

Review Article

The role of cholesterol metabolism in cancer

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Abstract: Cholesterol plays an important role in cancer development. Both clinical and experimental studies have found that hypercholesterolemia and a high-fat high-cholesterol diet can affect cancer development. External cholesterol can directly activate the oncogenic Hedgehog pathway, and internal cholesterol can induce mTORC1 signaling. Cholesterol is a key component of lipid rafts, which are the major platforms for signaling regulation in cancer, and chelating membrane cholesterol is an effective anti-cancer strategy that disrupts the functions of lipid rafts. Cholesterol metabolism is often reprogrammed in cancer cells. Targeting cholesterol metabolism as a new therapeutic approach has received increasing attention. Here, we summarize some key molecular mechanisms supporting the use of anti-cholesterol therapy for cancer treatment.

Keywords: Cancer, cholesterol, metabolism, oncogenic signaling

Introduction

Cholesterol has received increasing attention due its role in carcinogenesis. Clinical and experimental evidence supports that changes in cholesterol metabolism is involved in cancer development [1]. On the one hand, increased cholesterol levels are associated with a higher cancer incidence, and cholesterol-lowering drugs (e.g., statins) exhibit beneficial effects by reducing the risk and mortality of cancer, such as breast, prostate and colorectal cancer; on the other hand, cancers such as bladder and lung cancer are not associated with cholesterol levels, and statins may present carcinogenic properties [2-6]. Here, we summarize the current studies investigating the relationship between cholesterol metabolism and cancer.

Hypercholesterolemia and cancer

Increased serum cholesterol levels have been reported to be positively correlated with a higher risk of developing cancers, such as colon, rectal, prostatic and testicular cancer [7, 8]. A meta-analysis suggested that dietary cholesterol intake increases the risk of breast cancer. The pooled relative risk with a 95% confidence

interval of breast cancer in the highest vs lowest categories of dietary cholesterol intake was 1.29 (1.06-1.56). According to the dose-response analysis, a nonlinear relationship exists between dietary cholesterol and breast cancer, and this association was statistically significant when cholesterol intake was greater than 370 mg/d [9].

Observations based on cancer models further support the positive relationship between hypercholesterolemia and carcinogenesis. Using the murine MMTV-PyMT breast cancer model, it was found that a high cholesterol diet could reduce the tumor formation latency and enhance the growth and metastasis of tumors [10]. Another study found that cholesterol promoted colon cancer formation in azoxymethane (AOM)-treated mice by activating the NLRP3 inflammasome [11]. Moon H et al. found that diet-induced hypercholesterolemia promoted metastasis in orthotopic xenograft PC-3 cells (a prostate cancer cell line) by elevating the expression of the metastasis-associated protein IQGAP1 [12].

Despite these positive correlations between hypercholesterolemia and carcinogenesis, so-

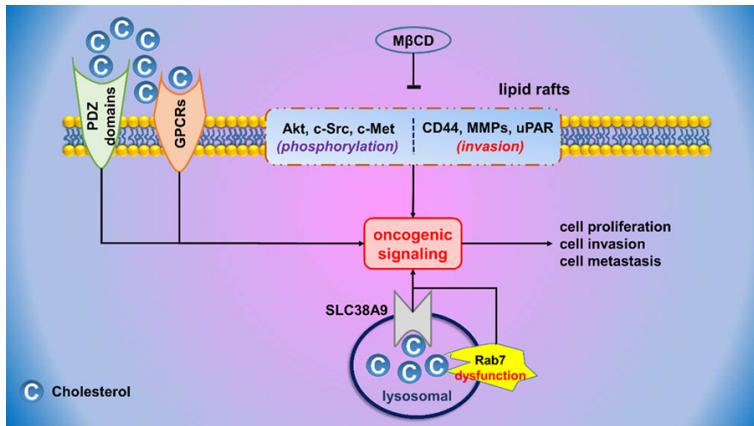


Figure 1. The functions of cholesterol and lipid rafts in oncogenic signaling pathways.

Cholesterol can directly activate oncogenic signaling

As an important component of the cell membrane, cholesterol may be closely related to membrane receptors through which cholesterol could directly activate oncogenic signaling (Figure 1).

The Hedgehog pathway is a well-known cancer-associated signaling pathway that is controlled by a G-protein-coupled receptor (GPCRs), i.e., Smoothened receptor [14, 15]. Two groups have reported that cholesterol can activate the oncogenic Hedgehog signaling by directly binding the Smoothened receptor [16, 17]. The activation of signaling is closely related to cell differentiation, cell proliferation and tumor formation [18]. Another study showed that cholesterol can spontaneously enter the binding site of another type of membrane GPCRs, i.e., adenosine A2A receptor (A2AR), in C6 glioma cells [19]. This ligand-receptor binding pattern was confirmed to be the same in tumors.

me epidemiologic observations suggest that no association exists between cholesterol and cancer progression. A recent meta-analysis found that five years of statin treatment had no effect on the risk of cancer-related death (relative risk, 1.00; 95% confidence interval, 0.93 to 1.08) [13]. More surprisingly, a clinical study involving patients with bladder cancer found that the tumors became more aggressive in 53% of the patients who took statins but only in 18% of the nonusers (P = 0.004) [5]. We searched for studies investigating the relationship between hypocholesterolemia and cancer and found nine cohort studies involving healthy individuals performed in 1980 showing that low cholesterol was associated with colon and lung cancer, yielding the opposite conclusion [4].

In addition, cholesterol can specifically bind the PDZ domains of scaffold proteins, such as the N-terminal PDZ domain of NHERF1/EBP50, and following NHERF1-cholesterol binding, the signal complex can be activated [20]. NHERF1/EBP50 is a major regulator of oncogenic signaling networks by assembling cancer-related proteins, including those belonging to the PI3K/Akt and Wnt/ β -catenin pathways [21]. The activation of the PI3K/Akt and Wnt/ β -catenin pathways has been found in several types of cancer and is related to cell proliferation and tumor formation [22-24].

In general, hypercholesterolemia may be an important factor in some types of cancer, such as breast and prostate cancer, which is supported by clinical analyses and animal experiments. However, because of the discrepant observations regarding the relationship between hypercholesterolemia and cancer, the relationship between cholesterol and cancer might not be a simple two-factor association, and the existence of a potential conditional factor capable of reverting the relationship between cholesterol and cancer progression is worthy of consideration. One possible third conditional factor is the tissue origin of the cancer. The cholesterol requirement and constituent ratio vary in different tissues. Another possible conditional factor is the daily intake of cholesterol, and different eating habits may represent an epigenetic regulator affecting cancer development.

In addition to the cell membrane, cholesterol functions in the cytoplasm. Recent studies have shown that lysosomal cholesterol could activate mTORC1 via the SLC38A9-Niemann-Pick C1 signaling complex [25]. mTORC1 activation results in increased cell proliferation, invasion and metastasis [26].

Cholesterol is an important component of lipid rafts: a vital structure for cancer signaling

Lipid rafts are special small lipid domains within the cell membrane that are rich in cholesterol

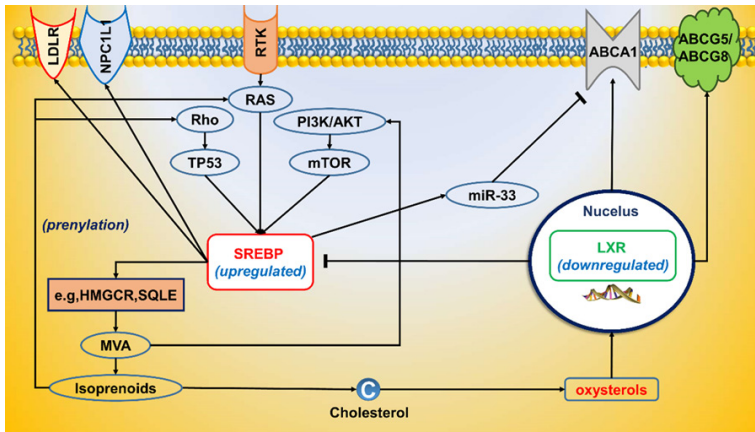


Figure 2. The regulatory mechanism of cholesterol metabolism and related molecules in cancer cell.

ol and sphingolipids. Lipid rafts are platforms for cellular signal transduction, and their structure and function depend on the composition of cholesterol and related phospholipids [27]. Changes in membrane cholesterol and cholesterol-rich membranes have been shown to affect cancer progression and invasion [28].

Lipid rafts also provide a signal transduction platform for oncogenic signaling pathways (Figure 1). Changes in the cholesterol level can lead to structural damage in lipid rafts, which may activate or inhibit the functions of raft-related proteins, such as death receptor proteins, protein kinases, and calcium channels [29]. Akt is a well-known serine/threonine protein kinase that plays an important role in the regulation of cancer cell survival [30] and can be more effectively activated when translocated to lipid raft domains. Gao et al. found that disruption of lipid raft domains by M β CD (a type of cholesterol chelator) could inhibit Akt phosphorylation at Thr308 and Ser473 and enhance apoptosis in cancer cells [31]. Another study showed that X-ray irradiation could induce lipid raft gathering in non-small cell lung cancer cells, which could induce c-Met and c-Src clustering in lipid rafts, while M β CD could inhibit the aggregation of c-Met and c-Src and reduce the expression of phosphorylated c-Met and c-Src [32]. In addition, lovastatin treatment has been reported to inhibit the migration of non-small cell lung cancer cells by 63.1-83.3%, whereas M β CD followed by lovastatin further inhibited such migration by 35.0-57.8%, indicating that cholesterol depletion in lipid rafts could inhibit the phosphorylation of lipid raft-

associated Src and the dislocation of the focal adhesion complex from lipid rafts [33]. c-Met, c-Src and Src are oncogenes that are activated by phosphorylation and are related to tumor formation, cell migration and invasion [34-36].

Cell surface glycoproteins (e.g., CD44) and their integration are essential for cell adhesion, migration and metastasis [37, 38]. A study reported that M β CD could lead to CD44 shedding from lipid rafts in human glioma cells

[39]. Various invasive cancer cells can form invadopodia, which can induce degradation. Lipid rafts are required for invadopodia formation in breast cancer cells and extracellular matrix (ECM) degradation [40]. The localization to lipid rafts is essential for the internalization of matrix metalloproteinases (MMPs), while concentrated MMPs at the surface of invadopodia are well-correlated with invadopodia activity [40, 41]. M β CD treatment has been shown to inhibit migration and invasion in breast carcinoma cells, which could be attributed to a reduction in the levels of uPAR and MMP-9 in lipid rafts [42].

Changes in cholesterol metabolism during cancer development

The upregulation of cell cholesterol biosynthesis and intake and the downregulation and damage to cell cholesterol efflux are relevant to cancer (Figure 2).

Cholesterol synthesis

Studies have shown that compared with untransformed cells, cholesterol synthesis is increased in cancer cells [43, 44]. The expression of many enzymes involved in cholesterol biosynthesis pathways is regulated by the family of sterol regulatory element binding protein (SREBP) transcription factors, which act as intracellular cholesterol level regulators [45]. TP53-mediated activation of cholesterol synthesis by the SREBP pathway has been found to induce breast cancer cell proliferation and self-renewal via the prenylation of Rho GTPases

[46]. The mutation and activation of RTK/Ras signaling has been shown to be common in pediatric acute myeloid leukemia, and this signaling induces major regulatory genes encoding cholesterol synthesis, leading to intracellular cholesterol accumulation by the activation of SREBP transcription factors [47, 48].

The activity of HMG CoA reductase (HMGCR), which is a key flux-controlling enzyme in the cholesterol synthesis pathway, is enhanced by both the transcriptional regulation of SREBP and changing the feedback control of HMGCR [10]. A study reported that HMGCR regulated cell migration in colon cancer induced by CCL17 (a type of chemokine) via the inhibition of geranylgeranylation and RhoA activation [49]. Another key flux-controlling enzyme, i.e., squalene epoxidase (SQLE), is also regulated by SREBP [50, 51]. Brown et al. confirmed that SQLE is an amplified oncogene with clinical relevance in breast cancer. These authors found that SQLE overexpression was usually observed in breast cancer with a high grade, HER2 positive, and hormone receptor negative cases and that the SQLE inhibitor could decrease the cancer cell viability and increase the replication time [52].

Cholesterol influx

Low-density lipoprotein (LDL) particles transport cholesterol to most surrounding tissues through receptor-mediated mechanisms [53]. The lipid profile of cancer patients reportedly exhibits decreased plasma lipoprotein levels, which return to normal after successful tumor remission, highlighting the importance of lipoproteins in tumor growth and development [54]. The upregulation of the intracellular cholesterol level can be achieved by the constitutive activation of PI3K/AKT/mTOR signaling, the activation of SREBP, or the induction of LDL receptor-mediated cholesterol influx because the activation of these pathways is mainly related to cell growth [55, 56].

Niemann Pick C1-like 1 (NPC1L1), which is another important protein mediating cholesterol influx, is located on the scrubbing membrane of intestinal epithelial cells and mediates the absorption of free cholesterol into intestinal epithelial cells [57]. The NPC1L1 knockout has been shown to prevent the occurrence of colitis-associated carcinogenesis by reducing

plasma cholesterol, inflammation, β -catenin, p-c-Jun and p-ERK [58].

Cholesterol efflux

ATP-binding cassette transporter A1 (ABCA1) is a membrane transfer protein that can transfer cholesterol from the intracellular compartment to the extracellular space [59]. The overexpression of mutant TP53 and Ras has been reported to decrease xenograft tumor growth by inhibiting ABCA1, which, in turn, leads to an increase in the mitochondrial cholesterol levels [60]. One study found that cancer-specific ABCA1 hypermethylation and the downregulation of ABCA1 expression resulted in high intracellular cholesterol levels, contributing to the establishment of an environment conducive to cancer progression [61]. The miR-33 families of microRNAs are encoded in the introns of the SREBP gene and were found to inhibit the expression of ABCA1 in mammals, suggesting a tumor promoting effect [62].

Additionally, in the basal membrane of enterocytes and hepatocytes, the ATP-binding cassette transporters G5/G8 (ABCG5/G8) inhibit the absorption of cholesterol by stimulating cholesterol export from enterocytes to the gut lumen and promoting efficient secretion of cholesterol from hepatocytes into the bile [63]. The sitosterolemia locus that encodes ABCG5/G8 has been found to be associated with a high risk of developing gallbladder cancer [64].

Key molecules in cholesterol anabolism and catabolism are cancer-related

Mevalonic acid

Mevalonic acid (MVA) is an important precursor of cholesterol and is synthesized by HMG-CoA by HMGCR. MVA can activate PI3K, resulting in a series of reactions, such as the activation of mTOR and NF κ B and the inhibition of P21 and P27 [65]. These series of reactions could lead to changes in the apoptosis, cycle, autophagy and migration of cancer cells [66-68]. Moreover, the activation of Hippo signaling is promoted by MVA through the transcriptional activation of the TP53/SREBP pathway in cancer cells [46].

Isoprenoids

During the process of cholesterol synthesis, the mevalonate pathway could produce a large amount of isoprenoids, such as isopenten-

yl-diphosphate (IPP), farnesyl-pyrophosphate (FPP) and geranylgeranyl-pyrophosphate (GGPP) [65]. FPP and GGPP are hydrophobic chains that are essential for protein isoprenylation. This type of posttranslational modification could immobilize proteins to cell membranes, enabling suitable protein function and localization [69]. Isoprenoids can cause the prenylation of many small GTPases, such as Ras and Rho, and their translocations to the cell membrane [70]. Many prenylated GTPases are involved in carcinogenesis and cancer-related signaling pathways. For example, one study showed that the activation of RhoA could enhance the degradation of P27kip1 and prevent its transfer to the nucleus, resulting in an imbalance in the cell cycle, particularly in stem cells [71].

Oxysterols

Oxysterols are oxygenated derivatives of cholesterol or its sterol precursors and the ligand of Liver X receptors (LXR) [72]. LXRs are members of the nuclear receptor superfamily of DNA-binding transcription factors and act as sensors of cholesterol homeostasis by disrupting the SREBP pathway and accelerating the degradation of HMGCR [73]. Studies have shown that the survival of glioblastoma (GBM), which is a highly lethal brain cancer, significantly depends on cholesterol and that these tumors are very sensitive to LXR agonist-induced cell death [74]. In addition, the activation of LXR significantly reduces proliferation, which has been confirmed in several human breast cancer cell lines [75]. In tumor immunotherapy, LXR activation therapy produces a strong anti-tumor response in mice and enhances the activation of T cells in various immunotherapy studies, suggesting that the LXR/ApoE axis is a target for improving the efficacy of tumor immunotherapy [76].

Current anticancer therapeutic strategies targeting cholesterol metabolism

Targeting cholesterol synthesis

The therapeutic effects of statins have been observed in several cancers, including prostatic, gastric, esophageal, and hepatic cancer [77]. Statins inhibit tumor growth, invasion and metastasis by blocking the production of isoprenoids, which are necessary for the post-

translational modifications of many proteins [77, 78].

Protein geranylgeranylation (GG), which is a branch of the cholesterol synthesis pathway, is critical for breast cancer stem cell (CSC) maintenance. A small molecule inhibitor of the geranylgeranyl transferase I (GGTI) enzyme called GGTI-288 reduced the breast CSC subpopulation both in vitro and in vivo [79].

Targeting cholesterol transport and intestinal absorption

LXR promote cholesterol efflux by regulating the transcription of some membrane proteins (ABCA1 and ABCG5/G8) and play a role in cholesterol coordination during the process of cell proliferation [73, 80]. The anti-proliferative effect of the LXR agonist T0901317 was demonstrated to suppress β -catenin transcriptional activity in colon cancer HCT116 cells in vitro [81]. In animal models of colon cancer, the activation of LXR can arrest the cell cycle at the G1 phase and activate cell apoptosis [82].

Currently, a cholesterol absorption inhibitor is widely used in clinical settings to treat hypercholesterolemia. Ezetimibe, which is a drug that inhibits cholesterol absorption by blocking NPC1L1-mediated cholesterol influx, was demonstrated to have antitumor activity in an in vivo prostate cancer model by inhibiting hypercholesterolemia-induced angiogenesis [83].

Concluding remarks and future directions

This paper expounds upon the role of cholesterol metabolism in cancer progression. Cholesterol metabolism is closely related to each phase of cancer progression. It is believed that cancer cells tolerate excessive metabolic consequences of plasma cholesterol intake to sustain cancer progression, which may explain why the level of serum cholesterol in some cancer patients is normal or even lower. Except for the serum cholesterol level, many studies lack measurement of genes associated with cholesterol metabolism. A simple measurement of the serum cholesterol level cannot explain the mechanism, and mutations in cholesterol metabolism regulation genes might be more informative. Lipid rafts, which are unique structures characterized by a high level of cholesterol, are essential for oncogenic signals (e.g.,

Fas and Akt). Quantity and structural changes in lipid rafts due to alteration in cholesterol may directly affect signal transduction, which can lead to different outcomes, and the mechanism underlying this process is more complex than previously thought. Lipid raft-related cholesterol metabolism needs further investigation. The “reprogramming of cellular metabolism” is one of the important characteristics of cancer. Several studies have confirmed that cholesterol synthesis and influx are increased while efflux is decreased in tumor cells. Targeting cholesterol metabolism may achieve beneficial therapeutic effects according to this characteristic of tumor cells.

In conclusion, although not conclusive, the deregulation of cholesterol homeostasis seems to be an important factor in the development of cancer. Population-based epidemiological data and mechanistic in vivo and in vitro studies are needed for a more thorough analysis of the role of cholesterol in cancer development to provide more directions and methods for the treatment and prevention of cancer.

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Disclosure of conflict of interest

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Cholesterol metabolism and cancer

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Cholesterol metabolism and cancer

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Cholesterol metabolism and cancer

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