol elimination but also exerts important immunomodulatory functions in extrahepatic tissues. 7 α -HC is predominantly synthesized in the liver via catalysis by CYP7A1, which catalyzes the rate-limiting step for cholesterol catabolism and bile acid synthesis in the human body.⁵⁷⁻⁵⁸ In contrast, in extrahepatic tissues such as the brain, immune cells, and tumors, 7 α -HC is mainly generated by CYP7B1.^{52,59-62}

Recent studies have identified 7 α -HC as an important signaling metabolite involved in inflammatory regulation and disease progression. 7 α -HC can activate THP-1 monocytes, upregulate CD14 expression and promote the release of soluble CD14 via matrix metalloproteinase 9 (MMP-9), thereby mediating inflammatory diffusion, endothelial cell activation, foam cell formation and impaired plaque stability, and ultimately accelerating the progression of atherosclerosis.⁶³ Interestingly, the pro-inflammatory activities of 7 α -HC appear to be therapeutically reversible. Glucocorticoids can significantly inhibit 7 α -HC-induced innate immune activation and inflammatory phenotypic polarization of THP-1 cells.⁶⁴ Beyond cardiovascular diseases, increasing evidence has linked 7 α -HC to neurodegenerative disorders. Clinically, studies have revealed that patients with physio-cognitive decline (PCD) have significantly elevated 7 α -HC levels. Moreover, upregulated hepatic CYP7A1 expression is correlated with increased cerebral A β levels, suggesting that 7 α -HC may increase the risk of developing AD (Figure 2).⁶⁵⁻⁶⁶

7-Ketocholesterol. 7-Ketocholesterol (7-KC) is a major cytotoxic oxysterol predominantly generated via non-enzymatic free radical oxidation of cholesterol. 7-KC is generated primarily through two pathways: ROS-mediated oxidation of cholesterol, and direct oxidation of 7-dehydrocholesterol (7-DHC) by CYP7A1.⁶⁷⁻⁶⁸ Biologically, 7-KC exerts pleiotropic detrimental effects: it triggers robust oxidative stress, mitochondrial/ER/lysosomal dysfunction, and multiple forms of programmed cell death including apoptosis, ferroptosis and oxiaoptophagy.⁶⁹⁻⁷¹

sis and oxiaoptophagy.⁶⁹⁻⁷¹

7-KC is the predominant in atherosclerotic plaques, accounting for 55% of totalplaques oxysterols.⁷²⁻⁷³ It mediated atherogenic injury through multiple axes. In human aortic endothelial cells (HAECs), 7-KC, activates focal adhesion kinase (FAK), downregulates vascular endothelial cadherin (VE-cadherin), and induces E-selectin and intercellular adhesion molecule 1 (ICAM1), thereby impairing the integrity of the vascular endothelial barrier and priming atherosclerosis onset.⁷⁴ In macrophages, 7-KC markedly promotes foam cell formation, and simultaneously upregulates the expression of cholesterol transporters ABCA1 and ABCG1, which participates in the regulation of lipid metabolic homeostasis within plaques.⁷⁵⁻⁷⁶ Further studies have confirmed that 7-KC can also upregulate Piezo1 expression and enhance its mechanogating function, triggering Ca²⁺-dependent inflammatory signaling to accelerate lesion advancement (Figure 2).⁷⁷

Roles of cholesterylation

Cholesterylation is a distinctive lipid post-translational proteins modification. Cholesterol covalently attaches to specific residues of target proteins via intrinsic autocatalytic reaction, independent of modifying enzymes.⁷⁸⁻⁷⁹ Hedgehog and Smoothened proteins, core effectors of the Hedgehog signaling pathway, are the best characterized cholesterylated proteins and regulate vital biological events including embryonic development.⁸⁰⁻⁸¹ Functionally, cholesterylation orchestrates embryonic development and tissue homeostasis, its dysregulation drives the initiation and progression of numerous severe disorders.

Cholesterylation of Hh signaling core proteins. Cholesterylation was initially discovered in Hedgehog (Hh) proteins,⁷⁸ whose self-catalyzed cholesterylation occurs simultaneously with intramolecular autocleavage of mediated by the N-terminal Hedgehog/Intein (Hint) domain.⁸²⁻⁸³ The Hh C-terminal domain segment possesses intrinsic cholesterol transferase activity, covalently attaching cholesterol to the signaling-competent N-terminal Hh fragment (Hh-Np). This structural-dependent modification is a critical step for Hh proteins to acquire complete signaling competence and often works alongside palmitoylation: Hh acyltransferase (Hhat) catalyzes palmitoylation at the N-terminal cysteine residue of Hh-Np concurrent with C-terminal cholesterylation.⁸⁴⁻⁸⁵ The dual lipidation synergistically drives Hh ligand multimerization and the membrane anchoring, while cholesterylation alone strengthens ligand-receptor binding to the Patched 1 (PTCH1) receptor.⁸⁶

Smoothened (SMO) is the only other verified cholesterylated component in the Hh cascade, which cholesterol covalently linked to its Asp95 residue.⁷⁹ This modification is an essential prerequisite for the physiological activation of the Hh signaling pathway activation and embryonic development.⁷⁹ In the resting state, Patched 1 (PTCH1) depletes membrane free cholesterol via efflux and binds to SMO in its cysteine-rich domain (CRD) and occlude the Asp95 site, blocking SMO cholesterylation.⁷⁹ SMO cholesterylation is a calcium-facilitated autocatalytic process. GRAMD1/ASTER proteins supply cholesterol substrates by shuttling lipids across ER-plasma membrane contact sites (MCS).⁸⁷ Upon binding of Hh ligand to PTCH1, PTCH1 dissociate from the primary cilium and undergo degradation, with raising membrane cholesterol levels, meanwhile, Ca²⁺ influx mediated by store-operated calcium entry (SOCE) accelerates the autocatalytic transesterification reaction of SMO, ultimately relieving the inhibition and activating the Hh signaling pathway.⁸⁷ Furthermore, emopamil-binding protein (EBP) negatively regulated SMO cholesterylation. Overexpression of EBP inhibits SMO cholesterylation and its downstream signal transduction, while EBP loss-of-function exerts the opposite biological effects (Figure 2).⁸⁸

Roles of cholesterylation in tumor. Cholesterylation is a key molecular event that mediates the cross-regulation between cholesterol metabolism and oncogenic signaling pathways. Numerous studies have confirmed that this modification serves as a core mechanism driving tumorigenesis, progression, and drug resistance, mainly via the targeted regulation of SMO, the core protein of the Hh signaling pathway. In Hh pathway-dependent tumors such as medulloblastoma and basal cell carcinoma, aberrant activation of SMO cholesterylation is a key link for tumors to maintain their malignant phenotype.⁸⁹⁻⁹⁰ The sterol analog Q29 can block the cholesterylation of SMO by binding to its CRD, thereby inhibiting the proliferation of Hh signaling-dependent medulloblastoma.⁹¹

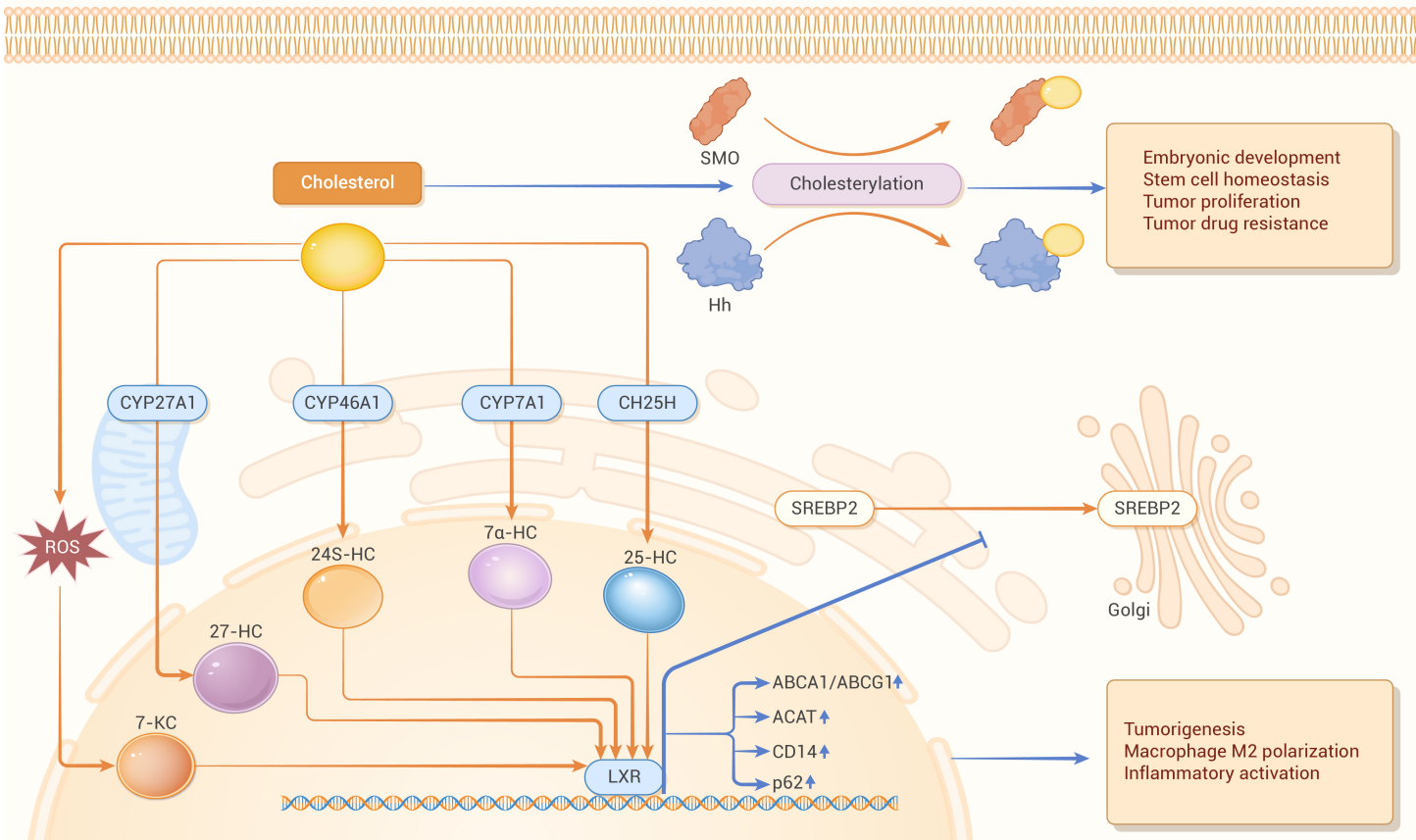


Figure 2. Cholesterol and its associated metabolites Cholesterol regulates diverse physiological and pathological processes through oxysterol metabolism and protein cholesterylation. Cholesterol can be enzymatically converted into major oxysterols, including 27-hydroxycholesterol (27-HC), 25-hydroxycholesterol (25-HC), 24(S)-hydroxycholesterol (24S-HC), and 7α-hydroxycholesterol (7α-HC), catalyzed by CYP27A1, CH25H, CYP46A1, and CYP7A1, respectively. In addition, reactive oxygen species (ROS)-mediated non-enzymatic oxidation generates 7-ketocholesterol (7-KC). These oxysterols regulate cholesterol efflux, cholesterol esterification, inflammation, macrophage polarization, and tumorigenesis mainly through liver X receptor (LXR)-dependent transcriptional programs. Furthermore, cholesterol can directly and covalently modify proteins through cholesterylation. The two best-characterized substrates are Hedgehog (Hh) and Smoothened (SMO), and dysregulated cholesterylation of these proteins contributes to multiple pathological processes, including tumor initiation, malignant progression, stem cell homeostasis imbalance, and therapeutic resistance.

In addition to driving the malignant progression of tumors, SMO cholesterylation also plays a pivotal role in tumor drug resistance. Although drug resistance-related mutations in the 7-transmembrane (7TM) domain of SMO (such as D473H/Y, G497W, W535L) do not directly affect its cholesterylation, they can stabilize the active conformation of SMO, rendering it refractory to targeted blockade by conventional inhibitors and ultimately leading to the development of drug resistance.⁹² Furthermore, cholesterylated SMO has a higher propensity to form a complex with the circular RNA-encoded protein SMO-193a.a., which continuously amplifies the activation of the Hh pathway via a positive feedback loop, acting as a critical driver of poor prognosis in patients with glioblastoma.⁹³

Pan-cancer studies have further validated the broad-spectrum oncogenic driving activity of SMO cholesterylation. In hematological malignancies including lymphoma and leukemia, aberrant activation of the Hh pathway is significantly associated with elevated SMO cholesterylation levels, and inhibiting cholesterol synthesis or interfering with SMO cholesterylation can effectively kill tumor cells.⁹⁴⁻⁹⁵ In a wide range of solid tumors, SMO cholesterylation also exerts a tumor-promoting effect in tumorigenesis and progression.

Collectively, these studies demonstrate that SMO cholesterylation is involved in the processes of tumorigenesis, proliferation, and drug resistance by precisely modulating the activity of the Hh pathway. This not only provides a core theoretical foundation for the development of novel anti-tumor strategies targeting cholesterol metabolism or SMO modification, but also opens a new intervention avenue for overcoming the clinical drug resistance of SMO inhibitors (Figure 2 & Table 1).

DYNAMIC REGULATION OF CHOLESTEROL METABOLISM

Cholesterol homeostasis relies on the coordinated interplay of synthesis,

uptake, efflux, and catabolism, which is precisely governed by a multi-layered regulatory network spanning genomic, epigenetic, transcriptional, post-transcriptional, and post-translational levels. This hierarchical regulatory system ensures that cholesterol metabolism can dynamically adapt to physiological signals and environmental changes, thereby avoiding the dual risks of deficiency and excess. Within the regulatory hierarchy, genomic variations establish the basis for interindividual variability in cholesterol metabolism, while epigenetic modifications and post-translational modifications enable rapid fine-tuning.

Genomic and epigenetic regulation

Genomic regulation of cholesterol homeostasis is primarily dictated by genetic variations that modulate the expression, structure, or function of key metabolic genes. These variations are major determinants of inter-individual differences in plasma cholesterol levels and confer susceptibility to cholesterol-related disorders, including familial hypercholesterolemia (FH) and atherosclerotic cardiovascular disease (ASCVD).

Single nucleotide polymorphisms (SNPs) within coding regions often cause amino acid substitutions that compromise protein integrity.¹¹¹ A classic example is the *LDLR* gene, where over 2000 variants have been cataloged.¹¹² Specifically, missense SNPs often disrupt the binding affinity of LDLR for LDL particles, impairing the endocytic clearance of circulating LDL-cholesterol (LDL-C) and precipitating FH. Similarly, variants in the coding region of *HMGCR* can alter the enzyme's active site, potentially conferring statins resistance.¹¹³

While non-coding region variants do not alter protein sequences, they frequently disrupt regulatory motifs, such as transcription factor binding sites or chromatin architecture. For instance, the cholesterol synthesis gene *HMGCS1* is regulated by the architectural protein CTCF. CTCF binds to the

Table 1. Phenotypes of mice with knockout or transgenic modification of key proteins.

Protein	Genotype	Phenotype	Reference
HMGCR	<i>Alb-Cre; Hmgcr^{fl/fl}</i>	Severe hepatic steatosis accompanied by apoptotic cells, hypercholesterolemia and hypoglycemia	96
	<i>Alb-Cre; Hmgcr^{fl/fl}</i>	Massive hepatocyte apoptosis, compensatory liver regeneration, endoplasmic ER stress, and impaired N-glycosylation	97
Squalene synthase	<i>Alb-Cre; Fdft1^{fl/fl}</i>	Transient liver dysfunction accompanied by moderate hepatomegaly	98
LDLR	<i>Ldlr^{-/-}</i>	Hypercholesterolemia	31
ApoE	<i>Apoe^{-/-}</i>	Increased levels of 27-HC and upregulated expression of CYP7A1	28
	<i>Apoe^{-/-}</i>	Reduced esterified cholesterol content in the adrenal gland and elevated plasma corticosterone levels	99
ABCA1	<i>Adipoq-Cre; Abca1^{fl/fl}</i>	Under a high-fat, high-cholesterol diet: increased plasma membrane cholesterol content, along with decreased lipogenesis and triglyceride accumulation	100
	<i>Alb-Cre; Abca1^{fl/fl}</i>	Development of selective insulin resistance: suppressed lipogenesis, while systemic glucose metabolism remains unaffected	101
ABCA1/ABCG1	<i>Mac-Cre; Abca1^{fl/fl}, Abcg1^{fl/fl} → Ldlr^{-/-}</i>	Enhanced plaque inflammation and accelerated atherosclerosis progression	102
ABCG5/ABCG8	<i>Abcg5/Abcg8^{-/-}</i>	Reduced biliary cholesterol concentration	103
NPC1	<i>Npc1l1^{-/-}</i>	NPC1L1 deficiency	2
ACAT1	<i>Acat1^{-/-}</i>	Attenuated cholesterol esterification and reduced cholesterol ester synthesis capacity	104
	<i>Acat1^{-/-}</i>	Enhanced uptake and degradation of Aβ by microglia	105
SREBP2	<i>Srebf2^{-/-}</i>	Embryonic lethality in mice	106
	<i>Srebf2^{2+/-}</i>	SREBP2 hypomorph with partial survival of mice	106
	<i>Srebf2^{F167A/F167A}</i>	Markedly impaired transcriptional activation capacity of cholesterol synthesis-related genes	107
	<i>Alb-Cre; Srebf2^{fl/fl}</i>	Significantly downregulated SREBP-1c expression, accompanied by decreased cholesterol synthesis and fatty acid synthesis	108
LXR	<i>Vil-Cre; Srebf2^{fl/fl}</i>	Global downregulation of the intestinal sterol synthesis pathway, and acute lethal intestinal injury induced by ezetimibe treatment	109
	<i>Nr1h3^{-/-}</i>	Hepatic cholesterol ester accumulation and impaired liver function	110
	<i>Nr1h3^{-/-}Nr1h2^{-/-}</i>	Dual deficiency of both LXR-α and LXR-β	25

promoter of *TMEM267*, which is located approximately 200 kb upstream of *HMGCS1*, to prevent the formation of abnormal chromatin interaction loops between the two, thereby avoiding the aberrant activation of *HMGCS1*.¹¹⁴

Epigenetic mechanisms, including DNA methylation and histone post-translational modifications (HPTMs), provide a layer of dynamic, reversible control essential for maintaining cholesterol homeostasis across different tissues and developmental stages. DNA methylation regulates cholesterol metabolism by modifying CpG islands to silence or activate key genes.¹¹⁵ For example, the restricted expression of *NPC1L1* in the duodenum, but not in the colon, is governed by differential promoter methylation. High methylation in the colon suppresses its transcription, thereby limiting cholesterol absorption.¹¹⁶ Furthermore, epigenetic enzymes act as metabolic rheostats: DNA methyltransferase 3A (DNMT3A) mediated hypermethylation of the *MEF2A* promoter suppresses the expression of this transcription factor, subsequently downregulating *CYP7A1* and impeding the conversion of cholesterol to bile acids.¹¹⁷⁻¹¹⁸ Conversely, TET1-mediated demethylation facilitates the activation of the scavenger receptor *CD36* in hepatocytes, promoting oxidized cholesterol uptake and contributing to lipid accumulation in metabolic syndrome.¹¹⁹

HPTMs modulate cholesterol metabolism by altering chromatin accessibility. Histone deacetylase 3 (HDAC3) serves as a negative regulator of cholesterol synthesis by deacetylating histones at the *SQLE* promoter.¹²⁰ In contrast, the histone lysine demethylase KDM4A enhances *SQLE* expression by removing the repressive H3K9me3 mark, thereby increasing chromatin accessibility for the transcription factor GABPa.¹²¹⁻¹²² Additionally, the crosstalk between structural proteins and enzymes is exemplified by the PRC2 complex, which is recruited by CTCF to the *HMGCS1* promoter region to catalyzes the repressive H3K27me3 mark, preventing the binding of

SREBP2.¹¹⁴ Additionally, in oncogenic contexts, aurora kinase AURKB-induced changes in histone H3K9me3 enrichment at the *NCEH1* promoter demonstrate how epigenetic remodeling can shift the metabolic landscape to support tumor growth (Figure 3).¹²³

Transcriptional and post-transcriptional regulation

As the central regulatory hub of cholesterol homeostasis, transcriptional regulation coordinates the expression of metabolism-related genes by integrating intracellular cholesterol signals. This tier of regulation relies on two opposing master transcription regulators: cholesterol-depletion activated SREBP2 and cholesterol-overload sense LXRα/β, whose activities are further modulated by auxiliary signaling cascades to accommodate diverse physiological stimuli.

SREBP2 is the primary transcriptional driver of endogenous cholesterol synthesis and extracellular cholesterol uptake, directly regulating the expression of rate-limiting enzymes (HMGCR, HMGCS1, SQLE) and transporters.¹²⁴ SREBPs are initially synthesized as inactive membrane-bound precursors, exist as a membrane-anchored transcription factor, and typically localized to the ER membrane via binding to SREBP-cleavage activating protein (SCAP).¹²⁵

When cholesterol is deficient (<5% of total lipids), the SCAP-SREBP2 complex dissociates from ER-resident inhibitory proteins (e.g., insulin-induced gene, INSIG) and is transported to the Golgi apparatus via COPII vesicles.¹²⁶⁻¹²⁷ Within the Golgi, SREBP2 undergoes sequential cleavage by two proteases. Firstly, site-1 protease (S1P) cleaves its membrane-anchored fragment. Subsequently, site-2 protease (S2P) cleaves the transmembrane domain, releasing the soluble N-terminal domain (N-SREBP2).¹⁰⁷ The activated N-SREBP2 resists proteasomal degradation, translocates to the

nucleus, and binds to sterol regulatory elements (SREs) in the promoters of target genes, activating the transcription of *HMGCR*, *SQLE*, and *LDLR* to promote cholesterol synthesis and uptake.¹²⁸

Under cholesterol depletion, cholesterol binds to the sterol-sensing domain of SCAP, inducing a conformational change that stabilizes SCAP-INSIG binding. This traps the SCAP-SREBP2 complex in the ER, blocking its transport to the Golgi.¹²⁹ Meanwhile, N-SREBP2 is rapidly degraded via ubiquitination, further terminating its transcriptional activity.¹²⁸ Additionally, endogenous oxysterols stabilize INSIG proteins, enhancing the inhibitory effect on SREBP2.²⁴

Insulin-activated CD36 forms a complex with INSIG2, disrupting the interaction between SCAP and INSIG2.¹³⁰ This effect relieves the ER retention of the SCAP-SREBP complex, promoting its transport to the Golgi apparatus and subsequent SREBP cleavage. UDP-glucose (UDPG), an intermediate in glycogen synthesis, enters the Golgi apparatus via the transporter SLC35F5 and directly binds to the Asn438 residue of S1P, inducing a conformational change.¹³¹ The allosterically modified S1P is recognized and degraded via the ubiquitin-proteasome pathway, thereby blocking the first cleavage step of SREBP.¹³¹

LXR α/β , as ligand-activated nuclear receptors, form an antagonistic balance with SREBP2 and initiate cholesterol clearance programs when intracellular cholesterol levels are excessively high. Their activity depends on binding to oxysterols, whose levels increase with cholesterol accumulation.¹³² When cholesterol is in excess, oxysterols bind to the ligand-binding domain of LXRs, inducing a conformational change that releases co-repressors and recruits co-activators.¹³³⁻¹³⁴ The activated LXRs then form heterodimers with retinoid X receptors (RXR).¹³⁵ This complex binds to LXR response elements (LXREs) in the promoters of target genes, driving the expression of genes involved in reverse cholesterol transport (*ABCA1*, *ABCG1*) and bile excretion (*ABCG5/ABCG8*).¹³⁶⁻¹³⁷ *ABCA1* and *ABCG1* promote cholesterol efflux to HDL, while *ABCG5/ABCG8* limit intestinal cholesterol absorption and enhance hepatic cholesterol excretion into bile.^{12,136,138}

LXRs also accelerate cholesterol catabolism by upregulating CYP7A1, which is the rate-limiting enzyme for bile acid synthesis.¹¹⁰ Simultaneously, LXRs inhibit cholesterol acquisition and synthesis through activating inducible degrader of the LDL receptor (IDOL) to promote ubiquitin-mediated degradation of LDLR.¹³⁹ As cholesterol levels return to normal, oxysterol concentrations decrease, and LXRs revert to an inactive state-completing the negative feedback regulatory loop.

Beyond SREBP2 and LXRs, other pathways fine-tune cholesterol metabolism by integrating non-sterol signals. Vitamin B12 deficiency impairs the biosynthesis of adenosylcobalamin, which is a coenzyme essential for methylmalonyl-CoA mutase activity, thereby leading to the accumulation of methylmalonic acid (MMA). This accumulated MMA directly inhibits HMGCR, ultimately reducing cholesterol synthesis.¹⁴⁰ VAV guanine nucleotide exchange factor 2/3 (VAV2/3), as guanine nucleotide exchange factors of the RHO family, can activate Ras-related C3 botulinum toxin substrate 1 (RAC1). This activation promotes the nuclear translocation of SREBF (the gene encoding SREBP) via the mTORC1/2 and MEK-ERK signaling pathways, thereby upregulating the expression of genes such as HMGCR and HMGCS1.¹⁴¹ Under hypoxia, the stability of hypoxia-inducible factor 1 α (HIF-1 α) increases. HIF-1 α not only inhibits the expression and DNA-binding ability of SREBP but also activates Runt-related transcription factor 3 (Runx3). Runx3 competes with SREBF for binding to the *HMGCR* promoter, thereby inhibiting the expression of *HMGCR*.¹⁴² These two effects synergistically inhibit HMGCR, reducing cholesterol synthesis.

Post-transcriptional regulation governs the abundance of cholesterol metabolism molecules via a tiered regulatory cascade independently of transcriptional activation, enabling cells to rapidly respond to abrupt changes in cholesterol demand and offset the slow kinetics of transcription factor-dependent regulation. For example, N6-methyladenosine (m6A), a common internal RNA modification, stabilizes the mRNAs of *ACLY* and *SCD1*, thereby enhancing their mRNA translation.¹⁴³⁻¹⁴⁴ On the other hand, miRNAs, a class of short non-coding RNAs, also regulate cholesterol metabolism by binding to the 3'-untranslated region (3'-UTR) of target mRNAs. Among them, miR-33a is a core metabolism-related miRNA. Its mature form, miR-33a-5p, directly targets and silences *ABCA1* expression, reducing *ABCA1*-mediated

ApoA-I-dependent cholesterol efflux and thus inhibiting HDL biogenesis.¹⁴⁵⁻¹⁴⁷ While miR-18a-5p represses cholesterol efflux by inhibiting LXR β .¹⁴⁸ miR-140-3p-1 binds to the 3'-UTRs of *HMGCR* and *HMGCS1*, inhibiting endogenous cholesterol synthesis.¹⁴⁹ miR-133b targets *SQLE*, further restricting the synthesis process.¹⁵⁰ Collectively, miRNAs form a multi-layered checkpoint network that effectively suppresses the excessive activation of either cholesterol efflux or synthesis pathways.

Additionally, RNA-Binding Proteins (RBPs) directly interact with specific sequences of mRNAs, regulating protein expression levels by altering mRNA stability or translational initiation efficiency. Human antigen R (HuR) enhances the stability of *ABCA1* mRNA by binding to its 3'-UTR, increasing *ABCA1* protein expression and promoting cholesterol efflux.¹⁵¹ Heterogeneous nuclear ribonucleoprotein R (hnRNP) recognizes the 3'-UTR of *HMGCR* mRNA via its RNA recognition motifs, inhibiting HMGCR translation and reducing endogenous cholesterol synthesis.¹⁵² RBPs thus act as bidirectional regulators, either boosting or repressing metabolic mRNAs to align with the cellular cholesterol status. Meanwhile, alternative splicing generates multiple mRNA isoforms from a single gene. Gene transcription first produces pre-mRNA, which undergoes different splicing patterns to generate mature mRNAs with distinct structures and functions.¹⁵³ The U2AF complex (U2AF1/U2AF2), a key splicing factor, recognizes the 3' splice site and initiates spliceosome assembly.¹⁵⁴ The lncRNA ZFAS1 enhances the stability of *HMGCR* mRNA by binding to U2AF2, and interacts with polyadenylate-binding protein 2 (PABP2) to stabilize *SREBP1* mRNA (Figure 3).¹⁵⁵⁻¹⁵⁶

Post-translational regulation

Post-translational modifications (PTMs) act as real-time responsive switches in cholesterol metabolism, directly regulating the activity, stability, or subcellular localization of key metabolic proteins. Commonly, they utilize a metabolite as donor or co-factor to modify protein function.

Phosphorylation of cholesterol metabolism associated proteins. As a ubiquitous PTM, phosphorylation regulates cholesterol metabolism by altering protein conformational structure, catalytic activity, or protein-protein interactions.¹⁵⁷ Its core function lies in coupling extracellular signals or intracellular states to the functional status of metabolic enzymes and transcription factors.

The activity of HMGCR strictly depends on its phosphorylation status. Under energy-deficient conditions, AMP-activated protein kinase (AMPK) specifically mediated Thr172 phosphorylation remodel the catalytic domain of HMGCR, blocking HMG-CoA substrate binding, suppressing HMGCR activity, and consequently curb cholesterol biosynthesis.¹⁵⁸⁻¹⁵⁹ Conversely, under anabolic signals (e.g., insulin stimulation), Protein Kinase B (AKT) is activated to antagonize AMPK function. It not only inhibits AMPK activity but also recruits protein phosphatase 2A (PP2A). PP2A removes the phosphate group from HMGCR, restoring its catalytic conformation and restarting cholesterol synthesis to ensure lipid supply for cell growth and membrane biosynthesis.¹⁶⁰

SREBP2 also relies on phosphorylation for fine-tuning of its activity. In response to cholesterol depletion, PP2A directly interacts with SREBP2 and dephosphorylates its serine/threonine residues. This dephosphorylation enhances the DNA-binding ability of SREBP2 to SREs in the *LDLR* promoter, thereby upregulating *LDLR* expression and promoting extracellular LDL-C uptake.¹⁶¹

In hepatocytes under high-glucose conditions, AMPK phosphorylates SREBP1c at the Ser372 residue and concurrently phosphorylates SREBP2, thereby inhibiting the proteolytic cleavage and nuclear translocation of SREBPs.¹⁶² This effect reduces the mRNA levels of *SREBPs* and suppresses the transcriptional activation of their downstream target genes.¹⁶² AMPK also directly phosphorylates insulin-induced gene 1 (INSIG1) at the Thr222 residue.¹⁶³ This phosphorylation modification abolishes the protein-protein interaction between INSIG1 and GP78, stabilizes INSIG1, and inhibits the proteolytic cleavage and processing of SREBP-1 in the mouse liver.¹⁶³

AKT phosphorylates phosphoenolpyruvate carboxykinase 1 (PCK1), and the phosphorylated PCK1 translocates to the ER, where it mediates the phosphorylation of INSIG1 at Ser207 and INSIG2 at Ser151.¹⁶⁴ This phosphorylation modification disrupts the protein-protein interaction between INSIGs and SCAP, resulting in the translocation of the SCAP-SREBP complex to the Golgi

apparatus and the subsequent activation of SREBP proteins.¹⁶⁴ Mechanistic target of rapamycin complex 1 (mTORC1) promotes the accumulation of mature SREBP through its downstream effector S6K1, and also phosphorylates Lipin-1 to relieve its repressive effect on SREBP.¹⁶⁵⁻¹⁶⁶ mTOR also phosphorylates CREB-regulated transcription coactivator 2 (CRTC2), thereby disrupting the COPII-dependent trafficking of SREBP1.¹⁶⁷

Acetylation of cholesterol metabolism associated proteins. Acetylation is a reversible PTM catalyzed by acetyltransferases that transfer acetyl groups from acetyl-CoA primarily to lysine residues on target amino acids, which can be reversed by deacetylases.¹⁵⁷ Nuclear SREBPs (nSREBPs) are stabilized by basal acetylation, which reinforces their tertiary structure and DNA-binding affinity to Sterol Regulatory Elements (SREs).¹⁶⁸ Conversely, sirtuin1 (SIRT1) acts as a metabolic sensor, it physically interacts with and deacetylates SREBP1c, facilitating its recognition by ubiquitin ligases and subsequent proteasomal degradation, thereby attenuating lipogenesis.¹⁶⁹ SIRT6 provides a distinct layer of regulation in the liver. SIRT6 is recruited by FoxO3 to the proximal promoter of the *PCSK9* gene, SIRT6 deacetylates histones H3K9 and H3K56 to epigenetically repress *PCSK9* transcription.¹⁷⁰ By limiting PCSK9 production, SIRT6 prevents LDLR degradation, thereby enhancing hepatic LDL-C uptake and maintaining systemic cholesterol homeostasis.¹⁷¹

Ubiquitination of cholesterol metabolism associated proteins. In cholesterol metabolism, ubiquitination primarily acts as a "degradation switch", governed by the interplay between E3 ubiquitin ligases and deubiquitinating enzymes (DUBs) to ensuring the rapid clearance of excess metabolic proteins.

The ubiquitination of HMGCR via the ER-associated degradation (ERAD) pathway is tightly controlled. When intracellular cholesterol levels are elevated, cholesterol prevents the degradation of ER-resident INSIG1/2 proteins, which then act as adaptors to recruit HMGCR to the RING-type E3 ligase GP78.¹⁷² GP78 catalyzes the polyubiquitination of HMGCR, marking it for proteasomal recognition and subsequent degradation, which directly reduces endogenous cholesterol synthesis.¹⁷² Ring Finger Protein 145 (RNF145) is a sterol-responsive ER-resident E3 ubiquitin ligase, which interacts with INSIG1/2 to promote the ubiquitination and proteasome-mediated degradation of HMGCR.¹⁷³ Oxysterols amplify this process. 25-HC and 24,25-dihydroxycholesterol (DHL) enhance the interaction between HMGCR and INSIGs, accelerating HMGCR ubiquitination and ERAD.¹⁷⁴

When the levels of geranylgeranyl pyrophosphate (GGpp) in the ER membrane rise, GGpp competes for binding to UbiA prenyltransferase domain-containing protein 1 (UBIAD1), thereby promoting the dissociation of HMGCR from UBIAD1.¹⁷⁵⁻¹⁷⁶ HMGCR is subsequently recognized by INSIG1 and undergoes ubiquitination and degradation via the ERAD pathway.¹⁷⁷⁻¹⁷⁸ When intracellular cholesterol is accumulated, Aldehyde dehydrogenase 2 (ALDH2), primarily responsible for aldehyde detoxification, translocates from mitochondria to the ER to promote the formation of the GP78/Insig1/HMGCR complex. This interaction enhances HMGCR ubiquitination and degradation.¹⁷⁹

Conversely, under anabolic conditions, DUBs inhibit HMGCR degradation. For example, ubiquitin-specific peptidase 20 (USP20) stabilizes HMGCR in the fed state. Increased postprandial insulin and glucose levels trigger USP20 phosphorylation, promoting its recruitment to the HMGCR complex.¹⁸⁰ USP20 removes polyubiquitin chains from HMGCR, preventing its proteasomal degradation and thus sustaining cholesterol synthesis.¹⁸⁰

During cholesterol metabolism, several other proteins are also regulated by ubiquitination. Studies have shown that under mechanistic target of rapamycin (mTOR) inhibition conditions, HMGCS1 is ubiquitinated and rapidly degraded as a growth-related protein.¹⁸¹ mTORC1 regulates the degradation of HMGCS1 via the Pro/N-degron pathway through the C-terminal to LisH (CTLH) E3 ubiquitin ligase complex.¹⁸² Under hypoxic conditions, membrane-associated RING-CH-type finger 6 (MARCH6) is activated by NADPH and promotes the degradation of SREBP2.¹⁸³ InHCC, unspliced X-box binding protein 1 (XBP1-u) inhibits the ubiquitination/proteasomal degradation of SREBP2.¹⁸⁴

Under low lipid levels, INSIG1 mediates the protein-protein interaction between ACAT2 and GP78, and GP78 catalyzes the ubiquitination and subsequent proteasomal degradation of ACAT2 at the Cys277 residue.¹⁸⁵

Conversely, USP19 mediates the deubiquitination of ACAT1 at the Lys120 residue, thereby enhancing the protein stability of ACAT1.¹⁸⁶ As an E3 ubiquitin ligase, inducible degrader of the IDOL promotes the ubiquitination and subsequent lysosomal degradation of the LDLR.¹³⁹ USP2 promotes the deubiquitination of LDLR by binding to IDOL, thus reducing the degradation of LDLR.¹⁸⁷

MARCH6 is the cognate E3 ubiquitin ligase for SQLE, and catalyzes the ubiquitination of SQLE within its N100 region.¹⁸⁸⁻¹⁸⁹ This ubiquitination process requires the participation of ubiquitin-conjugating enzyme E2 J2 (UBE2J2), and MARCH6 is recruited to SQLE and recognizes the serine residues adjacent to the cholesterol-dependent amphipathic helix of the protein.^{188,190}

Palmitoylation of cholesterol metabolism associated proteins. Palmitoylation is a reversible PTM that involves the covalent attachment of palmitoyl-CoA to cysteine residues of target proteins. It is tightly regulated by two opposing enzyme families: zinc finger DHHC-type (ZDHHC) palmitoyltransferases and cysteine deacylases.¹⁹¹ This dynamic balance allows palmitoylation to act as a molecular switch for protein function, precisely regulating the subcellular localization, stability, and interactome of key molecules in cholesterol synthesis, transport, and homeostasis.

Studies have shown that ZDHHC3 is highly expressed in HCC, and palmitoylates SCAP at the Cys264 residue to antagonize HECT Domain And Ankyrin Repeat Containing E3 Ubiquitin Protein Ligase 1 (HACE1)-mediated SCAP ubiquitination, thereby stabilizing SCAP and enhancing SREBP2 signaling.¹⁹² In turn, SREBP2 transcriptionally upregulates ZDHHC3 expression, forming a positive feedback regulatory loop.¹⁹²

ZDHHC23 mediates the palmitoylation of Plant Homeodomain Finger Protein 2 (PHF2) to promote its ubiquitin-proteasomal degradation, while PHF2 inhibits lipogenesis through ubiquitinating SREBP1c.¹⁹³ Studies have revealed that palmitoylation of Niemann-Pick C1 (NPC1) at Cys799 and Cys800 is indispensable for its cholesterol efflux function, without affecting the intracellular localization of NPC1.¹⁹⁴ Palmitoylation of NPC1 at the Cys97 residue promotes its correct folding and trafficking to the lysosomal membrane.¹⁹⁵ On the lysosomal membrane, NPC1 forms a complex with NPC2 to transport cholesterol from the lysosomal lumen to the cytoplasm, avoiding excessive cholesterol accumulation.¹⁹⁵

Research shows that ZDHHC8 palmitoylates ABCA1 at Cys3, Cys23, Cys1110 and Cys1111, which modulates ABCA1 plasma membrane localization and its lipid efflux capacity.¹⁹⁶ By contrast, the C311A or C311S mutation of ABCG1, which eliminates its palmitoylation, leads to a significant decrease in ABCG1-mediated cholesterol efflux.¹⁹⁷

ZDHHC4 mainly acts in the ER to catalyze the initial palmitoylation of CD36, which is required for its proper protein folding.¹⁹⁸ ZDHHC5 is predominantly localized in the Golgi apparatus and plasma membrane, where it mediates the anchoring of CD36 to the plasma membrane, and is essential for CD36 membrane localization and fatty acid uptake activity.¹⁹⁸⁻¹⁹⁹ Integrin Subunit Beta 3 (ITGB3) promotes the ubiquitin-dependent degradation of LYN, which relieves LYN-mediated inhibition of ZDHHC5 and further facilitates CD36 palmitoylation.²⁰⁰ Eva-1 Homolog A (EVA1A) promotes CD36 palmitoylation by upregulating the expression levels of ZDHHC4 and ZDHHC5, while downregulating the expression of the depalmitoylase APT1.²⁰¹

ZDHHC6 is another critical enzyme involved in CD36 palmitoylation. In macrophages, CD36 palmitoylation is mediated by ZDHHC6 and its cofactor Selenoprotein K (SelK).²⁰² This modification promotes the translocation and anchoring of CD36 to the lipid raft microdomains of the plasma membrane, and directly enhances the efficiency of ox-LDL uptake by macrophages.²⁰² Conjugated linoleic acid (CLA) inhibits the binding of CD36 to the ZDHHC7, thereby reducing the palmitoylation level of CD36 and its plasma membrane localization.²⁰³ Inhibition of ZDHHC9-mediated CD36 palmitoylation ameliorates high-fat diet-induced pubertal mammary gland dysplasia.²⁰⁴

Acyl Protein Thioesterase 1 (APT1) is one of the key depalmitoylases for CD36. Studies have shown that APT1 directly interacts with CD36 and specifically reduces its palmitoylation at Cys466, which promotes the sorting of CD36 from the plasma membrane to the lysosome for degradation.²⁰⁵ Under diabetic conditions, downregulation of APT1 redirects palmitoylated CD36 to the recycling pathway, leading to enhanced lipid uptake and lipotoxicity in podocytes.²⁰⁵

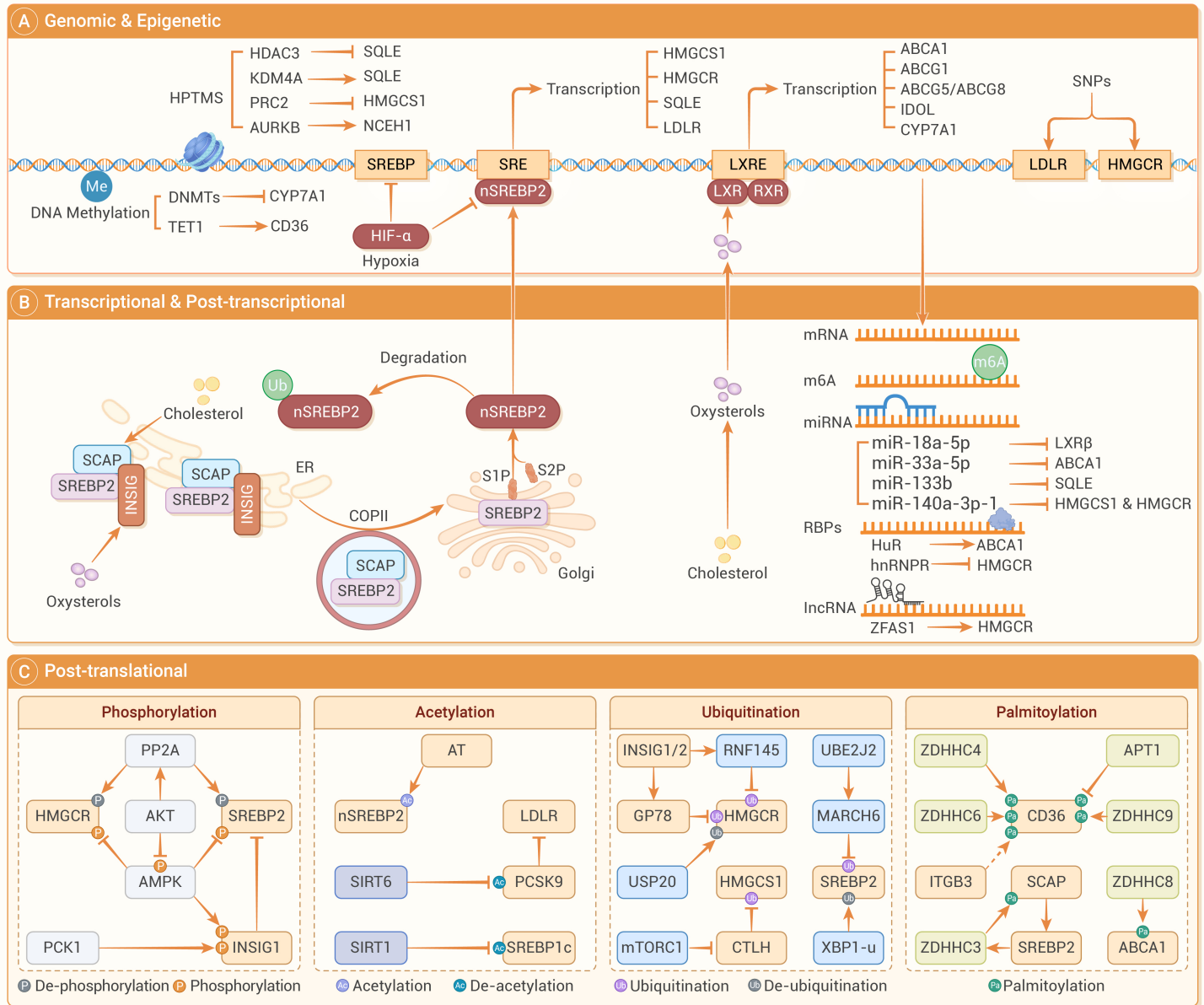


Figure 3. Hierarchical dynamic regulatory network of cholesterol metabolism Multilevel regulatory mechanisms governing cholesterol metabolism are depicted as follows: (A) Genomic and epigenetic regulation. Epigenetic modifications, including DNA methylation and histone modifications, govern the upstream transcription of cholesterol-related genes. At the core transcriptional level, nSREBP2 binds SREs to drive cholesterol synthesis and uptake genes, a process inhibited by HIF-1 α during hypoxia. Conversely, oxysterol-activated LXR/RXR heterodimers bind LXREs to upregulate cholesterol efflux and catabolism genes. Additionally, SNPs can directly modulate LDLR and HMGC1 expression. (B) Transcriptional and post-transcriptional regulation. SREBP2 activation is strictly controlled by intracellular cholesterol levels. Under depletion, the SCAP-SREBP2 complex dissociates from INSIG in the ER, translocates to the Golgi, and is cleaved by S1P/S2P into nuclear-active nSREBP2. Elevated cholesterol or oxysterols promote INSIG binding, retaining the complex in the ER and triggering nSREBP2 degradation. Post-transcriptionally, m6A methylation, miRNAs, RBPs, and lncRNAs precisely modulate target mRNA stability and translation. (C) Post-translational modification regulation. The activity and stability of proteins involved in cholesterol metabolism are dynamically regulated by post-translational modifications, including palmitoylation, ubiquitination, acetylation, phosphorylation and so on.

Other modifications of cholesterol metabolism associated proteins.

SUMOylation proceeds via a sequential three-enzyme cascade: SUMO E1 activating complex SAE1/UBA2, sole E2 conjugase UBC9, and a panel of SUMO E3 ligases.²⁰⁶ Whereas, de-SUMOylation is reversibly executed by Sentrin/SUMO-specific proteases (SENPs).²⁰⁶ The activated NLRP3 inflammasome as a key pro-inflammatory effector to upregulate CD36 transcription, thereby augmenting ox-LDL endocytosis and accelerating foam cell formation in macrophages.²⁰⁷ Conversely, the SUMO protease SENP3 inhibits NLRP3 inflammasome activation by removing SUMOylation of NLRP3, reducing CD36 expression and subsequent ox-LDL accumulation.²⁰⁷

Glycosylation modulates protein folding, stability, subcellular localization and function via covalent attachment of glycan chains to defined amino acid residues.²⁰⁸ It has been verified that N-linked glycosylation at Asn247, Asn321 and Asn417 is indispensable for CD36 intracellular trafficking.²⁰⁹ O-linked glycosylation of LDLR enhances its binding affinity to LDL.²¹⁰ N(e)-

(carboxymethyl) lysine (CML) promotes SCAP glycosylation by upregulating Golgi mannosidase activity, reinforcing its stability and cycling between the ER and Golgi apparatus.²¹¹ By contrast, glycosylation-deficient ABCA1 shows a markedly diminished binding ability to ApoA-I and impairs cellular cholesterol efflux.²¹²

Lactylation is a newly identified post-translational modification in recent years, which regulates protein function through covalent conjugation of lactate groups to lysine residues of proteins.²¹³ HIF-1 α is subject to lactylation under hypoxic conditions, and this modification augments its stability and transcriptional activity,²¹⁴ which in turn suppresses the nuclear binding of SREBP.¹⁴²

CHOLESTEROL METABOLISM IN CANCER AND RELATED DISEASE

Cholesterol metabolic dysregulation is closely associated with the onset and progression of a wide spectrum of diseases. Disruption of cholesterol

regulatory networks perturbs key cellular signaling pathways, microenvironmental homeostasis, and metabolic reprogramming, thereby constituting a central pathogenic basis for major disorders including cardiovascular diseases (CVDs), Alzheimer's disease (AD), and cancer.²¹⁵ In addition, as the essential precursor for steroid hormone biosynthesis, aberrant cholesterol metabolism may further impair age-related organ function, as well as endocrine and reproductive system homeostasis.

Roles of cholesterol metabolism in cancer

As a core component of cell membranes, cholesterol not only maintains cellular structural stability but also provides essential biosynthetic precursors for the rapid proliferation and invasion of tumor cells. Its metabolic reprogramming is one of the hallmarks of cancer.²¹⁶

In tumor initiation. Cholesterol metabolic reprogramming drives tumor initiation by upregulating endogenous synthesis and hijacking lipid metabolic cascade, fueling primary tumor formation. HMGCS1 and HMGR synergistically enhance cholesterol production to promote tumor angiogenesis and inhibit cancer cell apoptosis, ultimately driving primary tumor initiation. In breast cancer, HMGCS1 and HMGR are co-upregulated in early-stage tumor cells. Knockdown of either gene significantly reduces the volume and weight of primary tumors.¹⁴¹ In gliomas, heterogeneous nuclear ribonucleoprotein A2B1 (hnRNP A2B1) induces HMGR by stabilizing m6A-modified *SREBP2* mRNA, thereby triggering endogenous cholesterol synthesis and promoting tumorigenesis.²¹⁷

Liver-specific de novo lipogenesis (DNL) is an indispensable driver of HCC initiation, and ATP-citrate lyase (ACLY) acts as a core molecular hub linking DNL to cholesterol metabolism. ACLY catalyzes the conversion of mitochondrial citrate to cytosolic acetyl-CoA, which is a central carbon source for fatty acid and cholesterol synthesis.²¹⁸ In HCC, Methyltransferase-like 3/14 (METTL3/14) mediates site-specific m6A modification of *ACLY* mRNAs, and then enhances its stability and translational efficiency, directly activating cholesterol metabolic dysregulation and promoting the malignant transformation of hepatocytes into HCC cells (Figure 4).¹⁴⁴

In tumor migration and metastasis. Cholesterol metabolic reprogramming is not only essential for tumor cell proliferation, but also a core driver of tumor migration and metastasis. By regulating molecules involved in cholesterol synthesis, transport and storage, it modulates key steps in the metastatic cascade.

HMGR plays a pivotal regulatory role in the metastasis of multiple tumors. In breast cancer, HMGR-deficient tumor cells are trapped in pulmonary capillaries and fail to infiltrate into the lung parenchyma.¹⁴¹ In hepatocellular carcinoma, the transcription factor Pre-B-cell leukemia transcription factor 3 (PBX3) binds to the promoter region of *HMGR* and upregulates its expression.²¹⁹ In pancreatic cancer, the lncRNA ZFAS1 forms a complex with U2AF2, binds to *HMGR* mRNA, and enhances its stability.¹⁵⁵

Sterol regulatory element binding transcription factor 1 (SREBF1) enhances the expression of the lysosomal cholesterol transporter NPC2 and upregulates autophagy to hydrolyze lipid droplets. This dual regulation enables SREBF1 to actively mobilize cholesterol stored in lipid droplets, providing sufficient lipids for tumor cell migration and adaptation to the metastatic microenvironment.²²⁰⁻²²¹ In colorectal cancer (CRC), activating KRAS mutations promote the overexpression of the cholesterol transporter GRAMD1A, thereby increasing nSREBP2 levels.²²² In prostate cancer, PTEN deletion leads to constitutive expression of the LDLR, which, together with ACAT1-mediated cholesteryl ester synthesis, promotes massive cholesterol sequestration in lipid droplets (Figure 4).²²³

In tumor microenvironment (TME). The tumor microenvironment (TME) constitutes a highly dynamic and interactive ecosystem, within which cholesterol metabolic reprogramming has emerged as a critical regulatory node. It orchestrates tumor cell survival, immune cell functional polarization, and intercellular metabolic crosstalk, ultimately shaping an immunosuppressive microenvironment that supports tumor growth, invasion, and immunotherapy resistance.²²⁴

Tumor-associated macrophages (TAMs) are the dominant innate immune cells in the TME with high plasticity, categorized into two anti-tumor M1 and pro-tumor M2 subtypes. Cholesterol metabolic remodeling determines TAM polarization.²²⁵ In macrophages, 25-HC drives M2-type polarization of

macrophages via the lysosome-GPR155-mTORC1-AMPK α axis.²²⁶ M2-type macrophages rely on enhanced oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) maintain immunosuppressive phenotype,²²⁷ and build a metabolic symbiosis with tumor cells.²²⁸ Therefore, moderate lipid accumulation pushes TAMs toward the M2 phenotype, while excess lipids trigger macrophage apoptosis.²²⁹ Meanwhile, LXR-RXRs signaling prevents lipid accumulation by facilitating cholesterol efflux.¹³⁴ The low-pH conditions in the TME activate LXR and SREBP2 in macrophages, boosting cholesterol biosynthesis and efflux to satisfy the metabolic demands of tumor cells.²³⁰

Pancreatic cancer TAMs exhibit higher levels of SREBP2-mediated cholesterol biosynthesis and ABCG1-dependent cholesterol export.²³¹ Similarly, upregulation of ABCA1 in TAMs is positively correlated with reduced intracellular cholesterol and elevated serum cholesterol levels. Particularly, glioblastoma contains a unique lipid-laden macrophages (LLMs) subset.²³² Cholesterol accumulation in LLMs activates LXR, which transports cholesterol to tumor cells via ABCA1 to accelerate malignancy.²³² However, study found the modulation of apolipoprotein A1 (ApoA-I) restores the phagocytic function of LLMs and reactivates TAM-T cell anti-tumor immunity.²³³ In addition, cytokines including IL-4 and IL-13, together with lactic acid, jointly upregulates CH25H in TAMs, leading to the accumulation of 25-HC, sustaining the immunosuppressive phenotype of TAMs and fostering the formation of "cold tumors".²²⁶

Tumor cells actively regulate their own cholesterol metabolism by targeting the metabolic fitness and activation of T cells, thereby impairing CD8⁺ T cell-mediated adaptive immunity. METTL3-mediated m6A modification of *SCAP* mRNA enhances its translation efficiency, leading to excessive cholesterol secretion into the TME and accumulation in CD8⁺ T cells, which compromises their immune function.²³⁴ In CRC, dual specificity phosphatase 18 (DUSP18) dephosphorylates upstream stimulatory factor 1 (USF1) to reinforce SREBP2-USF1 promoter binding and trigger SREBP2-mediated cholesterol biosynthesis. However, instead of mature cholesterol, this cascade selectively enriches lanosterol, which is secreted into the TME and suppresses the activation of CD8⁺ T cells (Figure 4).²³⁵

In cell death. In recent years, accumulating evidence has demonstrated that dysregulated cholesterol metabolism plays a dual role in tumor cell death. On the one hand, cholesterol deficiency or metabolic disturbance can induce cell death. On the other hand, cholesterol metabolites such as oxysterols can directly trigger cell death programs.

Dysregulation of the cholesterol synthesis pathway is one of the key mechanisms that induce tumor cell death. Statins induce significant apoptosis in a variety of tumor cells by inhibiting HMGR activity.²³⁶⁻²³⁸ Loss of SREBP activity leads to fatty acid desaturation and severe lipotoxicity.²³⁹ Dysregulated cholesterol metabolism can trigger cell death programs by inducing endoplasmic reticulum stress. Altered membrane phospholipid saturation disrupts ER architecture and thereby impairs ER homeostasis.²⁴⁰ Free cholesterol overload increases the ER stress marker CHOP (C/EBP homologous protein), whereas cholesterol esterification inhibitors targeting SOAT1 (ACAT1) also activate activating transcription factor (ATF6), inositol-requiring enzyme (IRE1), PRK-like endoplasmic reticulum kinase (PERK), and unfolded protein response (UPR) sensors.²⁴¹⁻²⁴² Decreased ER cholesterol levels activate SREBF2, which upregulates CYP51A1 to prevent cholesterol accumulation in lysosomes, resulting in lysosomal proton efflux and ultimately inhibiting cell death.²⁴³

Cholesterol metabolites also can exert pro-apoptotic effects under specific contexts. 7-KC has been demonstrated that it can induce cell apoptosis by activating the mitochondrial pathway, and also markedly aggravate cellular oxidative stress in a concentration-dependent manner, subsequently triggering apoptosis.²⁴⁴ Treatment with the antioxidant N-acetylcysteine (NAC) can effectively attenuate this oxidative stress-mediated apoptotic effect.²⁴⁵ In addition, 7 β -hydroxycholesterol (7 β -HC) suppresses the proliferation of human colon carcinoma Caco-2 cells via inducing apoptosis.²⁴⁶ 25-HC induces apoptosis of extravillous trophoblasts by eliciting oxidative stress.²⁴⁷ Cholesterol and 24S-hydroxycholesterol upregulate intracellular iron levels by increasing ROS production, ultimately leading to cell apoptosis rather than ferroptosis.⁴⁷ On the other hand, several cholesterol metabolites exert prominent anti-apoptotic functions. 27-HC promotes tumor cell proliferation and represses apoptosis via the HNF4A/CYP27A1/cholesterol axis.²⁴⁸ Meanwhile,

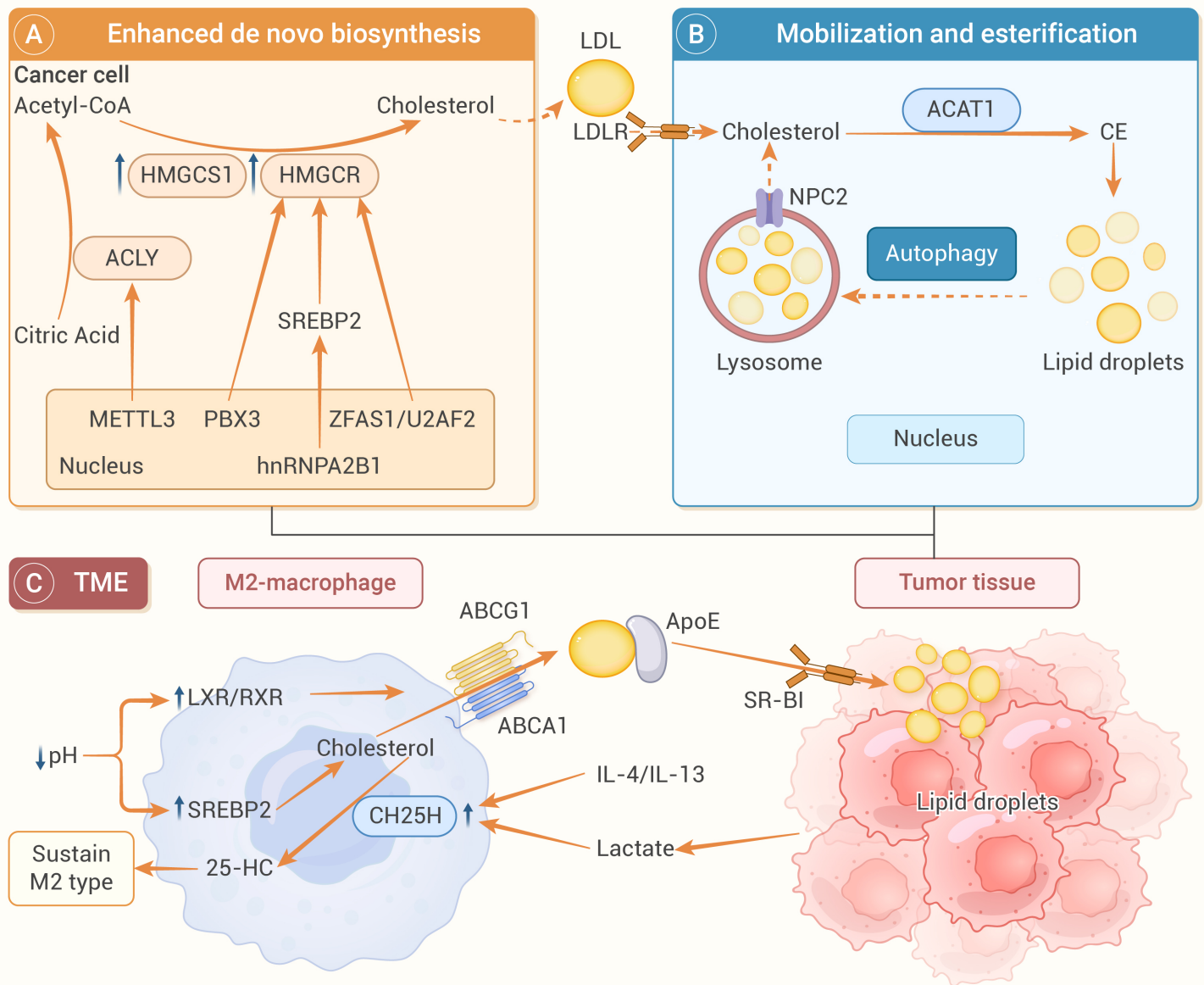


Figure 4. Cholesterol metabolic reprogramming driving tumor progression and shaping the immunosuppressive TME (A) Enhanced de novo cholesterol biosynthesis in tumor cells. Upstream regulators upregulate key cholesterol synthesis enzymes via transcription factor SREBP2, boosting acetyl-CoA-driven endogenous cholesterol production to support the malignant proliferation of tumor cells. (B) Cholesterol mobilization and esterification storage in tumor cells. Tumor cells uptake exogenous LDL cholesterol via LDLR. Free cholesterol is catalyzed by ACAT1 into CE for storage in lipid droplets. Meanwhile, the autophagy-lysosome pathway, mediated by lysosomal cholesterol transporter NPC2, mobilizes cholesterol from lipid droplets for lipid recycling, supporting tumor cell migration and invasion. (C) Metabolic crosstalk in the TME and immunosuppressive microenvironment shaping. Tumor cell-secreted lactate upregulates CH25H in macrophages, catalyzing 25-HC production to sustain the immunosuppressive M2 phenotype. The low-pH TME activates macrophage LXR/RXR signaling and SREBP2, enhancing macrophage cholesterol synthesis and ABCA1/ABCG1-mediated cholesterol efflux. The effluxed cholesterol is taken up by tumor cells via the ApoE-SR-BI axis, forming a metabolic symbiosis between tumor cells and macrophages, which ultimately shapes the immunosuppressive TME and drives tumor malignant progression.

it inhibits docetaxel-induced apoptosis in prostate cancer epithelial cells in a dose-dependent manner (Figure 5).²⁴⁹

Necroptosis is a programmed necrotic cell death pathway regulated by receptor-interacting serine/threonine-protein kinase 1 (RIPK1), RIPK3 and mixed lineage kinase domain-like pseudokinases (MLKL) kinases.²⁵⁰ Distinct from canonical apoptosis, this process can elicit a pro-inflammatory state.²⁵⁰ Necroptosis can be effectively inhibited by Necrostatin-1 (Nec-1), a specific inhibitor of RIPK1 kinase activity.²⁵¹ 24S-HC is the first oxysterol definitively confirmed to induce necroptosis.²⁵² In neuronal cells, 24S-HC treatment neither triggers nuclear fragmentation nor activates caspases, only presents necrotic morphological alterations, and does not cause ATP depletion.⁴⁸ Further studies have demonstrated that ACAT1 catalyzes the conversion of 24S-HC to 24S-HC esters, and administration of ACAT1 inhibitor F12511 can block this necroptotic process.²⁵³ In the cell death model induced by L-norephedrine (L-Nor), increased cholesterol uptake and biosynthesis do not lead to elevated cholesterol levels in the plasma membrane, but instead trig-

ger abnormal cholesterol accumulation in intracellular compartments.²⁵⁴ L-Nor-induced cell death can also be blocked by the necroptosis inhibitor Nec-1.²⁵⁴ In macrophages, when caspase-8 is inhibited, cell death induced by ox-LDL or oxysterols shifts from apoptosis to necroptosis (Figure 5).²⁵⁵

Pyroptosis is a pro-inflammatory form of programmed cell death, which relies on Gasdermin D (GSDMD) family-mediated plasma membrane pore formation and cell lysis.²⁵⁶ Multiple cholesterol-related molecules can regulate the process of pyroptosis. 25-HC induces and exacerbates cellular pyroptosis via activating the P2X purinoceptor 7 (P2X7) receptor and the NLRP3 inflammasome.²⁵⁷⁻²⁵⁸ 27-HC triggers pyroptosis by inducing lysosomal dysfunction and increasing lysosomal membrane permeability.²⁵⁹ Whereas cholesterol promotes the onset of pyroptosis by eliciting endoplasmic reticulum stress.²⁶⁰ LDLR deficiency aggravates NLRP3-mediated excessive maturation and release of IL-1 β and IL-18, thereby further exacerbating cellular pyroptosis, while NLRP3 blockade can significantly ameliorate this pathological effect.²⁶¹ A high-fat diet can also activate the NLRP3 inflamma-

some and induce pyroptosis through the caspase-1 signaling pathway.²⁶² In addition, CD36 induces pyroptosis in macrophages by regulating the uptake of ox-LDL.²⁶³ Simvastatin can inhibit pyroptosis in foam cells, and this effect can be reversed by NLRP3 overexpression (Figure 5).²⁶⁴

Ferroptosis is an iron-dependent form of programmed cell death, driven primarily by lipid peroxidation, and accompanied by massive accumulation of intracellular ROS, loss of plasma membrane integrity, and abnormal mitochondrial morphology.²⁶⁵ Cholesterol synthesis and uptake pathways significantly modulate cellular susceptibility to ferroptosis. Study showed that reduced cholesterol accumulation can lead to the negative regulator glutathione peroxidase 4 (GPX4) depletion, thereby potentiating ferroptosis.²⁶⁶ LILRB1 ablation blocks LDL uptake while elevating SQLE expression to trigger compensatory cholesterol synthesis.²⁶⁷ This adaptive response depletes intracellular squalene levels, and renders cancer cells more vulnerable to ferroptosis.²⁶⁷ The rate-limiting enzyme dihydroorotate dehydrogenase (DHODH) in *de novo* pyrimidine synthesis, can downregulate SQLE expression and thereby induce ferroptosis.²⁶⁸ LXR agonists also exert anti-tumor effects by inducing IDOL-mediated degradation of LDLR and suppressing LDL uptake.¹³⁹ Oxysterols exert a bidirectional regulatory effect on ferroptosis. 25-HC induces ferroptosis in extravillous trophoblasts by eliciting oxidative stress.²⁴⁷ Conversely, long-term exposure of breast cancer and hepatocellular carcinoma cells to 27-HC sustains the persistent expression of GPX4, thereby conferring resistance to ferroptosis.²⁶⁹⁻²⁷⁰ 7-DHC functions as a potent radical-trapping antioxidant that protects cells from ferroptosis. Inhibition of emopamil-binding protein (EBP) blocks 7-DHC synthesis, thereby sensitizing cancer cells to ferroptosis and suppressing tumor growth.²⁷¹ Conversely, inhibition of 7-DHC reductase (DHCR7) prevents the conversion of 7-DHC to cholesterol, leading to 7-DHC accumulation and protection against ferroptosis, as demonstrated in the context of hepatic ferroptosis.²⁷¹⁻²⁷² Lipid transporters involved in cholesterol ester metabolism also modulate ferroptosis sensitivity. In human pancreatic ductal adenocarcinoma (PDAC), the accumulation of polyunsaturated fatty acid-cholesterol ester (PUFA-CE) complexes serves as a marker of ferroptosis resistance. The lipid flippase SLC47A1 maintains PUFA-CE homeostasis through the SLC47A1/ACSL4/SOAT1 pathway, preventing excessive lipid peroxidation and thereby protecting cells from ferroptosis inducers.²⁷³ In addition, CD36 mediates fatty acid uptake in tumor-infiltrating CD8⁺ T cells, thereby triggering lipid peroxidation and ferroptosis (Figure 5).²⁷⁴

Cuproptosis is a copper ion-dependent form of regulated cell death, triggered by copper overload that results in abnormal aggregation of lipoylated enzymes in the TCA cycle and loss of iron-sulfur cluster proteins.²⁷⁵ This process is regulated by multiple molecules including METTL16 lactylation, ferredoxin 1(FDX1), ATPase copper transporting beta (ATP7B), and zinc transporter 1 (ZnT1).²⁷⁶⁻²⁷⁸ Cuproptosis can be antagonized by the Wnt/ β -catenin pathway, which consequently confers drug resistance, and can be specifically induced by copper ionophores such as elesclomol.^{277,279} Cuproptosis can be modulated by dysregulated cholesterol metabolism. In bladder cancer and glioblastoma, delivery of copper ions and relevant drugs via nanocarriers can induce a synergistic effect of cuproptosis and apoptosis in cancer cells, remodel the tumor immune microenvironment, and significantly enhance anti-tumor efficacy (Figure 5).²⁸⁰⁻²⁸¹

Drug resistance. Aberrant cholesterol reprogramming, particularly overactive cholesterol synthesis, confers tumor resistance to chemotherapy via signaling pathway, metabolite pool and lipid homeostasis, blunting clinical anti-tumor therapies. SQLE increases cholesterol content in lipid rafts and enhances the binding capacity of AKT to lipid rafts.²⁸² Activated AKT inactivates glycogen synthase kinase-3 β (GSK-3 β) by phosphorylating it, inhibits ubiquitination-mediated degradation of c-Myc, and ultimately enhances the resistance of drug-resistant tumor cells to cisplatin.²⁸² In CRC, the cholesterol synthesis intermediate(S)-2,3-oxidosqualene generated by SQLE promotes the ubiquitination and degradation of I κ B α , thereby activating the NF- κ B pathway, upregulating the anti-apoptotic gene baculoviral IAP repeat containing 3 (BIRC3), and ultimately mediating CRC resistance to 5-fluorouracil (5-FU).²⁸³ Additionally, in HCC, caspase-3 (CASP3) mediates the cleavage of SREBP2 from the ER to promote cholesterol biosynthesis. This, in turn, drives the activation of the sonic hedgehog signaling pathway, leading to resistance to sorafenib/lenvatinib treatment.²⁸⁴

Roles of cholesterol metabolism in cardiovascular diseases

Dysregulation of cholesterol metabolism is a core pathological driver of CVDs, with atherosclerosis being its most common and devastating clinical manifestation. Abnormal cholesterol accumulation triggers vascular wall inflammation, lipid deposition, and structural remodeling, ultimately leading to plaque formation, vascular stenosis, and acute cardiovascular events. These pathological processes are closely associated with dysregulated cholesterol uptake, intracellular trafficking, storage, and efflux within vascular cells.

The development and progression of atherosclerosis are tightly linked to imbalanced cholesterol metabolism. Circulating LDL-C penetrates the vascular endothelium and becomes retained within the subendothelial space, where it undergoes oxidative modification to form ox-LDL. The accumulation of ox-LDL initiates local inflammatory responses and promotes the recruitment of circulating monocytes into the vascular intima, where these monocytes subsequently differentiate into macrophages.²⁸⁵ Macrophages take up excessive ox-LDL via scavenger receptors CD36, leading to massive accumulation of cholesteryl esters in lipid droplets and formation of foam cells, which represents a hallmark event during the early stage of atherosclerotic plaques development.²⁸⁶⁻²⁸⁷ Beyond serving as lipid reservoirs, foam cells actively secrete pro-inflammatory cytokines, including IL-6 and TNF- α , thereby amplifying vascular inflammation and further aggravating endothelial dysfunction.²⁸⁶

Given the pivotal role of macrophage cholesterol overload in atherogenesis, multiple cholesterol-sensing pathways have evolved to maintain intracellular cholesterol homeostasis. LXRs, as key regulators of cholesterol efflux, exert anti-atherosclerotic effects by activating ABCA1/ABCG1 in macrophages to promote cholesterol efflux to HDL.¹³⁶ Additionally, LXRs inhibit the NF- κ B signaling pathway, reducing the production of pro-inflammatory mediators and limiting plaque inflammation.²⁸⁸ However, certain oxysterols generated during atherosclerosis may counteract these protective mechanisms and accelerate plaque progression. Macrophage-derived 25-HC promotes atherosclerotic plaque progression independently of the classical LXR/SREBP pathways. On the one hand, 25-HC alters membrane-accessible cholesterol in macrophages, facilitating TLR4 clustering within lipid rafts and activating downstream p38/IRF3/NF- κ B signaling.²⁸⁹ On the other hand, 25-HC acts in a paracrine manner on vascular smooth muscle cells (VSMCs), reducing membrane-accessible cholesterol and disrupting PDGFR β -AKT/ERK signaling.²⁸⁹ Through the coordinated modulation of inflammatory signaling and vascular remodeling, 25-HC exacerbates plaque inflammation and necrotic core formation, impairs fibrous cap stability, and ultimately increases plaque vulnerability.

Roles of cholesterol metabolism in Alzheimer's disease (AD)

The brain is a cholesterol-rich organ.²⁹⁰ Consequently, cholesterol homeostasis within the central nervous system is maintained almost exclusively through *de novo* synthesis and intercellular transport.²⁹¹ Dysregulation of cholesterol metabolism has emerged as a key pathogenic driver of Alzheimer's disease (AD), a progressive neurodegenerative disorder characterized by cognitive decline and neuronal loss.²⁹¹⁻²⁹³

AD is defined by two hallmark pathologies, β -amyloid (A β) aggregation and hyperphosphorylated tau protein (pTau) accumulation. Amyloid precursor protein (APP) is a transmembrane protein that undergoes two competing cleavage pathways. The non-amyloidogenic pathway (cleavage by α -secretase) produces soluble APP α , which exerts neuroprotective effects.²⁹⁴ In contrast, the amyloidogenic pathway (sequential cleavage by β -secretase [BACE1] followed by γ -secretase) generates toxic A β .²⁹⁴ Concurrently, reduced cerebral cholesterol levels promote tau hyperphosphorylation, driving tau dissociation from microtubules and its subsequent aggregation into neurofibrillary tangles (NFTs), another hallmark neuropathological feature of AD.²⁹⁵

The lipid raft hypothesis provides a central mechanistic framework linking cholesterol metabolism to AD.²⁹⁶ Lipid rafts are cholesterol-enriched membrane microdomains essential for memory consolidation, a process critically dependent on membrane cholesterol homeostasis.²⁹⁶ Alterations in membrane cholesterol content disrupt lipid raft integrity and consequently affect the localization and activity of proteins involved in APP processing and

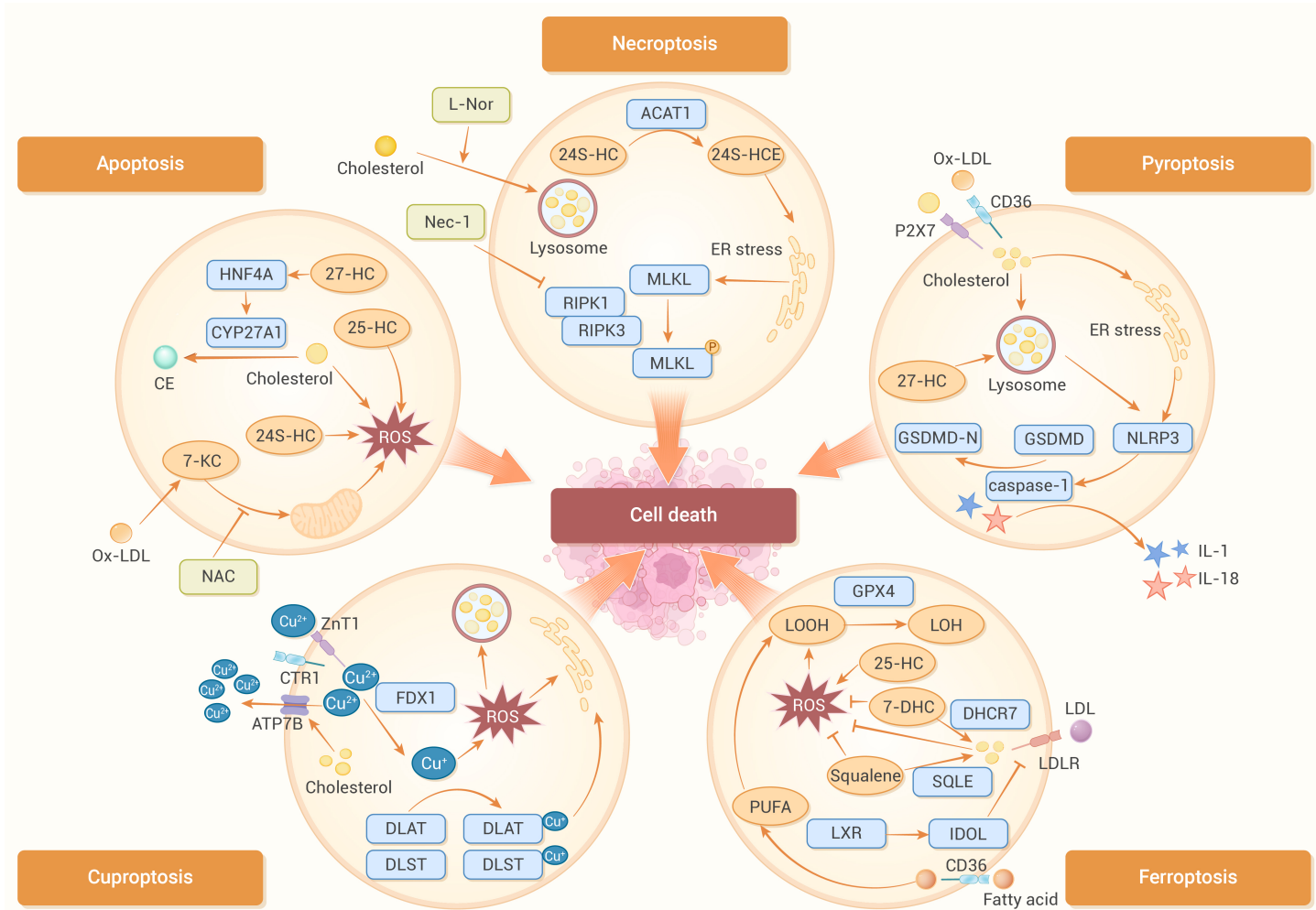


Figure 5. Roles of cholesterol and its associated metabolites in cell death Cholesterol and its metabolites are core regulators of five types of programmed cell death: apoptosis, necroptosis, pyroptosis, ferroptosis, and cuproptosis. They trigger or modulate distinct cell death programs by inducing ROS production, endoplasmic reticulum stress and lysosomal dysfunction, and targeting key signaling axes, including the mitochondrial damage pathway in apoptosis, RIPK1/RIPK3/MLKL cascade in necroptosis, NLRP3/Caspase-1/GSDMD inflammatory pathway in pyroptosis, GPX4-mediated lipid peroxidation in ferroptosis, and FDX1-related lipoylation regulation in cuproptosis. Meanwhile, lipid molecules such as ox-LDL and fatty acids participate in the crosstalk between cholesterol metabolism and cell death pathways via receptors like CD36, which jointly mediate cellular homeostasis imbalance and pathological injury.

tau regulation. In the brain, cholesterol is primarily synthesized by astrocytes and delivered to neurons via apolipoprotein E (ApoE). While ApoE2 efficiently mediates neuronal cholesterol transport, ApoE4 impairs this process.²⁹⁷ Neuronal cholesterol deficiency disrupts lipid raft integrity, leading to impaired memory formation, tau hyperphosphorylation and NFT formation, while simultaneously enhancing β - γ -secretase activity and promoting excessive A β production.²⁹⁶ These mechanistic findings are supported by clinical and pathological evidence. Postmortem studies have provided direct evidence of cholesterol metabolic dysfunction in AD brains, including reduced plasma membrane cholesterol levels, lipid raft disruption, and region-specific disturbances in cholesterol homeostasis.²⁹⁸⁻³⁰¹

Cholesterol metabolism in endocrine dysfunction and aging

Cholesterol serves as the fundamental precursor for steroid hormone biosynthesis, and its metabolic dysregulation drives systemic aging by disrupting steroidogenesis and endocrine homeostasis.³⁰²

Ovarian aging represents the earliest manifestation of female aging. Dysregulation of the mevalonate pathway in granulosa cells leads to meiotic defects and chromosomal aneuploidy in oocytes.³⁰³ Moreover, impaired ACAT1-mediated conversion of cholesterol to cholesteryl esters compromises oocyte mitophagy, resulting in mitochondrial dysfunction, reduced ATP production, and excessive ROS accumulation.³⁰⁴ Significant downregulation of cholesterol synthesis and transport genes reduces steroidogenic substrate availability and decreases CYP19A1 expression, thereby promoting early

ovarian aging (DOR).³⁰⁵ Similar to ovarian aging, testicular dysfunction is also an early hallmark of male aging and is closely associated with impaired cholesterol metabolism. Testosterone biosynthesis is highly dependent on cholesterol supply within Leydig cells, and impaired cholesterol utilization accelerates male reproductive endocrine decline.³⁰⁶ Silencing of *Hmgcs2* in mouse Leydig cells directly induces premature senescence in young cells.³⁰⁷ Cellular communication network factor 5 (CCN5) disrupts cholesterol transporter homeostasis, leading to lipid droplet depletion and diminished testosterone synthesis, whereas CCN5 knockdown reverses these aging phenotypes.³⁰⁸ Beyond reproductive aging, cholesterol metabolic disturbances are also closely linked to systemic aging. The cholesterol biosynthetic pathway activates the transcription factor ERR α , triggering mitochondrial dysfunction, ROS generation, and DNA damage, thereby directly driving cellular senescence.³⁰⁹ In addition, accumulation of oxysterols impairs ABCA1-mediated lysosomal transport, directly accelerating brain cell aging.³¹⁰ Thus, early detection of lipid metabolic abnormalities holds significant value not only for cancer prevention but also for the prevention of age-related dysfunction across multiple organ systems.

Cholesterol-based crosstalk of other diseases with tumor and therapy

Dysregulation of cholesterol metabolism has emerged as a core molecular hub linking metabolic disorders to tumor initiation and progression. Type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD) constitute a "metabolic syndrome cluster" with a high comorbidity rate, and their crosstalk with tumors is tightly regulated by aber-

rant cholesterol metabolism.

In patients with T2DM, elevated LDL-C and reduced HDL-cholesterol (HDL-C) are not only hallmarks of metabolic dysfunction but also key synergistic factors driving the progression of MASLD.³¹¹ Obesity and insulin therapy exacerbate this response by further aggravating cholesterol dysregulation. In patients with MASLD, T2DM significantly increases overall cancer risk, and cancer represents one of the leading causes of death.³¹² Dyslipidemia characterized by elevated LDL-C and reduced HDL-C is positively correlated with the triglyceride-glucose (TyG) index and serves as an independent risk factor for mortality in young T2DM patients.³¹³ In patients with MASLD, the expression of ACLY is markedly upregulated, which favors the formation of a lipid-rich microenvironment and promotes malignant transformation of hepatocytes.²¹⁸ MASLD can also drive CRC liver metastasis (CRLM) by inducing the upregulation of hepatic Golgi membrane protein 73 (GP73).³¹⁴

A high-cholesterol diet disrupts intestinal microbiota homeostasis, leading to the enrichment of pro-inflammatory microbiota and decreased production of anti-inflammatory metabolites.³¹⁵ These changes promote intestinal barrier dysfunction and systemic inflammation, thereby accelerating the progression of MASLD to non-alcoholic steatohepatitis (NASH). Dietary fiber, especially soluble cereal fiber, exerts pleiotropic effects by regulating cholesterol metabolism. On the one hand, it improves glucose metabolism in T2DM patients by modulating intestinal hormones, inhibiting glucose-dependent insulinotropic polypeptide (GIP), and regulating glucagon-like peptide-1 (GLP-1) and peptide YY (PYY).³¹⁶ On the other hand, it binds bile acids in the intestine, inhibits cholesterol absorption, optimizes cholesterol profiles, reduces LDL-C levels, ameliorates metabolic disorders, and suppresses chronic inflammation, thereby indirectly lowering cancer risk (Figure 6).³¹⁷

TARGETING AND MONITORING CHOLESTEROL METABOLISM FOR CANCER THERAPY

Cholesterol metabolic reprogramming is widely recognized as a hallmark of cancer, driving tumor initiation, progression, metastasis, and chemoresistance.^{1,216} Notably, dysregulated cholesterol homeostasis in both cancer cells and the TME confers a distinct metabolic vulnerability, which has emerged as a crucial target for anti-tumor therapy (Table 2).

Directly target cholesterol

This strategy aims to cut off cholesterol supply for rapidly proliferating cancer cells by directly targeting key steps in cholesterol metabolism. Leveraging the high dependence of tumors on cholesterol homeostasis, its efficacy has been validated in multiple preclinical and early-phase clinical studies. To meet the demand for cell membrane biosynthesis, the endogenous cholesterol synthesis pathway is often significantly upregulated in various cancers.^{155,164,219} HMGCR, the rate-limiting enzyme of this pathway, is a well-validated therapeutic target. In triple-negative breast cancer, statins (HMGCR inhibitors) exert a synergistic effect by suppressing HMGCR-driven cholesterol synthesis and reducing cancer cell viability.^{318,329,333,337,354} In HCC, simvastatin blocks the upregulation of HMGCR, which lowers intracellular cholesterol levels and significantly inhibits tumor metastasis.^{219,322} Another key enzyme SQLE promotes cancer cell proliferation.³⁴⁰ It also mediates resistance to chemotherapy and immunotherapy.^{283,341} Targeting SQLE with terbinafine can restore the sensitivity of cancer cells to 5-fluorouracil, cisplatin and anti-PD-1 immunotherapy.^{282,341}

Cancer cells often hijack cholesterol uptake pathways to compensate for metabolic demands. LDLR, the major receptor for LDL cholesterol endocytosis, is overexpressed in *PTEN*-deficient prostate cancer, promoting cholesterol accumulation and enhancing invasiveness.²²³ Targeting LDLR via antibody therapy or small-molecule inhibitors can reduce cholesterol supply to tumor cells. Additionally, NPC1L1 is a potential target for cancers with high cholesterol uptake. In preclinical models, NPC1L1 inhibitors ezetimibe reduces dietary cholesterol absorption and inhibit CRC cell proliferation by limiting extracellular cholesterol availability.² PCSK9 promotes LDLR degradation. Its inhibitors increase LDLR expression on the cancer cell surface, enhance cholesterol clearance, and suppress tumor growth.^{171,355}

Cholesterol efflux and esterification are critical for maintaining intracellular cholesterol homeostasis and supporting tumor cell survival. ABCA1 and ABCG1 are often downregulated in cancer to retain cholesterol. Restoring

ABCA1 expression by activating the RNA-binding protein HuR can promote cholesterol efflux, reduce foam cell formation in the tumor microenvironment, and inhibit glioblastoma progression.^{151,232} In contrast, ACAT1 is upregulated in prostate cancer and HCC. ACAT1 inhibitors Avasimibe block cholesteryl ester synthesis, leading to free cholesterol accumulation and ER stress-induced cancer cell apoptosis.²²³ In *PTEN*-deficient prostate cancer, combination therapy with ACAT1 inhibitors and statins synergistically suppresses tumor invasiveness by disrupting cholesterol storage.²²³

Target upstream regulators

The upstream regulatory network of cholesterol metabolism, encompassing transcription factors, signaling pathways, and epigenetic modifiers, synergistically regulates the global metabolic program of cancer cells. Targeting these regulators enables systematic regulation of cholesterol homeostasis, holding promise for overcoming the adaptive resistance of single-target therapies.

SREBPs are core transcriptional activators of cholesterol synthesis and uptake, and are highly activated in many cancers. Thus, targeting SREBP represents a key therapeutic strategy. Betulin significantly enhances the sensitivity of prostate cancer to ferroptosis.³⁴³ PF-429242 inhibits the growth of CRC cells by targeting S1P.³⁴⁴ Fatostatin induces ferroptosis in glioblastoma and apoptosis in prostate tumor cells.³⁴⁵⁻³⁴⁶ Melittin suppresses ovarian cancer growth by inhibiting the nuclear translocation of SREBP1.³⁴⁷ In pancreatic cancer and glioblastoma, the mTORC1 inhibitor rapamycin reduces the dissociation of SREBP2 from the ER and its nuclear translocation, thereby inhibiting the self-renewal of cancer stem cells.³⁵⁶

LXR activates cholesterol efflux and bile acid synthesis, and its dysfunction promotes immunosuppression in the TME. LXR agonists T0901317 upregulate the expression of ABCG5/ABCG8 in colorectal cancer, enhancing cholesterol excretion and inhibiting tumor growth.^{138,348} Additionally, LXR activation reduces PD-L1 expression in cancer cells by inhibiting IDOL-mediated LDLR degradation, and synergizes with immune checkpoint inhibitors to restore CD8+ T cell function.^{139,235,349}

Epigenetic alterations contribute to dysregulated cholesterol metabolism in cancer. The m6A methyltransferase METTL3 mediates m6A modification of SCAP mRNA, enhancing its translation and driving cholesterol synthesis in HCC.²³⁴ METTL3 inhibitors can reduce SCAP expression, suppress cholesterol accumulation, and enhance the sensitivity of HCC to anti-PD-1 therapy.²³⁴ Similarly, the DNA methyltransferase DNMT3A induces hypermethylation of the *MEF2A* promoter, downregulating CYP7A1 and reducing cholesterol catabolism in NAFLD-associated HCC.¹¹⁷ DNMT3A inhibitors can restore *CYP7A1* expression, promoting bile acid synthesis and cholesterol clearance. Histone modifiers such as the histone demethylase KDM4A activate *SQLE* transcription by removing H3K9me3.¹²¹ Small molecules targeting KDM4A can inhibit *SQLE* expression and block bladder cancer growth.

Target downstream effectors

Cholesterol metabolism exerts pro-tumor effects through downstream effectors. Targeting these effectors disrupts the functional outputs of cholesterol homeostasis dysregulation while addressing both intrinsic and extrinsic oncogenic mechanisms of cancer cells. Cholesterol metabolites act as signaling molecules to promote tumor progression and immunosuppression. 25-HC in TAMs activates the GPR155-AMPK pathway in macrophages, sustaining their M2-like immunosuppressive phenotype.²²⁶ In preclinical models, CH25H inhibitors reduce 25-hydroxycholesterol levels, restore the anti-tumor activity of macrophages, and enhance the efficacy of PD-1 blockers.²²⁶

Cells in the TME rely on cholesterol metabolism to support tumor growth. In glioblastoma, LLMs phagocytose myelin debris and transfer cholesterol to tumor cells via ABCA1.²³² Targeting ABCA1 in LLMs with small interfering RNA (siRNA) blocks cholesterol transfer and inhibits glioblastoma cell proliferation.²³² In colorectal cancer, DUSP18-mediated SREBP2 activation in cancer cells leads to lanosterol accumulation in the TME, inhibiting CD8+ T cell activation. DUSP18 inhibitors reduce lanosterol levels and restore anti-tumor immunity.²³⁵ Cancer stem cells (CSCs) rely on cholesterol metabolism to maintain self-renewal and drug resistance. The lipid flippase solute carrier family 47 member 1 (SLC47A1) regulates polyunsaturated fatty acid-

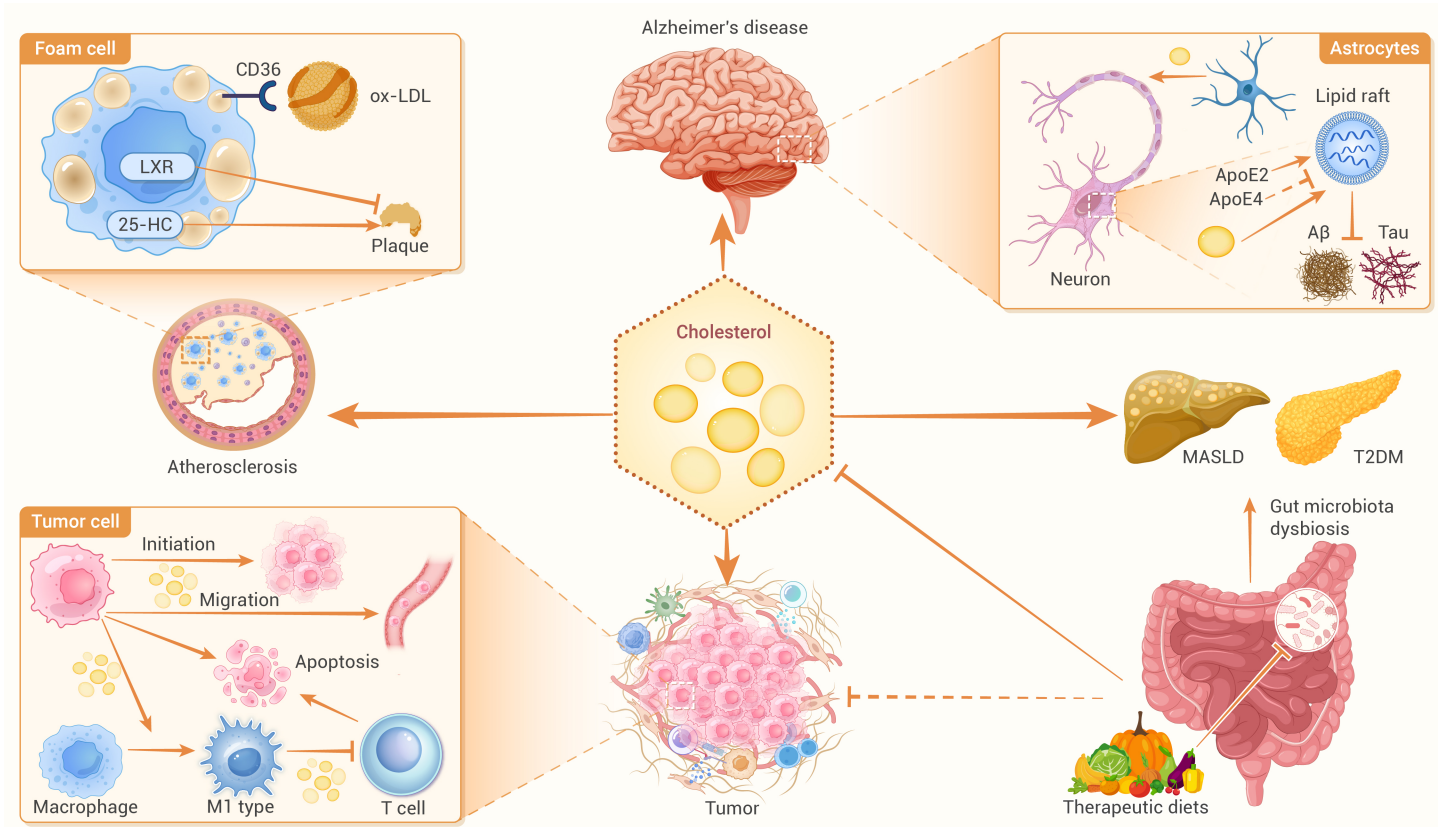


Figure 6. Pathological roles of dysregulated cholesterol metabolism in major diseases and crosstalk between metabolic disorders and cancer Dysregulated cholesterol metabolism acts as a central hub driving the pathological processes of multiple diseases. In atherosclerosis, macrophages excessively take up ox-LDL via CD36 to form foam cells and promote plaque development. 25-HC exacerbates plaque progression, whereas LXR signaling exerts anti-atherogenic effects. In Alzheimer's disease, ApoE4-mediated impairment of cholesterol transport disrupts lipid raft integrity, promoting A β plaque formation and tau hyperphosphorylation, whereas ApoE2 maintains lipid raft stability. In cancer, cholesterol metabolic reprogramming supports tumor initiation, migration, and immune evasion by inhibiting T-cell activation and inducing macrophage polarization toward an M2 phenotype. In metabolic disorders, dysregulated cholesterol metabolism links T2DM and MASLD, and gut microbiota dysbiosis exacerbates metabolic dysfunction and tumor progression via bidirectional crosstalk, while dietary fiber can ameliorate cholesterol imbalance.

cholesteryl ester (PUFA-CE) homeostasis in CSCs of PDAC, promoting ferroptosis resistance. SLC47A1 inhibitors disrupt PUFA-CE synthesis, induce ferroptosis, and inhibit tumor progression.²⁷³

Nutritional and microbiota-based interventions

Apart from pharmacotherapy, a growing body of evidence suggests that dietary and microbiota-based strategies hold potential in improving cholesterol metabolism, alleviating chronic inflammation, and promoting long-term metabolic health. Dietary fiber, omega-3 fatty acids, plant sterols, and probiotic/prebiotic interventions can reshape cholesterol trafficking dynamics and systemic metabolic homeostasis.

Dietary fiber exerts pleiotropic effects within the intestinal tract. Dietary fiber inhibits the micellar formation of cholesterol, thereby reducing intestinal cholesterol absorption and enhancing fecal sterol excretion.³⁵⁷ Dietary fiber can also bind bile acids in the intestinal lumen, diminishing their enterohepatic return to the liver and consequently promoting the hepatic conversion of cholesterol into bile acids.³⁵⁸ Omega-3 fatty acids modulate the distribution of cholesterol within membranes and, through the generation of specialized pro-resolving mediators (SPMs), attenuate foam cell formation.^{359–361} Plant sterols, structurally analogous to cholesterol, suppress intestinal cholesterol absorption via a classical substrate competition mechanism.³⁶² They displace cholesterol from mixed micelles, reducing its solubility and absorptive bioavailability.^{363–364} Probiotics and prebiotics support cholesterol homeostasis via the gut microbiota-bile acid signaling axis, an effect mediated largely by bile salt hydrolase (BSH)-producing bacteria, such as *Lactobacillus* and *Bifidobacterium* species.³⁶⁵ BSH catalyzes the deconjugation of conjugated bile acids, reducing their lipophilicity and thereby curtailing intestinal reabsorption while augmenting fecal bile acid excretion.³⁶⁶ BSH profoundly remodels the composition and distribution of the bile acid pool, enabling fine-tuned regulation of the farnesoid X receptor (FXR) and Takeda G protein-

coupled receptor 5 (TGR5) signaling pathways.³⁶⁷ Collectively, these gut microbiota-nutrition axis strategies may offer safer and more sustainable options for early disease prevention and precision intervention.

Emerging biomarkers for precision management

Beyond conventional lipid profiles, a growing array of emerging biomarkers facilitates earlier identification of high-risk individuals and enables the implementation of personalized prevention strategies. These include the apolipoprotein B/apolipoprotein A-I (ApoB/ApoA-I) ratio, remnant cholesterol, ox-LDL, oxysterols, bile acid signatures, and metabolomics-based lipid profiling.

The ApoB/ApoA-I ratio reflects the balance between cholesterol deposition and reverse cholesterol transport. ApoB is the principal structural protein of LDL, VLDL, and IDL, whereas ApoA-I is the major protein constituent of HDL.^{368–369} Dysregulation of the ApoB/ApoA-I ratio is causally associated with cardiometabolic diseases, including ischemic heart disease, aortic aneurysm, and cerebral ischemic disease.³⁷⁰ Remnant cholesterol refers to the cholesterol content carried by triglyceride-rich lipoprotein remnants, and it is recognized as a highly pro-inflammatory lipid component that promotes endothelial dysfunction, vascular inflammation, and atherosclerotic plaque formation.^{371–372} Ox-LDL, the biologically active product of oxidized LDL, not only mediates macrophage recognition and endocytosis of cholesterol via CD36, but also activates inflammatory signaling pathways such as NF- κ B.^{373–374} Accordingly, elevated ox-LDL levels signify dysregulated lipid metabolism and chronic inflammatory activity.^{375–376} Oxysterols, oxygenated derivatives of cholesterol including 27-HC, 25-HC, and 24S-HC, function as potent signaling molecules that modulate LXR activity, immune responses, inflammatory processes, and tumor progression, thereby providing complementary information beyond that offered by traditional lipid profiles.^{42,377–378} Bile acids regulate diverse physiological processes through activation of receptors such as

Table 2. Cancer Therapies Targeting Cholesterol Metabolism.

Targets	Drugs	Cancers	References
HMGCR	Simvastatin	Breast cancer	318
		Prostate cancer	319
		Gastric cancer	320
		Colorectal cancer	321
		Hepatocarcinoma	322
		Lung cancer	323
		Glioblastoma	324
		Melanoma	325
		Cholangiocarcinoma	326
		Osteosarcoma	327
		Leukemia	328
	Atorvastatin	Breast cancer	329
		Prostate cancer	330
		Liver cancer	331
SQLE	Lovastatin	Leukemia	332
		Breast cancer	333
		Ovarian cancer	334
		Colorectal cancer	335
	Pitavastatin	Pancreatic cancer	336
		Breast cancer	337
		Liver cancer	338
		Cervical cancer	339
	Terbinafine	Colorectal cancer	340
		Hepatocarcinoma	341
SCAP-SREBPs	MiR-205	Prostate cancer	342
	Betulin	Prostate cancer	343
	PF-429242	Renal cell carcinoma	344
	Fatostatin	Gioblastoma	345
		Prostate cancer	346
LXR	Melittin	Ovarian cancer	347
	TO901317	Lung cancer	348
	GW3965	Ovarian cancer	349
SR-B1	BLT-1	Leukemia	350
		Melanoma	351
SOAT1	Avasimibe	Gallbladder cancer	352
		Hepatocarcinoma	186
		Breast cancer	353

FXR and TGR5.³⁷⁹⁻³⁸⁰ FXR is preferentially activated by primary bile acids, whereas TGR5 exhibits higher affinity for secondary bile acids.³⁸¹⁻³⁸² Alterations in bile acid composition reflect changes in hepatic cholesterol metabolism, gut microbial activity, and systemic metabolic homeostasis.³⁸³⁻³⁸⁵ Metabolomics-based lipid profiling enables comprehensive characterization of hundreds to thousands of lipid species, including cholesterol metabolites, oxysterols, phospholipids, sphingolipids, and bile acids.³⁸⁶ This high-resolu-

tion analytical approach can reveal subtle metabolic perturbations that may precede overt clinical manifestations, thereby enabling earlier detection of disease susceptibility. Collectively, these emerging biomarkers hold significant promise for the early detection and precision management of cholesterol metabolism disorders.

CONCLUSION AND PERSPECTIVE

Dynamic regulation of cholesterol metabolism is a key determinant of tumorigenesis and cancer therapies. Cholesterol not only as a structural component of cellular membranes but also as a key signaling molecule that modulates oncogenic pathways, immune cell function, and the tumor microenvironment. Dysregulated cholesterol homeostasis, driven by alterations in uptake (LDLR), de novo synthesis (SREBP2/HMGCR), storage (ACAT1), and efflux (ABCA1/ABCG1), drives cancer cell proliferation, survival, and metastasis. Cholesterol-rich membrane microdomains (lipid rafts) serve as platforms for growth factor receptors and integrins, amplifying pro-survival signals such as PI3K/AKT and MAPK pathways. Furthermore, cholesterol metabolites such as oxysterols serve as ligands for LXRs and nuclear receptors, controlling gene expression programs with cell cycle progression and EMT. In T cells, cholesterol maintains plasma membrane fluidity and TCR clustering, whereas excessive cholesterol can trigger T cells exhaustion and dysfunction. The balance between cholesterol synthesis and uptake regulates effector and memory T cell differentiation. In tumor-associated macrophages (TAMs), cholesterol accumulation induces an immunosuppressive M2-like phenotype, while ABC transporters mediated efflux can restore antigen presentation and pro-inflammatory functions. Regulatory T cells (Tregs) reprogram cholesterol metabolism to sustain immunosuppressive function in the lipid-rich TME, limiting immunotherapy efficacy. Thus, pharmacological modulators of cholesterol homeostasis, including statins (HMGCR inhibitors), ACAT inhibitors (Avasimibe), and LXR agonists, have shown promising preclinical effects in remodeling the immunosuppressive TME and enhancing immune checkpoint blockade efficacy. Given the context-dependent nature of cholesterol regulation, optimized treatment timing, dosage, and combination strategies are essential to avoid disrupting beneficial anti-tumor immunity.

Future research should move beyond static bulk measurements to characterize the dynamic cholesterol flux in specific cell types and subcellular compartments. Advances in single-cell metabolomics, imaging mass spectrometry, and lipid biosensors enable real-time, high-resolution mapping of cholesterol distribution and utilization in the TME, which is critical for delineating its context-dependent pro- or anti-tumorigenic effects. Moreover, cholesterol metabolism also operates within an integrated metabolic network, cross talking with fatty acid oxidation, glycolysis, and glutaminolysis to collectively determines cell fate. Deciphering how cholesterol synthesis integrates with these pathways under nutrient and therapeutic stress will reveal new targets for tumor metabolic intervention.

However, a major challenge stems from the dual role of cholesterol: it supports physiological immunofunction while being hijacked by tumors to fuel malignant progression. Future efforts should focus on developing therapies that selectively target cholesterol handling in cancer cells or immunosuppressive subsets (e.g., Tregs, TAMs) while preserving effector T cells anti-tumor activity. Precision delivery strategies, including antibody-drug conjugates, TME-responsive nanoparticles, and TME-activated prodrugs, offering viable solutions for this selective modulation. Additionally, robust predictive biomarkers are urgently needed to stratify patients who may benefit from cholesterol-modulating therapies. Candidates include tumor expression of cholesterol metabolic genes (SREBP2, HMGCR, ABCA1), circulating oxysterol levels, TME lipidomic profiles, and genetic variants in cholesterol metabolism pathways. Beyond their catalytic roles, some enzymes such as HMGCR, SREBPs, and LXRs may exert non-metabolic functions through protein-protein interactions or transcriptional programs. Mapping these "moonlighting" activities could reveal unexpected therapeutic targets. Emerging evidence suggests that gut microbiota influence systemic and intratumoral cholesterol metabolism via production of secondary bile acids and short-chain fatty acids, providing novel avenues for dietary and probiotic-based immunotherapy adjuvants.

In conclusion, the dynamic regulation of cholesterol metabolism stands at the crossroads of tumor biology and immunology. Integrating mechanistic insights into cholesterol trafficking and signaling with TME immune characteristics will guide the rational design of targeted combination therapies that exploit metabolic vulnerabilities. The next decade will witness the clinical translation of these finding, establishing cholesterol metabolism as a key pillar of next-generation immuno-oncology strategies.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.