Review

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Cholesterol lowering: role in cancer prevention and treatment

Abstract: The accumulation of cholesterol is a general feature of cancer tissue, and recent evidence suggests that cholesterol plays critical roles in the progression of cancers, including breast, prostate, and colorectal cancers. The dysregulation of metabolic pathways, including those involved in cholesterol biosynthesis, is implicated in tumor development and cancer progression. Lipid rafts are highly dynamic cholesterol-enriched domains of the cell membrane, involved in various cellular functions, including the regulation of transmembrane signaling at the cell surface. It was recently demonstrated that lipid rafts also play critical roles in cancer cell adhesion and migration. This review focuses on our current understanding of how cholesterol regulation, lipid rafts, and dysregulated cholesterol biosynthesis contribute to cancer development and progression, and the therapeutic potential of cholesterol lowering for cancer prevention and treatment.

Keywords: lipid raft; microdomain; membrane remodeling; metabolic reprogramming; tumor invasion; statin.

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Introduction

Cancer is a major public health concern in developed countries worldwide (Siegel et al., 2013). Altered cell adhesion and enhanced migratory ability are the most prominent features of cancer cells; these properties affect the cell’s ability to invade tissue and metastasize (Hanahan and Weinberg, 2011). Cholesterol is required for the assembly and maintenance of cell membranes and modulates membrane fluidity and function, including transmembrane signaling and cell adhesion to the extracellular matrix. In mammals, cholesterol is a precursor for bile acid and steroid hormone synthesis and is either absorbed from dietary sources or synthesized de novo in the liver, from which it is transported by apolipoproteins to the systemic circulation. Under physiological conditions, the circulating levels of cholesterol are regulated by its rate of biosynthesis. More than a century ago, cholesterol was observed to accumulate in malignant tissues (White, 1909; Jowett, 1931; Yasuda and Bloor, 1932), and this is now regarded as a general feature of cancer cells (Freeman and Solomon, 2004). Accumulating evidence suggests that cholesterol plays a critical role in cancer progression. This review focuses on the current understanding of the mechanisms by which cholesterol contributes to cancer development and the therapeutic potential of cholesterol lowering in cancer prevention and treatment.

Cholesterol metabolism in cancer

Cholesterol biosynthesis in cancer cells

The maintenance of cholesterol homeostasis is a fundamental requirement for the normal growth of eukaryotic cells, and the metabolic pathway of cholesterol synthesis is highly conserved, from yeast to humans (Figure 1). Cholesterol synthesis begins with the conversion of citrate, derived from the tricarboxylic acid (TCA) cycle in the mitochondria, to acetyl-coenzyme A (acetyl-CoA), followed by a cascade of enzymatic reactions in the endoplasmic reticulum known as the mevalonate pathway, in which acetyl-CoA is converted to lanosterol. This series of reactions is primarily regulated by a rate-limiting step catalyzed by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (EC 1.1.1.34), which converts HMG-CoA to mevalonate. Finally, lanosterol is converted to cholesterol via the Bloch pathway or the Kandutsch-Russell pathway (Figure 1).

Various metabolic pathways have been implicated in the multistep development of tumors, and a metabolic
shift from catabolic to anabolic metabolism is a classic hallmark of cancer cells (Hanahan and Weinberg 2011). This metabolic reprogramming of cancer cells – resulting in increased glucose uptake and conversion to lactate by glycolysis – is known as the Warburg effect (Warburg et al., 1927; Warburg, 1956), and leads to the acidification of the tumor environment (Parks et al., 2011). Glucose is normally metabolized through the glycolytic pathway into two molecules of pyruvate, which are then converted to acetyl-CoA by a complex of pyruvate dehydrogenase (PDH) in the mitochondria. Acetyl-CoA then enters the TCA cycle, resulting in the generation of substrates for oxidative phosphorylation. Cancer cells, in contrast, consume an excessive quantity of glucose, metabolizing it via both catabolic and anabolic pathways, resulting in the synthesis of large amounts of precursors for macromolecule biosynthesis; thus, these cells have highly proliferative phenotypes. An isozyme of the first enzyme in the glycolytic pathway, hexokinase 2 (HK2), is highly expressed in certain cancer cells and is thought to support anabolic
metabolism, including prostate cancer cells (Mathupala et al., 2006). The product of hexokinase catalysis, glucose 6-phosphate (G6P), undergoes one of two fates: glycolysis via the Embden-Meyerhof (EM) pathway or metabolism via the pentose phosphate pathway (PPP). The PPP is indispensable for NADPH homeostasis, and plays critical roles in highly proliferating cells such as cancer cells. In these cells, G6P is shuttled through the PPP, producing NADPH, which is required for cholesterol biosynthesis. PPP intermediates can also re-enter the glycolytic pathway to produce pyruvate, which may also be utilized for cholesterol biosynthesis (Vander Heiden et al., 2010). In addition, cancer cells exhibit increased glucose uptake and glutaminolysis, which replenish TCA cycle metabolites (DeBerardinis et al., 2007). Tumor hypoxia prevents pyruvate entry into the TCA cycle, and mitochondrial oxidative metabolism may be impaired in cancer cells as a result of mutations in enzymes involved in the TCA cycle or electron transport chain. Under these conditions, reductive carboxylation supports cell growth through the activity of a cytosolic isozyme of isocitrate dehydrogenase, IDH1, which catalyzes the first step in the production of acetyl-CoA from glutamine-derived α-ketoglutarate (Mullen et al., 2012) (Figure 1).

In addition to the shift in glucose and glutamine metabolism, increased lipid synthesis is also recognized as a common feature of the metabolic reprogramming in cancer cells (Hirsch et al., 2010). Many cancer cell types exhibit a reactivation of de novo fatty acid synthesis (Menendez and Lupu, 2007) and the enhanced expression of enzymes of the mevalonate pathway (Freed-Pastor et al., 2012). Most of the de novo synthesized fatty acids and cholesterol are derived from glucose, but in certain cancer cells they are synthesized from glutamine. Cholesterol synthesis is tightly regulated in normal cells, but dysregulated cholesterol synthesis and sterol-dependent proliferation are frequently found in various cancer cell types, and may lead to cancer progression (Hirsch et al., 2010). In addition, proliferating cancer cells exhibit increased HMG-CoA reductase and low-density lipoprotein (LDL) receptor activities, resulting in increased cholesterol levels and higher cholesterol consumption compared to normal proliferating cells (Ho et al., 1978; Azrolan and Coleman 1989).

**Cancer-related regulators of cholesterol metabolism**

The expression of HMG-CoA reductase is transcriptionally regulated by the sterol response element-binding proteins (SREBPs). The SREBPs, which belong to the leucine zipper family of transcription factors, consist of three isoforms: SREBP-1a, -1c, and -2, and their regulation has been explored and recently reviewed (Brown and Goldstein, 2009). The upregulation of SREBPs in cancer cells leads to the activation of genes controlling lipid synthesis, such as HMG-CoA reductase, which is known to be increased in tumors (Azrolan and Coleman 1989). The tumor suppressor p53 maintains mitochondrial activity by regulating the expression of cytochrome c oxidase 2, and a loss of p53 causes a metabolic switch to glycolysis, providing an explanation for the Warburg effect (Matoba et al., 2006). P53 also serves as a co-activator of SREBPs (Freed-Pastor et al., 2012), potentially contributing to the regulation of cholesterol synthesis.

In addition to the classic transcriptional regulation of cholesterol metabolism by SREBPs, a class of non-coding RNAs termed microRNAs (miRNAs) has been identified as potent post-transcriptional regulators of genes involved in cholesterol metabolism (Moore et al., 2010). Recently, a number of miRNAs were found to be aberrantly expressed in cancer cells, and to play a role in regulating cancer progression (Huang and He, 2011). An intronic miRNA located within the gene encoding sterol-regulatory element-binding factor-2 (SREBF-2), miR-33, regulates cholesterol metabolism in concert with SREBPs, contributing to tumor growth (Rayner et al., 2010; Ibrahim et al., 2011), suggesting a therapeutic potential for miRNA modulation.

HMG-CoA reductase acts very early in the cholesterol biosynthesis pathway, during the third step in the mevalonate pathway, with over 20 subsequent enzymes required to produce cholesterol. How these later enzymes are regulated is largely unexplored, but there is growing evidence that some of them serve as flux-controlling points (Sharpe and Brown, 2013). In renal cancer cells, for example, another enzyme of the mevalonate pathway, squalene monoxygenase (SM), which converts squalene to squalene-2,3-epoxide (Figure 1), has been proposed as a second rate-limiting enzyme in cholesterol synthesis, and may contribute to renal cancer development (Gonzalez et al., 1979). In addition, in a breast cancer cell model of metastasis, an enzyme in the Kandutsch-Russell pathway, NAD(P) H-dependent steroid dehydrogenase-like protein (NSDHL) was found to translocate to the plasma membrane as its expression increases (Xue et al., 2013). This translocation may contribute to the signal transduction involved in cancer metastasis by facilitating the formation of lipid rafts, which are cholesterol-enriched cell-membrane domains.
Cholesterol lowering and cancer

Epidemiological studies originally revealed a negative correlation between serum cholesterol levels and the risk of certain type of cancers (Kritchevsky and Kritchevsky, 1992), although this may be an effect rather than a cause of cancer, and it is difficult to draw conclusions from epidemiological studies because of their intrinsic limitations. More recently, however, low plasma cholesterol levels were inversely correlated with the risk of prostate cancer (Pelton et al., 2012), and statin-induced cholesterol lowering was positively associated with a decrease in cancer incidence (Farwell et al., 2008). In addition, a metabolite of cholesterol contributes to breast cancer growth (Kiberstis, 2013). These findings support the notion that cholesterol lowering may be a useful strategy for cancer prevention and treatment.

Breast cancer

Breast cancer is the most commonly diagnosed malignancy in women (Siegel et al., 2013). Dietary cholesterol intake is positively associated with the risk of breast cancer (Hu et al., 2012), and oxysterol 27-hydroxycholesterol (27HC), a primary metabolite of cholesterol (Figure 2A), increases tumor growth and metastasis in mouse models of breast cancer (Nelson et al., 2013). Furthermore, cholesterol is a precursor of estrogen, and high estrogen levels are associated with an increased risk of breast cancer (Yager and Davidson, 2006) (Figure 2A). Thus, the lowering of circulating cholesterol levels may be a useful strategy for breast cancer prevention or treatment.

Prostate cancer

Prostate cancer is the most commonly diagnosed cancer among men, and a leading cause of death in Western countries (Siegel et al., 2013). The increased cholesterol content of benign prostatic hyperplasia was reported 70 years ago (Swyer, 1942), and evidence of a role for cholesterol in prostate cancer has increased over the past decade (Pelton et al., 2012). In prostate cancer cells, fatty acid and cholesterol synthesis pathways are highly upregulated (Rossi et al., 2003; Platz et al., 2008). In SCID mice injected with prostate cancer cells, an elevation in circulating cholesterol increases the cholesterol content of lipid rafts, alters raft-mediated downstream signaling, and promotes tumor growth (Zhuang et al., 2005). These findings suggest that novel molecules involved in cholesterol-dependent tumor progression may be identified in the lipid rafts. The mevalonate pathway, which promotes cholesterol accumulation, is highly upregulated in prostate cancers, and epidemiological studies have been performed to examine the association between high serum cholesterol and an increased risk of prostate cancer (Pelton et al., 2012). Treating prostate cancer cells with simvastatin, an inhibitor of cholesterol synthesis, lowers the cholesterol content of the plasma membrane and inhibits raft-mediated signaling related to cancer progression (Zhuang et al., 2005), while the long-term administration of statins reduces the risk of human prostate cancer (Solomon and Freeman, 2008).

Prostate cancer cells proliferate in response to androgen via the nuclear androgen receptor, and androgen is produced by steroidogenesis, in which cholesterol is the precursor (Figure 2A). Recent studies demonstrated that prostate cancer cells produce androgen by intratumoral steroidogenesis, leading to their enhanced proliferation (Locke et al., 2008). Thus, cholesterol may play multiple roles in promoting prostate cancer, supporting the
potential use of cholesterol-reducing treatments for this disease.

Colorectal cancer

Colorectal cancer is the second leading cause of cancer death in the world (Siegel et al., 2013). Colorectal cancer is a distinct type of genetic disease in which not one, but several mutations are required, and the majority of colorectal cancer occurs without identifiable genetic risk factors, suggesting that environmental factors are critical in the development of this disease (Vogelstein and Kinzler, 1993). One of the major environmental factors that affect the colorectal cancer risk is dietary fat, and high levels of serum cholesterol are associated with an increased risk of colorectal cancer (Holtzman et al., 1987). In contrast, the long-term use of statins is associated with a significantly reduced relative risk of colorectal cancer (Poynter et al., 2005). Bile acids are synthesized from cholesterol mostly in the liver, and an increased incidence of colorectal cancer is associated with high levels of bile acids. Thus, bile acids may function as cancer promoters in the colon (Bernstein et al., 2005).

Colitis-associated cancer is the type of colorectal cancer which is preceded by inflammatory bowel disease (IBD) including ulcerative colitis (UC), and the risk of colorectal cancer for any patient with UC is estimated to be 18% after 30 years of disease (Grivennikov, 2013). The disruption of intestinal epithelial lipid rafts is a feature of inflammatory conditions in IBD, suggesting the possibility that the role of cholesterol relates to the chronic inflammation step toward cancer initiation (Bowie et al., 2012).

Lipid rafts and cancer

Lipid rafts and cancer cell migration and invasion

There is growing interest in targeting lipid rafts for cancer prevention and treatment, because of their role in regulating various steps of cancer progression, including cancer cell migration and invasion (Murai, 2012). Cell adhesion is a key factor associated with the metastatic spread of cancer cells, and regulating this process is critical for the therapeutic intervention of cancer. CD44 is a major cell
adhesion receptor expressed in cancer cells and implicated in cancer cell migration, invasion, and metastasis (Lesley et al., 1993). However, despite numerous reports demonstrating that CD44 is present in lipid rafts (Murai, 2012), the role of lipid rafts in cancer cell adhesion and migration has not been elucidated.

It was recently demonstrated that lipid rafts play a crucial role in the localization and functionality of CD44 (Murai et al., 2011) (Figure 2B). Treating human glioma cells with the lipid-raft-disrupting agent methyl-β-cyclodextrin (MβCD), which extracts cellular membrane cholesterol, results in increased CD44 shedding mediated by a disintegrin and metalloprotease 10 (ADAM10) (Murai et al., 2011). Moreover, the CD44 shedding induced by cholesterol lowering is not limited to glioma cells, but is also seen in other tumor cells such as pancreatic cancer cells (Murai et al., 2011). CD44 shedding can also be induced by filipin, a polyene macrolide antibiotic that binds cholesterol and disperses it in the membrane, thereby disrupting lipid rafts by a different mechanism from MβCD (Murai et al., 2011). The cholesterol-lowering clinical medicine simvastatin also enhances CD44 shedding, and concomitantly blocks the stimulation of glioma cell migration by hyaluronan oligosaccharides or epidermal growth factor (EGF) (Sugahara et al., 2003; Murai et al., 2004, 2006, 2009). Taken together, these results suggest that cholesterol lowering results in disordered CD44 localization, raft-dependent CD44 shedding, and the suppression of tumor cell migration (Adler, 2011). Cholesterol lowering also enhances the CD44-mediated adhesion of lymphocytes, suggesting that lipid rafts regulate lymphocyte interactions under physiological flow conditions (Murai et al., 2013a,b). The lipid raft affiliation of CD44 is likely to occur through its palmitoylation, which may affect malignancy of breast cancer (Babina et al., 2014).

Studies on other membrane proteins in cancer cells revealed that depleting the cholesterol in cell membranes also triggers the shedding of L1-cell adhesion molecule (L1-CAM) (Mechtersheimer et al., 2001), amyloid precursor protein (APP) (Kojro et al., 2001), interleukin-6 (IL-6) receptor (Matthews et al., 2003), CD30 (von Tresckow et al., 2004), and lipoprotein receptor-related protein-1

<table>
<thead>
<tr>
<th>Table 1 Cancer-related proteins associated with lipid rafts.</th>
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<tbody>
<tr>
<td><strong>Protein</strong></td>
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<tr>
<td>Raft markers</td>
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<tr>
<td>Flotillin-1</td>
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<tr>
<td>Flotillin-2</td>
</tr>
<tr>
<td>Flotillin-2</td>
</tr>
<tr>
<td>Caveolin-1</td>
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<tr>
<td>Cell adhesion molecules</td>
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<tr>
<td>CD44</td>
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<tr>
<td>N-cadherin</td>
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<tr>
<td>β1 Integrin</td>
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<td>Oncogenes</td>
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<td>H-Ras</td>
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<tr>
<td>Src</td>
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<td>Csk</td>
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<td>Cbp</td>
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<td>Fyn</td>
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<td>Lyn</td>
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<td>Lck</td>
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<td>Receptors</td>
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<td>EGFR</td>
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<td>uPAR</td>
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<td>Apoptotic molecules</td>
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<td>Fas</td>
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<td>TRAIL</td>
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<tr>
<td>FADD</td>
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<td>Caspase-8</td>
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<td>Bid</td>
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<td>JNK</td>
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EGFR, epidermal growth factor receptor; uPAR, urokinase-type plasminogen activator receptor; TRAIL, tumor necrosis factor (TNF)-related apoptosis-inducing ligand; FADD, Fas-associated death domain protein; Bid, BH3-interacting domain death agonist; JNK, c-jun N-terminal kinase.
(LRP-1) (Selvais et al., 2011) (Table 2). These proteins are shed by the action of ADAM family proteinases, triggered by cholesterol lowering with MβCD or other lipid-raft disrupting agents, such as filipin or statins. In addition, type XVII and type XXIII collagens are shed from keratinocytes upon treatment with MβCD or filipin (Zimina et al., 2005; Veit et al., 2007). These findings indicate that lipid rafts may play a critical role in regulating the accessibility of sheddases to their substrate proteins under constitutive and induced conditions.

**Lipid rafts and apoptosis**

In addition to increased proliferation and invasion, reduced apoptosis is another hallmark of cancer cells, and contributes to the drug resistance and poor prognosis of cancer treatments (Hanahan and Weinberg, 2011). Lipid rafts are reported to serve as platforms for the accumulation of signaling molecules involved in cancer cell apoptosis. An anti-tumor agent, edelfosine (1-O-octadecyl-2-O-methyl-glycero-3-phosphocholine), was found to induce the translocation of the death receptor Fas/CD95 into lipid rafts, followed by Fas/CD95 co-clustering and activation, leading to tumor cell death (Gajate and Mollinedo, 2001). The edelfosine-induced co-clustering of Fas/CD95 in lipid rafts was later shown to be independent of its cognate ligand (Gajate et al., 2004). In the intrinsic apoptosis pathway, the functions of the Fas receptor and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors 1 and 2 were also found to depend on their translocation into lipid rafts, as the depletion of membrane cholesterol attenuated the apoptosis mediated by these factors (Gajate et al., 2004). Subsequent studies revealed that other apoptosis-related signaling molecules, such as Fas-associated death domain protein (FADD), caspase-8, BH3-interacting domain death agonist (Bid), and c-jun N-terminal kinase (JNK) are also translocated to lipid rafts upon treatment with anti-tumor agents (Gajate and Mollinedo, 2007; Nieto-Miguel et al., 2008; Mollinedo et al., 2010a,b) (Table 1). In addition, certain cancer cell types with higher membrane cholesterol levels are more sensitive to the cholesterol-depletion-induced apoptosis, suggesting that apoptosis is another target in the therapeutic application of cholesterol lowering for cancer (Li et al., 2006).

**Cancer prevention and therapy**

**Statins**

Statins are HMG-CoA reductase inhibitors with cholesterol-lowering properties. Statins inhibit the conversion of HMG-CoA to mevalonic acid by serving as structural analogues of HMG-CoA. Several different compounds in this drug class have been developed: atorvastatin (Lipitor), cerivastatin (Baycol; withdrawn from the market in 2001), fluvastatin (Lescol), lovastatin (Mevacor), mevastatin (Compactin), pravastatin (Pravachol), rosuvastatin (Crestor), and simvastatin (Zocor). Statins lower cholesterol content and are thus widely prescribed for the treatment of cardiovascular diseases. Furthermore, prevention studies in which high-risk individuals were treated with statins confirmed the efficacy of these drugs in preventing cardiovascular diseases (Collins et al., 2002). In addition, a retrospective study demonstrated that statins may be effective for preventing neurodegenerative diseases, including Alzheimer’s disease (Jick et al., 2000). Although the various population-based reports of the effects of statins on cancer are controversial, recent epidemiologic studies suggest that statins inhibit the progression of certain cancers (Solomon and Freeman, 2008).

**Table 2** Transmembrane proteins that undergo shedding upon cholesterol depletion.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Cell type</th>
<th>Reagent</th>
<th>Sheddases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD44</td>
<td>Glioblastoma, pancreatic carcinoma</td>
<td>MβCD, simvastatin, filipin</td>
<td>ADAM10</td>
<td>Murai et al., 2011</td>
</tr>
<tr>
<td>L1-CAM</td>
<td>Breast carcinoma</td>
<td>MβCD</td>
<td>ADAM10</td>
<td>Mechtersheimer et al., 2001</td>
</tr>
<tr>
<td>APP</td>
<td>Astrocytoma</td>
<td>MβCD, lovastatin</td>
<td>ADAM10</td>
<td>Kojro et al., 2001</td>
</tr>
<tr>
<td>IL-6 receptor</td>
<td>AMoL, hepatoma</td>
<td>MβCD</td>
<td>ADAM 10, 17</td>
<td>Matthews et al., 2003</td>
</tr>
<tr>
<td>CD30</td>
<td>Lymphoma</td>
<td>MβCD, simvastatin, filipin</td>
<td>ADAM17</td>
<td>von Tresckow et al., 2004</td>
</tr>
<tr>
<td>LRP-1</td>
<td>Fibrosarcoma</td>
<td>MβCD, lovastatin</td>
<td>ADAM 12, MT1-MMP</td>
<td>Selvais et al., 2011</td>
</tr>
<tr>
<td>Collagen XVII</td>
<td>Keratinocyte</td>
<td>MβCD, filipin</td>
<td>ADAM17</td>
<td>Zimina et al., 2005</td>
</tr>
<tr>
<td>Collagen XXIII</td>
<td>Keratinocyte</td>
<td>MβCD, filipin</td>
<td>Furin</td>
<td>Veit et al., 2007</td>
</tr>
</tbody>
</table>

L1-CAM, L1-cell adhesion molecule; APP, amyloid precursor protein; IL-6, interleukin-6; AMoL, acute monocytic leukemia; LRP-1, lipoprotein receptor-related protein-1; MT1-MMP, membrane-type 1 matrix metalloproteinase.
Recent evidence suggests that statins block the adhesion and migration processes of cancer cells by disrupting membrane lipid rafts (Murai, 2012), supporting the potential therapeutic use of cholesterol lowering for suppressing various pathogenic features of cancer cells. In addition, dysregulation of the mevalonate pathway promotes transformation, suggesting that HMG-CoA reductase is a candidate metabolic oncogene, and providing further rationale for the exploration of statins as anticancer agents (Clendening et al., 2010).

Non-statin cholesterol-lowering agents

Although statins are effective cholesterol-lowering agents, they elicit many side effects. In addition to the statin target enzyme HMG-CoA reductase, many other enzymes are involved in the multistep pathway leading to cholesterol synthesis. Inhibitors that target enzymes required for the conversion of lanosterol to cholesterol may also be effective for lowering cholesterol (Trapani et al., 2011). In addition, another class of compounds that prevent cholesterol absorption from dietary intake may also be useful cholesterol-lowering agents with anticancer activity. For example, ezetimibe (Zetia), a cholesterol uptake-blocking drug, decreases circulating cholesterol levels and reduces the growth of prostate tumors by inhibiting tumor angiogenesis (Solomon et al., 2009).

Conclusion

Here I have summarized the roles of cholesterol and its lowering on cancer cell adhesion and migration, focusing on the current state of knowledge, with particular emphasis on lipid rafts. Although a number of recent studies have linked these membrane structures to the pathogenesis of cancer cells, many questions about the nature of lipid rafts remain unanswered. Future studies will be required to elucidate the mechanism(s) underlying the lipid-raft-mediated regulation of cancer cell adhesion and migration. These investigations and other studies of cholesterol regulation and metabolism will provide new insights into the mechanisms of cancer pathogenesis and a wealth of new targets for cancer treatment and prevention.

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induce CD44 cleavage and promote cell migration in CD44-expressing tumor cells. J. Biol. Chem. 278, 32259–32265.


