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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 treatment 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 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 (PPAR α), 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 colestesvelam, 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	PPAR α	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]

*PPAR α , 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 μ M 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 GDI α 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 <i>H. pylori</i> -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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References

- [1] Grouleff J, Irudayam SJ, Skeby KK, Schiøtt B. The influence of cholesterol on membrane protein structure, function, and dynamics studied by molecular dynamics simulations. *Biochim Biophys Acta*. 2015; 1848:1783-95.
- [2] Mesmin B, Maxfield FR. Intracellular sterol dynamics. *Biochim Biophys Acta*. 2009; 1791:636-45.

- [3] Wüstner D, Solanko K. How cholesterol interacts with proteins and lipids during its intracellular transport. *Biochim Biophys Acta*. 2015; 1848:1908-26.
- [4] Sengupta D, Chattopadhyay A. Molecular dynamics simulations of GPCR-cholesterol interaction: an emerging paradigm. *Biochim Biophys Acta*. 2015; 1848:1775-82.
- [5] Du X, Brown AJ, Yang H. Novel mechanisms of intracellular cholesterol transport: oxysterol-binding proteins and membrane contact sites. *Curr Opin Cell Biol*. 2015; 35:37-42.
- [6] Papadopoulos V, Aghazadeh Y, Fan J, Campioli E, Zirkin B, Midzak A. Translocator protein-mediated pharmacology of cholesterol transport and steroidogenesis. *Mol Cell Endocrinol*. 2015; 408:90-8.
- [7] Issop L, Rone MB, Papadopoulos V. Organelle plasticity and interactions in cholesterol transport and steroid biosynthesis. *Mol Cell Endocrinol*. 2013; 371:34-46.
- [8] Simons K, Ikonen E. How cells handle cholesterol. *Science*. 2000; 290:1721-6.
- [9] Cruz PM, Mo H, McConathy WJ, Sabnis N, Lacko AG. The role of cholesterol metabolism and cholesterol transport in carcinogenesis: a review of scientific findings, relevant to future cancer therapeutics. *Front Pharmacol*. 2013; 4:119.
- [10] Nelson ER, Chang CY, McDonnell DP. Cholesterol and breast cancer pathophysiology. *Trends Endocrinol Metab*. 2014; 25:649-55.
- [11] Danilo C, Frank PG. Cholesterol and breast cancer development. *Curr Opin Pharmacol*. 2012; 12:677-82.
- [12] Krycer JR, Brown AJ. Cholesterol accumulation in prostate cancer: a classic observation from a modern perspective. *Biochim Biophys Acta*. 2013; 1835:219-29.
- [13] Drabkin HA, Gemmill RM. Cholesterol and the development of clear-cell renal carcinoma. *Curr Opin Pharmacol*. 2012; 12:742-50.
- [14] Jacobs RJ, Voorneveld PW, Kodach LL, Hardwick JC. Cholesterol metabolism and colorectal cancers. *Curr Opin Pharmacol*. 2012; 12:690-5.
- [15] Murai T. Cholesterol lowering: role in cancer prevention and treatment. *Biol Chem*. 2015; 396:1-11.
- [16] Silvente-Poirot S, Poirot M. Cancer. Cholesterol and cancer, in the balance. *Science*. 2014; 343:1445-6.
- [17] Pelton K, Freeman MR, Solomon KR: Cholesterol and prostate cancer. *Curr Opin Pharmacol* 2012; 12:751-759.
- [18] Gorin A, Gabitova L, Astsaturov I: Regulation of cholesterol biosynthesis and cancer signaling. *Curr Opin Pharmacol*. 2012; 12:710-716.
- [19] Hilvo M, Denkert C, Lehtinen L, Muller B, Brockmoller S, Seppanen-Laakso T, Budczies J, Bucher E, Yetukuri L, Castillo S, Berg E, Nygren H, Sysi-Aho M, Griffin JL, Fiehn O,

- Loibl S, Richter-Ehrenstein C, Radke C, Hyötyläinen T, Kallioniemi O, Iljin K, Oresic M: Novel theranostic opportunities offered by characterization of altered membrane lipid metabolism in breast cancer progression. *Cancer Res* 2011; 71:3236-3245.
- [20] Nelson DL and Cox MM eds. *Lehninger Principles of Biochemistry*. 6th edition, 2012, W.H. Freeman & Company, New York.
- [21] Berg JM, Tymoczko JL and Stryer L. *Biochemistry*. 7th edition, 2012, W.H. Freeman & Company, New York.
- [22] Porter FD, Herman GE. Malformation syndromes caused by disorders of cholesterol synthesis. *J Lipid Res*. 2011; 52:6-34.
- [23] Fu Z, Voynova NE, Herdendorf TJ, Miziorko HM, Kim JJ. Biochemical and structural basis for feedback inhibition of mevalonate kinase and isoprenoid metabolism. *Biochemistry* 2008; 47: 3715-24.
- [24] Gaylor JL. Membrane-bound enzymes of cholesterol synthesis from lanosterol. *Biochem Biophys Res Commun* 2002; 292:1139-46.
- [25] Goldstein JL, Brown MS. Regulation of the mevalonate pathway. *Nature* 1990; 343:425-30.
- [26] Miziorko HM. Enzymes of the mevalonate pathway of isoprenoid biosynthesis. *Arch Biochem Biophys* 2011; 505:131-43.
- [27] Houten SM, Frenkel J, Waterham HR. Isoprenoid biosynthesis in hereditary periodic fever syndromes and inflammation. *Cell Mol Life Sci* 2003; 60:1118-34.
- [28] Luu W, Sharpe LJ, Gelissen IC, Brown AJ. The role of signalling in cellular cholesterol homeostasis. *IUBMB Life*. 2013; 65:675-84.
- [29] van der Wulp MY, Verkade HJ, Groen AK. Regulation of cholesterol homeostasis. *Mol Cell Endocrinol*. 2013; 368:1-16.
- [30] Goedeke L, Fernández-Hernando C. Regulation of cholesterol homeostasis. *Cell Mol Life Sci*. 2012; 69:915-30.
- [31] Sharpe LJ, Cook EC, Zelcer N, Brown AJ. The UPS and downs of cholesterol homeostasis. *Trends Biochem Sci*. 2014; 39:527-35.
- [32] Malgrange B, Varela-Nieto I, de Medina P, Paillasse MR. Targeting cholesterol homeostasis to fight hearing loss: a new perspective. *Front Aging Neurosci*. 2015; 7:3.
- [33] Nestel PJ, Whyte HM, Goodman DS. Distribution and turnover of cholesterol in humans. *J Clin Invest*. 1969; 48:982-991.
- [34] Nestel PJ. Cholesterol turnover in man. *Adv Lipid Res*. 1970; 8:1-39.
- [35] Ho KJ, Taylor CB. Control mechanisms of cholesterol biosynthesis. *Arch Pathol*. 1970; 90:83-92.

- [36] Wang DQ. Regulation of intestinal cholesterol absorption. *Annu Rev Physiol.* 2007; 69:221-48.
- [37] Bertolotti M, Gabbi C, Anzivino C, Carulli L, Loria P, Carulli N. Nuclear receptors as potential molecular targets in cholesterol accumulation conditions: insights from evidence on hepatic cholesterol degradation and gallstone disease in humans. *Curr Med Chem* 2008; 15:2271–2284.
- [38] Czarnicka H, Yokoyama S. Lecithin:cholesterol acyltransferase reaction on cellular lipid released by free apolipoprotein-mediated efflux. *Biochemistry* 1995; 34:4385-4392.
- [39] Tomimoto S, Tsujita M, Okazaki M, Usui S, Tada T, Fukutomi T, Ito S, Itoh M, Yokoyama S. Effect of probucol in lecithin:cholesterol acyltransferase-deficient mice: inhibition of 2 independent cellular cholesterol-releasing pathways in vivo. *Arterioscler Thromb Vasc Biol* 2001; 21:394-400.
- [40] Yokoyama S. Release of cellular cholesterol: molecular mechanism for cholesterol homeostasis in cells and in the body. *Biochim Biophys Acta.* 2000; 1529:231-44.
- [41] Gumbs PD, Verschuren MW, Mantel-Teeuwisse AK, de Wit AG, de Boer A, Klungel OH. Economic evaluations of cholesterol-lowering drugs: a critical and systematic review. *Pharmacoeconomics.* 2007; 25:187-99.
- [42] Alla VM, Agrawal V, DeNazareth A, Mohiuddin S, Ravilla S, Rendell M. A reappraisal of the risks and benefits of treating to target with cholesterol lowering drugs. *Drugs.* 2013; 73:1025-54
- [43] Bardou M, Barkun A, Martel M. Effect of statin therapy on colorectal cancer. *Gut.* 2010; 59:1572-85.
- [44] Sassano A, Plataniias LC. Statins in tumor suppression. *Cancer Lett.* 2008; 260:11-9.
- [45] Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell.* 2015; 161:161-72.
- [46] Seo HS, Choi MH. Cholesterol homeostasis in cardiovascular disease and recent advances in measuring cholesterol signatures. *J Steroid Biochem Mol Biol.* 2015; 153:72-9.
- [47] Varbo A, Nordestgaard BG. Remnant cholesterol and ischemic heart disease. *Curr Opin Lipidol.* 2014; 25:266-73.
- [48] Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. *Nat Rev Immunol.* 2015; 15:104-16.
- [49] Zhang J, Liu Q. Cholesterol metabolism and homeostasis in the brain. *Protein Cell.* 2015; 6:254-64.

- [50] Leoni V, Caccia C. The impairment of cholesterol metabolism in Huntington disease. *Biochim Biophys Acta*. 2015; 1851:1095-105.
- [51] Hannaoui S, Shim SY, Cheng YC, Corda E, Gilch S. Cholesterol balance in prion diseases and Alzheimer's disease. *Viruses*. 2014; 6:4505-35.
- [52] Simons K, Toomre D. Lipid rafts and signal transduction. *Nat Rev Mol Cell Biol*. 2000; 1:31-39.
- [53] Brown DA, London E. Functions of lipid rafts in biological membranes. *Annu Rev Cell Dev Biol*. 1998; 14:111-136.
- [54] Mollinedo F, Gajate C. Lipid rafts as major platforms for signaling regulation in cancer. *Adv Biol Regul*. 2015; 57:130-46.
- [55] Reeves VL, Thomas CM, Smart EJ. Lipid rafts, caveolae and GPI-linked proteins. *Adv Exp Med Biol*. 2012; 729:3-13.
- [56] Lajoie P, Nabi IR. Lipid rafts, caveolae, and their endocytosis. *Int Rev Cell Mol Biol*. 2010; 282:135-63.
- [57] Sun Y, Sukumaran P, Varma A, Derry S, Sahmoun AE, Singh BB. Cholesterol-induced activation of TRPM7 regulates cell proliferation, migration, and viability of human prostate cells. *Biochim Biophys Acta*. 2014; 1843:1839-50.
- [58] dos Santos CR, Domingues G, Matias I, Matos J, Fonseca I, de Almeida JM, Dias S. LDL-cholesterol signaling induces breast cancer proliferation and invasion. *Lipids Health Dis*. 2014; 13:16.
- [59] Xu F, Rychnovsky SD, Belani JD, Hobbs HH, Cohen JC, Rawson RB. Dual roles for cholesterol in mammalian cells. *Proc Natl Acad Sci U S A*. 2005; 102:14551-6.
- [60] Chen BY, Wei JG, Wang YC, Yu J, Qian JX, Chen YM, Xu J. Effects of cholesterol on proliferation and functional protein expression in rabbit bile duct fibroblasts. *World J Gastroenterol*. 2004; 10:889-93.
- [61] Franco SJ, Huttenlocher A. Regulating cell migration: calpains make the cut. *J Cell Sci* 2005; 118:3829-3838.
- [62] Sukumaran P, Lof C, Pulli I, Kemppainen K, Viitanen T, Tornquist K. Significance of the transient receptor potential canonical 2 (TRPC2) channel in the regulation of rat thyroid FRTL-5 cell proliferation, migration, adhesion and invasion. *Mol Cell Endocrinol* 2013; 374:10-21.
- [63] Riobo NA. Cholesterol and its derivatives in Sonic Hedgehog signaling and cancer. *Curr Opin Pharmacol*. 2012; 12:736-41.
- [64] Callahan BP, Wang C. Hedgehog cholesterolysis: specialized gatekeeper to oncogenic signaling. *Cancers (Basel)*. 2015; 7:2037-53.

- [65] Sewer MB, Li D. Regulation of steroid hormone biosynthesis by the cytoskeleton. *Lipids*. 2008; 43:1109-15.
- [66] Mani SK, Mermelstein PG, Tetel MJ, Anesetti G. Convergence of multiple mechanisms of steroid hormone action. *Horm Metab Res*. 2012; 44:569-76.
- [67] Javitt NB. Biologic role(s) of the 25(R),26-hydroxycholesterol metabolic pathway. *Biochim Biophys Acta*. 2000; 1529:136-41.
- [68] Ren S, Ning Y. Sulfation of 25-hydroxycholesterol regulates lipid metabolism, inflammatory responses, and cell proliferation. *Am J Physiol Endocrinol Metab*. 2014; 306:E123-30.
- [69] White, C.P. On the occurrence of crystals in tumours. *J Pathol Bacteriol*. 1909; 13: 3-10.
- [70] Clayman RV, Gonzalez R, Elliott AY, Gleason DE, Dempsey ME. Cholesterol accumulation in heterotransplanted renal cell cancer. *J Urol*. 1983; 129:621-4.
- [71] Wang J, Wang WJ, Zhai L, Zhang DF. Association of cholesterol with risk of pancreatic cancer: a meta-analysis. *World J Gastroenterol*. 2015; 21:3711-9.
- [72] Touvier M, Fassier P, His M, Norat T, Chan DS, Blacher J, Hercberg S, Galan P, Druesne-Pecollo N, Latino-Martel P. Cholesterol and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Br J Nutr*. 2015; 114:347-57.
- [73] Vílchez JA, Martínez-Ruiz A, Sancho-Rodríguez N, Martínez-Hernández P, Noguera-Velasco JA. The real role of prediagnostic high-density lipoprotein cholesterol and the cancer risk: a concise review. *Eur J Clin Invest*. 2014; 44:103-14.
- [74] Freeman MR, Solomon KR. Cholesterol and prostate cancer. *J Cell Biochem*. 2004; 91:54-69.
- [75] Kato S, Smalley S, Sadarangani A, Chen-Lin K, Oliva B, Brañes J, Carvajal J, Gejman R, Owen GI, Cuello M. Lipophilic but not hydrophilic statins selectively induce cell death in gynaecological cancers expressing high levels of HMGCoA reductase. *J Cell Mol Med*. 2010; 14:1180-93.
- [76] Millatt LJ, Bocher V, Fruchart JC, Staels B. Liver X receptors and the control of cholesterol homeostasis: potential therapeutic targets for the treatment of atherosclerosis. *Biochim Biophys Acta*. 2003; 1631:107-18.
- [77] Oosterveer MH, Grefhorst A, Groen AK, Kuipers F. The liver X receptor: control of cellular lipid homeostasis and beyond Implications for drug design. *Prog Lipid Res*. 2010; 49:343-52.
- [78] Bovenga F, Sabbà C, Moschetta A. Uncoupling nuclear receptor LXR and cholesterol metabolism in cancer. *Cell Metab*. 2015; 21:517-26.
- [79] Simon TG, Butt AA. Lipid dysregulation in hepatitis C virus, and impact of statin therapy upon clinical outcomes. *World J Gastroenterol*. 2015; 21:8293-303.

- [80] Antoniou GA, Fisher RK, Georgiadis GS, Antoniou SA, Torella F. Statin therapy in lower limb peripheral arterial disease: systematic review and meta-analysis. *Vascul Pharmacol.* 2014; 63:79-87.
- [81] Pang J, Chan DC, Watts GF. Critical review of non-statin treatments for dyslipoproteinemia. *Expert Rev Cardiovasc Ther.* 2014; 12:359-71.
- [82] Szajnman SH, Ravaschino EL, Docampo R, Rodriguez JB. Synthesis and biological evaluation of 1-amino-1,1-bisphosphonates derived from fatty acids against *Trypanosoma cruzi* targeting farnesyl pyrophosphate synthase. *Bioorg Med Chem Lett.* 2005; 15:4685-90.
- [83] Graaf MR, Richel DJ, van Noorden CJ, Guchelaar HJ. Effects of statins and farnesyl-transferase inhibitors on the development and progression of cancer. *Cancer Treat Rev.* 2004; 30:609-41.
- [84] Ugawa T, Kakuta H, Moritani H, Matsuda K, Ishihara T, Yamaguchi M, Naganuma S, Iizumi Y, Shikama H. YM-53601, a novel squalene synthase inhibitor, reduces plasma cholesterol and triglyceride levels in several animal species. *Br J Pharmacol.* 2000; 131:63-70.
- [85] Nishimoto T, Ishikawa E, Anayama H, Hamajyo H, Nagai H, Hirakata M, Tozawa R. Protective effects of a squalene synthase inhibitor, lapaquistat acetate (TAK-475), on statin-induced myotoxicity in guinea pigs. *Toxicol Appl Pharmacol.* 2007; 223:39-45.
- [86] Amin D, Rutledge RZ, Needle SN, Galczynski HF, Neuenschwander K, Scotese AC, Maguire MP, Bush RC, Hele DJ, Bilder GE, Perrone MH. RPR 107393, a potent squalene synthase inhibitor and orally effective cholesterol-lowering agent: comparison with inhibitors of HMG-CoA reductase. *J Pharmacol Exp Ther.* 1997; 281:746-52.
- [87] Chuang JC, Valasek MA, Lopez AM, Posey KS, Repa JJ, Turley SD. Sustained and selective suppression of intestinal cholesterol synthesis by Ro 48-8071, an inhibitor of 2,3-oxidosqualene:lanosterol cyclase, in the BALB/c mouse. *Biochem Pharmacol.* 2014; 88:351-63.
- [88] Eisele B, Budzinski R, Müller P, Maier R, Mark M. Effects of a novel 2,3-oxidosqualene cyclase inhibitor on cholesterol biosynthesis and lipid metabolism in vivo. *J Lipid Res.* 1997; 38:564-75.
- [89] Ryder NS. Terbinafine: mode of action and properties of the squalene epoxidase inhibition. *Br J Dermatol.* 1992; 126 Suppl 39:2-7.
- [90] Nutescu EA, Shapiro NL. Ezetimibe: a selective cholesterol absorption inhibitor. *Pharmacotherapy.* 2003; 23:1463-74.
- [91] Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. *Atherosclerosis.* 2011; 217:492-8

- [92] Wierzbicki AS. Fibrates: no ACCORD on their use in the treatment of dyslipidaemia. *Curr Opin Lipidol*. 2010; 21:352-8.
- [93] Corsini A, Windler E, Farnier M. Colesevelam hydrochloride: usefulness of a specifically engineered bile acid sequestrant for lowering LDL-cholesterol. *Eur J Cardiovasc Prev Rehabil*. 2009; 16:1-9.
- [94] Hou R, Goldberg AC. Lowering low-density lipoprotein cholesterol: statins, ezetimibe, bile acid sequestrants, and combinations: comparative efficacy and safety. *Endocrinol Metab Clin North Am*. 2009; 38:79-97.
- [95] Llaverías G, Laguna JC, Alegret M. Pharmacology of the ACAT inhibitor avasimibe (CI-1011). *Cardiovasc Drug Rev*. 2003; 21:33-50.
- [96] Koo SI, Noh SK. Green tea as inhibitor of the intestinal absorption of lipids: potential mechanism for its lipid-lowering effect. *J Nutr Biochem*. 2007; 18:179-83.
- [97] Perry CM. Lomitapide: a review of its use in adults with homozygous familial hypercholesterolemia. *Am J Cardiovasc Drugs*. 2013; 13:285-96.
- [98] Ricotta DN, Frishman W. Mipomersen: a safe and effective antisense therapy adjunct to statins in patients with hypercholesterolemia. *Cardiol Rev*. 2012; 20:90-5.
- [99] Gutstein DE, Krishna R, Johns D, Surks HK, Dansky HM, Shah S, Mitchel YB, Arena J, Wagner JA. Anacetrapib, a novel CETP inhibitor: pursuing a new approach to cardiovascular risk reduction. *Clin Pharmacol Ther*. 2012; 91:109-22.
- [100] Tavori H, Melone M, Rashid S. Alirocumab: PCSK9 inhibitor for LDL cholesterol reduction. *Expert Rev Cardiovasc Ther*. 2014; 12:1137-44.
- [101] Cicero AF, Tartagni E, Ertek S. Efficacy and safety profile of evolocumab (AMG145), an injectable inhibitor of the proprotein convertase subtilisin/kexin type 9: the available clinical evidence. *Expert Opin Biol Ther*. 2014; 14:863-8.
- [102] Preta G, Cronin JG, Sheldon IM. Dynasore - not just a dynamin inhibitor. *Cell Commun Signal*. 2015; 13:24.
- [103] Gbelcová H, Leníček M, Zelenka J, Knejzlík Z, Dvůráková G, Zadinová M, Poucková P, Kudla M, Balaz P, Ruml T, Vitek L. Differences in antitumor effects of various statins on human pancreatic cancer. *Int J Cancer*. 2008; 122:1214-21.
- [104] Benakanakere I, Johnson T, Sleightholm R, Villeda V, Arya M, Bobba R, Freter C, Huang C. Targeting cholesterol synthesis increases chemoimmuno-sensitivity in chronic lymphocytic leukemia cells. *Exp Hematol Oncol*. 2014; 3:24.
- [105] Lin CJ, Liao WC, Lin HJ, Hsu YM, Lin CL, Chen YA, Feng CL, Chen CJ, Kao MC, Lai CH, Kao CH. Statins attenuate *Helicobacter pylori* CagA translocation and reduce incidence of gastric cancer: in vitro and population-based case-control studies. *PLoS One*. 2016; 11:e0146432.

- [106] Bjarnadottir O, Romero Q, Bendahl PO, Jirström K, Rydén L, Loman N, Uhlén M, Johannesson H, Rose C, Grabau D, Borgquist S. Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial. *Breast Cancer Res Treat.* 2013; 138:499-508.
- [107] Sehdev A, O'Neil BH. The role of aspirin, vitamin D, exercise, diet, statins, and metformin in the prevention and treatment of colorectal cancer. *Curr Treat Opt Oncol.* 2015; 16:43.
- [108] Peng YC, Lin CL, Hsu WY, Chang CS, Yeh HZ, Tung CF, Wu YL, Sung FC, Kao CH. Statins are associated with a reduced risk of cholangiocarcinoma: a population-based case-control study. *Br J Clin Pharmacol.* 2015; 80:755-61.
- [109] Jacobs EJ, Rodriguez C, Bain EB, Wang Y, Thun MJ, Calle EE. Cholesterol-lowering drugs and advanced prostate cancer incidence in a large U.S. cohort. *Cancer Epidemiol Biomark Prev.* 2007; 16:2213-7.
- [110] Vinogradova Y, Hippisley-Cox J, Coupland C, Logan RF. Risk of colorectal cancer in patients prescribed statins, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors: nested case-control study. *Gastroenterology.* 2007; 133:393-402.
- [111] Jacobs EJ, Rodriguez C, Brady KA, Connell CJ, Thun MJ, Calle EE. Cholesterol-lowering drugs and colorectal cancer incidence in a large United States cohort. *J Natl Cancer Inst.* 2006; 98:69-72.
- [112] Raval AD, Thakker D, Negi H, Vyas A, Salkini MW. Association between statins and clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis.* 2016; doi: 10.1038/pcan.2015.58.
- [113] McKay RR, Lin X, Albiges L, Fay AP, Kaymakcalan MD, Mickey SS, Ghoroghchian PP, Bhatt RS, Kaffenberger SD, Simantov R, Choueiri TK, Heng DY. Statins and survival outcomes in patients with metastatic renal cell carcinoma. *Eur J Cancer.* 2016; 52:155-62.
- [114] Freeman SR, Drake AL, Heilig LF, Graber M, McNealy K, Schilling LM, Dellavalle RP. Statins, fibrates, and melanoma risk: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2006; 98:1538-46.
- [115] Hwa JJ, Zollman S, Warden CH, Taylor BA, Edwards PA, Fogelman AM, Lusis AJ. Genetic and dietary interactions in the regulation of HMG-CoA reductase gene expression. *J Lipid Res.* 1992; 33:711-25.
- [116] Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest* 2002; 109:1125–31.
- [117] Wu N, Sarna LK, Hwang SY, Zhu Q, Wang P, Siow YL, O K. Activation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase during high fat diet feeding. *Biochim Biophys Acta.* 2013; 1832:1560-8.

- [118] Martínez-Botas J, Suárez Y, Ferruelo AJ, Gómez-Coronado D, Lasuncion MA. Cholesterol starvation decreases p34(cdc2) kinase activity and arrests the cell cycle at G2. *FASEB J*. 1999; 13:1359-70.
- [119] Tsubaki M, Yamazoe Y, Yanae M, Satou T, Itoh T, Kaneko J, Kidera Y, Moriyama K, Nishida S. Blockade of the Ras/MEK/ERK and Ras/PI3K/Akt pathways by statins reduces the expression of bFGF, HGF, and TGF- β as angiogenic factors in mouse osteosarcoma. *Cytokine*. 2011; 54:100-7.
- [120] Zhu Y, Casey PJ, Kumar AP, Pervaiz S. Deciphering the signaling networks underlying simvastatin-induced apoptosis in human cancer cells: evidence for non-canonical activation of RhoA and Rac1 GTPases. *Cell Death Dis* 2013; 4:e568.
- [121] Woodard J, Sassano A, Hay N, Plataniias LC. Statin-dependent suppression of the Akt/mammalian target of rapamycin signaling cascade and programmed cell death 4 up-regulation in renal cell carcinoma. *Clin Cancer Res* 2008; 14:4640-4649.
- [122] Weis M, Heeschen C, Glassford AJ, Cooke JP. Statins have biphasic effects on angiogenesis. *Circulation*. 2002; 105:739-45.
- [123] Kidera Y, Tsubaki M, Yamazoe Y, Shoji K, Nakamura H, Ogaki M, Satou T, Itoh T, Isozaki M, Kaneko J, Tanimori Y, Yanae M, Nishida S. Reduction of lung metastasis, cell invasion, and adhesion in mouse melanoma by statin-induced blockade of the Rho/Rho-associated coiled-coil-containing protein kinase pathway. *J Exp Clin Cancer Res*. 2010; 29:127.
- [124] Murai T. The role of lipid rafts in cancer cell adhesion and migration. *Int J Cell Biol*. 2012; 2012:763283.
- [125] Jeon JH, Kim SK, Kim HJ, Chang J, Ahn CM, Chang YS. Lipid raft modulation inhibits NSCLC cell migration through delocalization of the focal adhesion complex. *Lung Cancer*. 2010; 69:165-71.
- [126] Coleman PS. Membrane cholesterol and tumor bioenergetics. *Ann N Y Acad Sci*. 1986; 488:451-67.
- [127] Swyer G. The cholesterol content of normal and enlarged prostates. *Cancer Res* 1942; 2:372-375.
- [128] Singer SJ, Nicolson GL. The fluid mosaic model of the structure of cell membranes. *Science* 1972; 175:720-731.
- [129] Bonovas S, Filioussi K, Sitaras NM. Statins are not associated with a reduced risk of pancreatic cancer at the population level, when taken at low doses for managing hypercholesterolemia: evidence from a meta-analysis of 12 studies. *Am J Gastroenterol*. 2008; 103:2646-51.

- [130] Khurana V, Sheth A, Caldito G, Barkin JS. Statins reduce the risk of pancreatic cancer in humans: a case-control study of half a million veterans. *Pancreas*. 2007; 34:260-5.
- [131] Singh PP, Singh S. Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. *Ann Oncol*. 2013; 24:1721-30.
- [132] Tsan YT, Lee CH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. *J Clin Oncol*. 2012; 30:623-30.
- [133] Chen HH, Lin MC, Muo CH, Yeh SY, Sung FC, Kao CH. Combination therapy of metformin and statin may decrease hepatocellular carcinoma among diabetic patients in Asia. *Medicine (Baltimore)*. 2015; 94:e1013.
- [134] Zhang XL, Geng J, Zhang XP, Peng B, Che JP, Yan Y, Wang GC, Xia SQ, Wu Y, Zheng JH. Statin use and risk of bladder cancer: a meta-analysis. *Cancer Causes Control*. 2013; 24:769-76.
- [135] Yi X, Jia W, Jin Y, Zhen S. Statin use is associated with reduced risk of haematological malignancies: evidence from a meta-analysis. *PLoS One*. 2014; 9:e87019.
- [136] Pradelli D, Soranna D, Zambon A, Catapano A, Mancina G, La Vecchia C, Corrao G. Statins use and the risk of all and subtype hematological malignancies: a meta-analysis of observational studies. *Cancer Med*. 2015;4(5):770-80.
- [137] Wang J, Li C, Tao H, Cheng Y, Han L, Li X, Hu Y. Statin use and risk of lung cancer: a meta-analysis of observational studies and randomized controlled trials. *PLoS One*. 2013; 8:e77950.
- [138] Bansal D, Undela K, D'Cruz S, Schifano F. Statin use and risk of prostate cancer: a meta-analysis of observational studies. *PLoS One*. 2012; 7:e46691.
- [139] Undela K, Srikanth V, Bansal D. Statin use and risk of breast cancer: a meta-analysis of observational studies. *Breast Cancer Res Treat*. 2012; 135:261-9.
- [140] Lytras T, Nikolopoulos G, Bonovas S. Statins and the risk of colorectal cancer: an updated systematic review and meta-analysis of 40 studies. *World J Gastroenterol*. 2014; 20:1858-70.
- [141] Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation*. 2007; 115:27-33.
- [142] Kuoppala J, Lamminpää A, Pukkala E. Statins and cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2008; 44:2122-32.
- [143] Song C, Park S, Park J, Shim M, Kim A, Jeong IG, Hong JH, Kim CS, Ahn H. Statin use after radical prostatectomy reduces biochemical recurrence in men with prostate cancer. *Prostate*. 2015; 75:211-7.

- [144] Cai H, Zhang G, Wang Z, Luo Z, Zhou X. Relationship between the use of statins and patient survival in colorectal cancer: a systematic review and meta-analysis. *PLoS One*. 2015; 10:e0126944.
- [145] Cardwell CR, Hicks BM, Hughes C, Murray LJ. Statin use after colorectal cancer diagnosis and survival: a population-based cohort study. *J Clin Oncol*. 2014; 32:3177-83.
- [146] Kozak MM, Anderson EM, von Eyben R, Pai JS, Poultides GA, Visser BC, Norton JA, Koong AC, Chang DT. Statin and metformin use prolongs survival in patients with resectable pancreatic cancer. *Pancreas*. 2016; 45:64-70.
- [147] Jeon CY, Pandol SJ, Wu B, Cook-Wiens G, Gottlieb RA, Merz CN, Goodman MT. The association of statin use after cancer diagnosis with survival in pancreatic cancer patients: a SEER-medicare analysis. *PLoS One*. 2015; 10:e0121783.
- [148] Wu BU, Chang J, Jeon CY, Pandol SJ, Huang B, Ngor EW, Difronzo AL, Cooper RM. Impact of statin use on survival in patients undergoing resection for early-stage pancreatic cancer. *Am J Gastroenterol*. 2015; 110:1233-9.
- [149] Lacerda L, Reddy JP, Liu D, Larson R, Li L, Masuda H, Brewer T, Debeb BG, Xu W, Hortobágyi GN, Buchholz TA, Ueno NT, Woodward WA. Simvastatin radiosensitizes differentiated and stem-like breast cancer cell lines and is associated with improved local control in inflammatory breast cancer patients treated with postmastectomy radiation. *Stem Cells Transl Med*. 2014; 3:849-56.
- [150] Winiarska M, Bil J, Wilczek E, Wilczynski GM, Lekka M, Engelberts PJ, Mackus WJ, Gorska E, Bojarski L, Stoklosa T, Nowis D, Kurzaj Z, Makowski M, Glodkowska E, Issat T, Mrowka P, Lasek W, Dabrowska-Iwanicka A, Basak GW, Wasik M, Warzocha K, Sinski M, Gaciong Z, Jakobisiak M, Parren PW, Golab J. Statins impair antitumor effects of rituximab by inducing conformational changes of CD20. *PLoS Med*. 2008; 5:e64.
- [151] Hoffmeister M, Jansen L, Rudolph A, Toth C, Kloor M, Roth W, Bläker H, Chang-Claude J, Brenner H. Statin use and survival after colorectal cancer: the importance of comprehensive confounder adjustment. *J Natl Cancer Inst*. 2015; 107:djv045.

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