Chapter 6

Cholesterol Lowering in Cancer Prevention and Therapy

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Abstract

The accumulation of cholesterol in cancer cells and tumor tissues promotes cell growth, proliferation, and migration as well as tumor progression. Cholesterol synthesis is catalyzed by a series of enzymatic reactions. Regulation of these key enzymes can control cholesterol synthesis and modulate cellular cholesterol levels in the cells. Meanwhile, controlling cholesterol transportation, absorption, and depletion could also significantly reduce cellular cholesterol levels. The current evidence supports that cholesterol lowering agents, beyond the expected cholesterol-lowering properties, also display an important anticancer activity in reducing cancer cell growth, proliferation and migration, and inducing apoptosis in a variety of cancer cells. Understanding the mechanisms of cholesterol metabolism and cholesterol lowering could potentially benefit cancer patients in cancer prevention and treatment.

Keywords: cholesterol metabolism, cholesterol-lowering agents, cancer, prevention, therapy

1. Introduction

Cholesterol is an essential component of cellular membrane. It serves as a spacer between the hydrocarbon chains, functions as dynamic glue during membrane assembly, and plays a crucial role in the stability, architecture, dynamics, and function of cellular membrane [1, 2]. In addition, cholesterol is involved in vesicle trafficking and transmembrane receptor signaling [3–6]. Meanwhile, cholesterol itself is also as a precursor of steroid hormones and sterols in the steroidogenesis [6–8]. The vesicle trafficking, receptor-mediated signaling, and steroidogenesis further lead to specific biological responses and regulate different cellular functions such as membrane biogenesis, cell growth, proliferation, apoptosis and migration, as well as tumor progression [6–8].

Due to the key physiological roles that cholesterol plays, the circulating and cellular cholesterol levels in our body are tightly regulated by a physiological balance of cholesterol biosynthesis, cholesterol catabolism, cholesterol transportation (influx and efflux), dietary cholesterol absorption, and cholesterol depletion. Higher cholesterol, also known as hypercholesterolemia, is a risk factor for a variety of human diseases such as cardiovascular diseases, dyslipidemia, Alzheimer's disease, HIV dyslipidemia, chronic inflammation, and developing diabetes. Earlier data also indicates that accelerated cholesterol metabolism and elevated cholesterol levels contribute to the hallmarks of cancer development and malignant transformation [9–15]. Cancer cells need excess cholesterol and intermediates of the cholesterol biosynthetic pathway to maintain a high level of cell growth and proliferation. Meanwhile, cholesterol is capable of regulating multiple signaling pathways involved in carcinogenesis, cancer cell migration, and tumor progression and is also involved in chemosensitivity and chemotherapy resistance of cancer cells [9–19]. It is very important to understand cholesterol as an important factor contributing to carcinogenesis and tumor progression and to elucidate the regulation of cholesterol metabolism as a new strategy for searching cancer prevention and therapy drugs.

2. Cell biology of cholesterol

2.1. De novo cholesterol biosynthesis

Cholesterol is a 27-carbon and tetracyclic ring steroid that is catalyzed by a series of more than 26 separate enzymatic reactions in several subcellular compartments [20, 21]. The de novo biosynthesis can be considered as five major steps: (1) From acetyl-CoA to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA): the acetyl-CoA can be derived from the oxidation of fatty acids or synthesized from cytosolic acetate precursors (metabolites or taken up from dietary or exogenous sources), and three acetyl-CoAs condense to form acetoacetyl-CoA by acetoacetyl-CoA acetyltransferases or thiolase and then HMG-CoA by HMG-CoA synthase. (2) The formation of mevalonate: HMG-CoA is reduced to mevalonate by HMG-CoA reductase, a rate-limiting and irreversible step in the metabolic pathway that produces cholesterol and other isoprenoids. (3) From mevalonate to isopentenyl pyrophosphate (IPP): mevalonate is further converted to IPP through two phosphorylation steps and one decarboxylation step. This conversion is involved in seven different enzymes (mevalonate-3-kinase, mevalonate-5-kinase, mevalonate-3-phosphate-5-kinase, phosphomevalonate kinase, mevalonate-5-phosphate decarboxylase, mevalonate pyrophosphate decarboxylase, and isopentenyl phosphate kinase) via different avenues. (4) From IPP to squalene: three molecules of IPP further condense to form a farnesyl pyrophosphate (FPP) and two molecules of FPP then condense to form squalene. The enzymes involved in the process are IPP isomerase, farnesyl-diphosphate synthase, and squalene synthase. (5) From squalene to lanosterol to cholesterol: the oxidation of squalene by squalene epoxidase forms 2,3-oxidosqualene which is further cyclized to lanosterol by squalene oxidocyclase. Lanosterol is finally converted to cholesterol by a series of demethylations, desaturations, isomerizations, and reductions. Demethylation reactions produce zymosterol as an intermediate and further converted to cholesterol by at least two pathways that differ in the order of the desaturations, isomerizations, and reductions (**Figure 1**) [22–27].

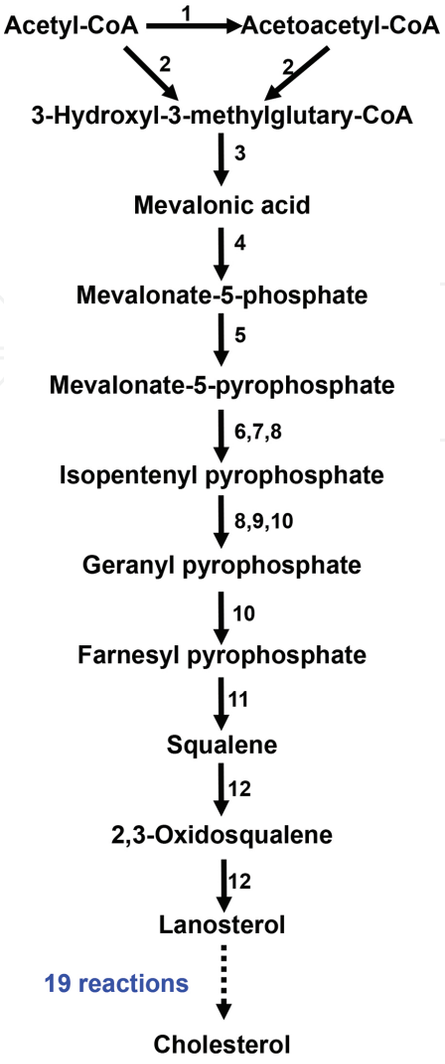

Figure 1. Scheme of the cholesterol biosynthesis pathway. (1) Thiolases or acetyl-coenzyme A acetyltransferases, (2) hydroxy-3-methylglutaryl-CoA synthase, (3) hydroxy-3-methylglutaryl-CoA reductase, (4) mevalonate-3-kinase or mevalonate-5-kinase, (5) mevalonate-3-phosphate-5-kinase or phosphomevalonate kinase, (6) mevalonate-5-phosphate decarboxylase, (7) mevalonate pyrophosphate decarboxylase, (8) isopentenyl phosphate kinase, (9) isopentenyl pyrophosphate isomerase, (10) farnesyl-diphosphate synthase, (11) squalene synthase, (12) squalene monooxygenase or squalene epoxidase, and 19 reactions are included multiple demethylations, desaturations, isomerizations, and reductions.

2.2. Cholesterol homeostasis

Cholesterol is a vital lipid and plays well-described biochemical roles and diverse functions at cellular level [1–3]. The homeostasis of cholesterol is among the most intensely regulated processes in our body. High cholesterol is a risk factor to numerous pathologies such as cardiovascular disease, atherosclerosis, dyslipidemia, and neurodegenerative diseases and is associated with the development of diabetes and cancer. Cholesterol homeostasis is achieved through intricate mechanisms involving biosynthesis, catabolism, dietary absorption, transportation (influx or efflux), and depletion (**Figure 2**) [28–32]. Slightly less than half of cholesterol in our body derives from de novo biosynthesis every day. The liver is the dominant site of

cholesterol biosynthesis, and in vivo liver cholesterol production has been estimated at 1–2 g/day. Cholesterol is synthesized in liver and then secreted as circulating lipoproteins into bloodstream. The intestine and skin are also very important for cholesterol synthesis [33–35]. Although the majority of cholesterol sources comes from cholesterol biosynthesis, it is under feedback regulation. The absorption of cholesterol mainly derives from three sources: diet, bile, and intestinal epithelial sloughing. The average intake of cholesterol in the Western diet is approximately 300–500 mg per day. Bile is estimated to contribute nearly 800–1200 mg of cholesterol per day to the intraluminal pool. A third source of intraluminal cholesterol comes from the turnover of intestinal mucosal epithelium, which provides roughly 300 mg of cholesterol per day [36]. In cholesterol catabolism, the conversion of cholesterol into excretable bile acids represents the most relevant mechanism of irreversible elimination of cholesterol from the body, which plays a key role in hepatic and systemic cholesterol homeostasis. Under physiological conditions, approximately 300–400 mg of cholesterol is disposed in the liver daily [37]. Because peripheral cells do not catabolize the cholesterol molecule, there are two distinct mechanisms for maintaining cellular cholesterol homeostasis. One is the nonspecific classical pathway mediated by physicochemical diffusion of cholesterol through the aqueous phase and the other is cholesterol esterification on high-density lipoprotein (HDL) by lecithin: cholesterol acyltransferase reaction [38, 39]. The reaction is initiated by the interaction of lipid-free or lipid-poor apolipoproteins with cellular surface resulting in the assembly of HDL particles with phospholipid and cholesterol as well as extracellular cholesterol esterification mainly on HDL [40]. Furthermore, changing dietary style to control cholesterol absorption and using pharmaceutical drugs to inhibit several key enzymes in cholesterol synthesis can also significantly reduce the level of cellular cholesterol. All of these pharmaceutical drugs and dietary style have been commonly used for keeping a healthy life and preventing heart disease [41–44].

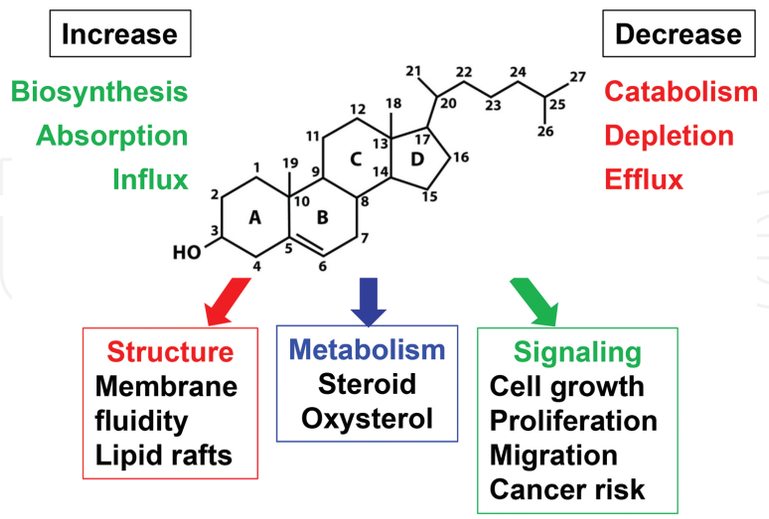

Figure 2. Cholesterol homeostasis and functions. Cholesterol homeostasis is tightly regulated in our body and can be achieved through intricate mechanisms involved in biosynthesis, dietary absorption, transportation (influx or efflux), catabolism, and depletion. The functions of cholesterol are composed of distinct membrane, control membrane fluidity and protein recruitment, produce steroid and oxysterol, and are involved in cell signaling to regulate cell growth, proliferation, and migration.

2.3. Biological functions of cholesterol

Disruption to cholesterol homeostasis leads to a variety of diseases such as coronary heart disease, atherosclerosis, and metabolic syndrome as well as cancer [9–19, 45–51]. This indicates that cholesterol plays a crucial role in the regulation of cellular function (**Figure 2**). In the cells, cholesterol is mandatory for cellular growth and serves as one of the necessary building blocks for new membranes demanded by dividing cells during proliferation. Cell membranes have been recognized as heterogeneous structures composed of distinct membrane microdomains with different proteins and lipids. Lipid rafts, cholesterol-rich domains, play an important platform as a signaling station for many cellular processes, including membrane sorting and trafficking, cell polarization, and signal transduction [52–56]. Cholesterol promotes cell proliferation by inducing the activation of the AKT and/or the ERK signaling pathway as well as Ca^{2+} channel [57–60] and cell migration by increasing the activity of calpain that is also Ca^{2+} dependent [61, 62] and is also involved in Hedgehog processing, diffusion, and reception [63, 64]. Cholesterol can be converted to steroid hormones which activate nuclear receptors and thus help to control metabolism, inflammation, immune functions, salt and water balance, the development of sexual characteristics, and the ability to withstand illness and injury [65, 66]. Meanwhile, the metabolites of cholesterol such as hydroxycholesterols play multiple biological functions in the body [67, 68]. Cholesterol also contributes to chemotherapy resistance which leads to treat failure [11–14]. Taken together, cholesterol is tightly associated with cancer cell growth, proliferation and therapy.

3. The balance of cholesterol and cancer

Cholesterol accumulation in cancer cells and tumor tissues was discovered in cancer cells and tumor tissues started in earlier 1900s [12, 69, 70]. Since then, researchers have studied the relationship between cellular cholesterol and cancer in depth. Recent epidemiological studies suggest the correlation between serum cholesterol level and the risk of certain types of cancer [15, 71–74]. It is difficult to draw conclusions from epidemiological studies on whether cholesterol is a key factor of cancer incidence because of of their intrinsic limitations. On the other hand, experimental evidence from cell and animal models indicates that cholesterol plays a promotional role in cancer cell growth and cancer development and progression [57–60]. These findings support the notion that lowering cholesterol level may be a useful and effective strategy for cancer prevention and a therapeutic potential for cancer treatment.

3.1. Lowering cholesterol level

As described above, cholesterol homeostasis is controlled by its biosynthesis, catabolism, dietary absorption, transportation, and depletion [28–32]. Among these, cholesterol biosynthesis and absorption with low-density lipoprotein (LDL) receptor (LDLR) which mediates the endocytosis of cholesterol-rich LDL are key to elevate cellular cholesterol. By contrast, there are also two common avenues to achieve cholesterol lowering: (1) pharmacological treatment which inhibits cholesterol biosynthesis [41–45] and (2) dietary control that reduces cholesterol

absorption [36, 75]. Meanwhile, cholesterol metabolite, 27-hydroxycholesterol, and other oxysterols can activate the liver X receptors (LXR), resulting in a reduction of intracellular cholesterol [76–78]. Modulation of LXR and their downstream targets has appeared to be involved in cholesterol and lipid metabolism in response to changes in cellular cholesterol status [76–78]. This also draws attention to the therapeutic interest of developing LXR agonists as a bona fide therapeutic approach in cancer treatment. The cross talk of LDLR-SREBP (sterol regulatory element-binding protein) signaling and LXR signaling in the regulation of cholesterol metabolism is potential as a new strategy to develop cancer therapeutic drugs and treatment regimen.

3.2. Cholesterol-lowering drugs

There are many different agents that can inhibit cholesterol biosynthesis at different enzymatic steps or reduce cholesterol level by different regulation pathways. **Table 1** summaries the targets and effects of different cholesterol-lowering agents. Statins, first marketed in 1987, are the most common drugs to lower cholesterol level. As structural analogues of HMG-CoA, statins inhibit HMG-CoA reductase to block the conversion of HMG-CoA to mevalonic acid in a rate-limiting step of cholesterol biosynthesis. Up to date, a number of different compounds in this class drugs have been developed: atorvastatin (Lipitor), cerivastatin (Baycol; withdrawn from the market in 2001), fluvastatin (Lescol), lovastatin (Mevacor), mevastatin (Compactin), pitavastatin (Livalo), pravastatin (Pravachol or Selektine), rosuvastatin (Crestor), and simvastatin (Zocor). They are effective for treating cardiovascular disease, atherosclerosis, dyslipoproteinemia, and liver disease [79–81] and are also recommended for those who do not meet their lipid-lowering goals through diet and lifestyle changes. Statins are also considered as an anticancer agent to prevent and treat cancer patients [42–44]. Because of multiple side effects of statins, such as muscle pain, increased risk of diabetes mellitus, and abnormalities in liver enzyme tests, many other enzymes that are involved in cholesterol biosynthetic pathway beyond HMG-CoA reductase are also being considered as targets for developing cholesterol-lowering drugs. These drugs include bisphosphonates which inhibit farnesyl-diphosphate synthase [82] and lonafarnib (SCH66366) and tipifarnib (R115777) which inhibit farnesyltransferase [83]. YM-53601, RPR-107393, and TAK-475 (Lapaquistat) can inhibit squalene synthase [84–86], and Ro 48-8071, BIBB515, and terbinafine (Lamisil) are potent inhibitors of 2,3-oxidosqualene cyclase or squalene epoxidase [87–89]. These agents are used in clinic and in clinic trials.

In addition, several another classes of compounds which can lower cholesterol level via different molecular mechanisms have recently been developed. Ezetimibe (Zetia), a cholesterol uptake-blocking drug, prevents cholesterol absorption from dietary intake [90]. Fibrate drugs (Gemfibrozil, Tricor, Atromid-S), an activator of peroxisome proliferator-activated receptor α (PPARα), can reduce very-low-density lipoprotein (VLDL) - and LDL-containing apoprotein B and increase HDL-containing apoprotein AI and AII [91, 92]. Cholestyramine, colestipol, and colesevelam, bile acid sequestrants, can remove bile acids from the body and further convert more plasma cholesterol to bile acids to reduce cholesterol level [93, 94]. Some other cholesterol-lowering agents are also on the market or available for research. Acyl-CoA:cholesteryl

acyltransferase inhibitor (avasimibe or CI-1011) induces cholesterol 7-α-hydroxylase and increases bile acid synthesis [95]. Green tea or catechins can inhibit the intestinal absorption of dietary lipids [96]. Lomitapide (Juxtapid) inhibits the microsomal triglyceride transfer protein required for VLDL assembly and secretion [97]. Mipomersen is a second-generation antisense oligonucleotide targeted to human apolipoprotein B-100 which is the structural core of LDL cholesterol [98]. Anacetrapib is a novel inhibitor of cholesteryl ester transfer protein [99]. Evolocumab (AMG145) and alirocumab are monoclonal antibodies which inactivate the proprotein convertase subtilisin/kexin type 9 (PCSK9) and lower LDL level [100, 101]. Dynasore reduces labile cholesterol in the plasma membrane [102]. Some of these cholesterol-lowering drugs have demonstrated their anticancer property and have the potential of cancer pharmacological prevention [41–45].

Agents	Targets	Effects	References
Statins	HMG-CoA reductase	Block the conversion of HMG-CoA to mevalonic acid	[79–81]
Bisphosphonate	FPP synthase	Attenuate the formation of FPP	[82]
SCH66366 R115777	Farnesyltransferase	Reduce adding a farnesyl group to proteins	[83]
YM-53601 RPR-107393 TAK-475	Squalene synthase	Inhibit the conversion of FPP to squalene	[84–86]
Ro 48-8071	2,3-Oxidosqualene synthase	Block the formation of 2,3 oxidosqualene	[87, 88]
BIBB515 Terbinafine	Squalene epoxidase		
Ezetimibe Catechins	Cholesterol absorption	Block cholesterol uptake in the small intestine	[89, 90]
Gemfibrozil Tricor Atromid-S	PPARα	Reduce VLDL and LDL level	[91, 92]
Cholestyramine Colesevelam and the conversion of cholesterol to bile acid Colestipol	Bile acid sequestrants	Increase bile acid removal	[93, 94]
Avasimibe CI-1011	ACAT	Increase cholesterol oxidation and bile acid synthesis	[95, 96]
Lomitapide	Triglyceride transfer protein	Reduce VLDL assembly and secretion	[97]
Mipomersen	Apolipoprotein B-100	Reduce LDL level	[98]
Evolocumab Alirocumab	PCSK9 antibody	Inactivate PCSK9 and lower LDL level	[99, 100]
Dynasore	Dynamin	Reduce membrane cholesterol	[101]

*PPARα, peroxisome proliferator-activated receptor α; ACAT, Acyl-CoA:cholesteryl acyltransferase.

Table 1. Targets and effects of different cholesterol-lowering agents.

3.3. Anticancer property of cholesterol-lowering drugs

Accumulating evidence supports that deregulation of any steps in cell growth, proliferation, and migration may result in cell malignant transformation. More than a century ago, cholesterol was observed to accumulate in malignant tissues [69]. Now, more and more evidence shows that cholesterol plays a critical role in the regulation of cancer cell growth and proliferation and tumor progression [8, 10–18, 70]. The key regulators in cholesterol metabolism attract many researchers around the world to search for novel anticancer agents. Based on cholesterol biofunctions and experimental data, the role of cholesterol-lowering drugs may not limit on the property of LDL-cholesterol lowering but may also be involved in the prevention or treatment of cancer. Statins are the most common cholesterol-lowering drugs and are also the most studied drugs. Whether statins exhibit anticancer properties is based on experimental studies, epidemiological studies, and clinical studies. In experimental studies, statins reduce a variety of cancer cell viability (**Figure 3**) [75, 103–105]. The epidemiologic data also support that statins reduce the incidence of gastric cancer, breast cancer, advanced prostate cancer, colorectal cancer, and cholangiocarcinoma [105–109]. However, there are also some studies that do not support the association of statin use with cancer risk [110, 111]. In clinical studies, statins can significantly reduce prostate cancer-specific mortality and reduce the risk of biochemical recurrence among the patients treated with radiation therapy [112] and are also associated with improved survival in patients with metastatic renal cell carcinoma [113]. So far, statins show some promising results in certain types of cancer. The potential of statins in modern cancer prevention and treatment is very promising. Meanwhile, it is also important to search other cholesterol-lowering agents that are more effective and reduce adverse side effects. Some of these agents have already been studied at the different stages [89, 114].

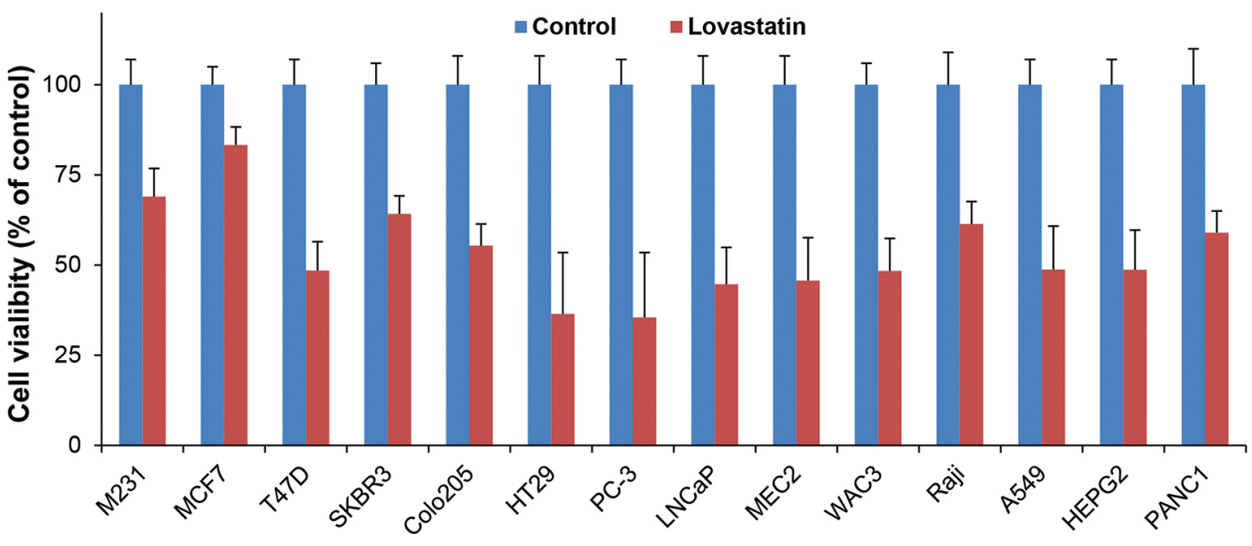

Figure 3. Treatment of lovastatin reduces cell viability in different cancer cell lines. Different cancer cells were cultured in 96-well plates and treated with 10 μM lovastatin for 3 days; the samples analyzed cell viability by MTT assay (n = 16). The values of lovastatin treatment were statistically different from the controls. $P < 0.05$. M231, MDA-MB-231.

3.4. Molecular mechanism of anticancer properties of cholesterol-lowering drugs

Expression of HMG-CoA reductase gene can be regulated by genetic or dietary interaction [115], in which it is transcriptionally regulated by endoplasmic reticulum-based transcription factor, SREBP-2 [116], or high-fat diet feeding [117]. Statins inhibit HMG-CoA reductase to block cholesterol biosynthesis which attenuate cell proliferation and arrest cell cycle progression by interrupting growth-promoting signals and involving in RAS/RAF/MEK/ERK, PI3K/AKT/mTOR and Wnt/β-catenin signaling cascades [118, 119]. Statins also selectively induce proapoptotic potential in tumor cells and synergistically enhance proapoptotic potential of several cytotoxic agents. The mechanism for this effect has been demonstrated by disrupted binding of RhoA inhibitor GDIα which leads to increased levels of GTP-bound forms of RhoA, Rac1, and cdc42 proteins.These proteins induce apoptosis 1) by suppression of anti-apoptotic proteins such as Bcl2 or activation of the superoxide-activated JNK pathway [120] or 2) by inhibiting Akt/mTOR pathway and inducing programmed cell death 4 expression in renal cell cancer cells [121]. Statins alter the angiogenic potential of cells by modulating apoptosis inhibitory effects of VEGF and decrease secretion of metalloproteases and suppress the rate of activation of multiple coagulation factors and thus prevent coagulation-mediated angiogenesis [122]. Statins suppress the Rho/Rho-associated coiled-coil-containing protein kinase pathways, thereby inhibiting cell migration, invasion, adhesion, and metastasis [123]. Other cholesterol-lowering agents have not been widely studied as statins. However, all cholesterol-lowering agents could affect membrane composition, in particular cholesterol-rich domain, termed lipid rafts. Membrane lipid rafts are highly ordered membrane domains that are enriched in cholesterol, sphingolipids, and gangliosides and selectively recruit certain classes of proteins (a large number of cancer-related signaling and adhesion molecules) and act as major modulators of membrane geometry, lateral movement of molecules, and traffic and signal transduction [52, 54]. Cholesterol-lowering drugs lead to membrane cholesterol depletion which could disrupt membrane lipid rafts, block the adhesion and migration processes of cancer cells, and induce cancer cell apoptosis [124, 125].

4. Cholesterol-lowering drugs in cancer prevention and therapy

A growing body of evidence from cell biology and animal models has strongly demonstrated the anticancer activity of cholesterol-lowering drugs such as statins [7, 83–89, 104–108]. Epidemiological studies also suggest an anticancer effect of statins evidenced by the reductions of cancer incidence and cancer-related mortality, although the association between statin use and cancer incidence based on different cancer remains controversial from different laboratories around the world. Statins as part of pharmacological cancer prevention and chemotherapy have generated interest in the oncology community and have been investigated in a variety of cancers at early and late stages and in the combination with chemotherapy and radiation therapy. Here, we summarize the current data that statin use affects cancer incidence and therapy.

Study	No. of subjects/ studies	Results	References
Bonovas, 2008	12 studies	No significant relationship between statins and pancreatic cancer risk	[129]
Khurana, 2007	483,733	Protective against the development of pancreatic cancer	[130]
Lin, 2016	19,727	Prevent *H. pylori*-associated gastric cancer	[105]
Singh, 2013	11 studies	Prevent gastric cancer risk in both Asian and Western population	[131]
Tsan, 2012	33,413	Reduce the risk for hepatocellular carcinoma in HBV-infected patients	[132]
Chen, 2015	2,053	Decrease hepatocellular carcinoma in diabetic patients	[133]
Zhang, 2013	13 studies	No association between statin use and risk of bladder cancer	[134]
Peng, 2015	3,174	Reduce the risk of cholangiocarcinoma	[108]
Yi, 2014	20 studies	Preventive effects against hematological malignancies	[135]
Pradelli, 2015	14 studies	Negatively associated with all hematological malignancies	[136]
Wang, 2013	20 studies	Nonsignificant association between statin users and lung cancer risk	[137]
Bansal, 2012	27 studies	Reduce the risk of total and advanced prostate cancer	[138]
Jacobs, 2007	55,454	Reduce the risk of advanced prostate cancer	[109]
Undela, 2012	24 studies	Do not support that statins have a protective effect against breast cancer	[139]
Lytras, 2014	40 studies	Do not support that statin users reduce the risk of colorectal cancer	[140]
Setoguchi, 2007	24,439	No effect in the risk of colorectal, lung, or breast cancer in older patients	[141]
Kuoppala, 2008	42 studies	No effect on the incidence of lung, breast, or prostate cancer Protect from stomach and liver cancer and from lymphoma Increase the incidence of both melanoma and nonmelanoma skin cancer	[142]

Table 2. Effect of statins on cancer incidence.

4.1. Cholesterol-lowering drugs in cancer prevention

Cholesterol is accumulated in different solid tumors and cancer cells [12, 69–71, 126, 127], raising questions concerning the role of cholesterol in cancer cell growth, proliferation, and migration as well as tumor progression [57–61]. Although cholesterol-lowering drugs have also been shown to possess an important antitumor activity that reduces cell growth, proliferation, and migration through ERK-mediated and Akt-mediated signaling pathways and is capable of inducing apoptosis through extrinsic and intrinsic pathways using different cancer cells as models [43–45, 75, 78, 104, 118–123], it is still unclear whether statins are suitable to prevent the incidence of cancer. More than a hundred of epidemiological studies around the world have been performed to evaluate the effect of statin on the risk of cancer incidence [105, 108, 109, 126–142]. These studies have been focused on statin type, potency, lipophilic or hydrophobicity status, and duration of use. Due to the limitation of epidemiological studies with the patients different in age, sex, living regions, and life style, the results are controversial. **Table 2** summarizes the association of cancer risk and statin use in pancreatic cancer, gastric cancer, liver cancer, lung cancer, bladder cancer, breast cancer, prostate cancer, colorectal cancer, blood cancer, and other malignancies. The clinical studies have provided conflicting

data regarding whether statins may reduce or may be no effect on the risk of cancer. It is clear that current data cannot rule out the association of statin use with the risk of some cancers. Analyses of larger numbers of cases, subgroup design (participant ethnicity or confounder adjustment), randomized controlled trials, and high-quality cohort studies with longer duration of follow-up are needed to further confirm this association. Meanwhile, we also need to study cancer patient genetic mutations and determine whether the effect of statins on cancer prevention and therapy is associated with genetic mutation. It is clear that defining the underlying mechanisms of how cholesterol lowering contributes to cancer prevention and the search for other cholesterol-lowering agents with better outcome has emerged as future objectives. Whether cholesterol-lowering agents are used in cancer prevention will be based on the analysis of responses to these agents with cancer patient genetic information.

4.2. Cholesterol-lowering drugs in cancer treatment

Cholesterol is implicated in various cellular processes including the involvement of cell proliferation/apoptosis balance regulation in various types of cancers. Statins and other cholesterol-lowering agents are very common and effective medication used in preventing heart disease in those with high cholesterol, but no history of heart disease. The anticancer activity of these drugs has also attracted oncologists to consider whether cholesterol-lowering drugs can be a tool for cancer treatment. A variety of studies have focused on the effect of statins alone or in combination with other chemo- or/and immune-therapeutic drugs or radiation therapy on the treatment of different cancer patients. McKay et al. [113] showed some promising data that statin use improved survival in patients with metastatic renal cell carcinoma. Raval et al. found that statin significantly reduced the prostate cancer-specific mortality and improved the biochemical recurrence in certain subgroup of men with prostate cancer [112]. Song et al. found that statin use also reduces biochemical recurrence in men with prostate cancer after radical prostatectomy [143]. Statin use is related to reductions in overall and cancer-specific mortality [144] and associated with longer rates of survival [145] in colorectal cancer survivors. Two recent studies indicate that statin use is associated with improved overall survival in patients with resectable pancreatic ductal adenocarcinoma [146, 147]. Statin use also improves overall survival among patients undergoing resection for pancreatic cancer [148]. Lipophilic statins are associated with a reduced risk of breast cancer recurrence and inflammatory breast cancer [149]. Because statins negatively interfere with CD-20 and rituximab-mediated activity, statins have a negatively effect on clinical outcome in patients with rituximab-treated leukemia [150]. No association of statin use with patient survivals was also reported from colorectal cancer study [151]. Future studies are needed to further evaluate which cancer patients may benefit from statin treatment, what the best treatment is, and which cholesterol-lowering drugs are better to use in cancer treatment.

5. Concluding remarks and future perspectives

Cholesterol is tightly regulated by a physiological balance of cholesterol metabolism (biosynthesis and degradation), dietary absorption, transportation (efflux and influx), and depletion.

Importantly, cholesterol is accumulated in cancer cells and tumor tissues and is implicated in various cellular processes including cell growth, proliferation, and migration. The increase and decrease in cellular and circulating cholesterol levels have demonstrated the involvement of cell proliferation/apoptosis balance regulation. This chapter reviewed our current understanding of how cholesterol metabolism contributes to cancer development and progression and cholesterol-lowering drugs may be associated with the therapeutic potential of cancer prevention and treatment. Current evidence cannot exclude the relevance of cancer risk with statin use as seen in a variety of studies. Whether the genetic mutations of cancer patients are associated with the response of statins is also unknown. It is clear that more studies are needed to better characterize potential statin-mediated mechanisms that prevent cancer incidence. On the other hand, statins alone or used in combination with certain anticancer drugs or radiation therapy can improve survival in patients with several different tumors. Further research using large cohort studies in different cancers is needed to clarify these issues. In addition, searching for novel classes of cholesterol-lowering drugs with more effects and less side effects could provide new therapeutic options for cancer prevention and therapy.

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