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High-density lipoprotein functionality and breast cancer: A potential therapeutic target

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Abstract

Breast cancer is a major cause of death globally, and particularly in developed countries. Breast cancer is influenced by cholesterol membrane content, by affecting the signaling pathways modulating cell growth, adherence, and migration. Furthermore, steroid hormones are derived from cholesterol and these play a key role in the pathogenesis of breast cancer. Although most findings have reported an inverse association between serum high-density lipoprotein (HDL)-cholesterol level and the risk of breast cancer, there have been some reports of the opposite, and the association therefore remains unclear. HDL is principally known for participating in reverse cholesterol transport and has an inverse relationship with the cardiovascular risk. HDL is heterogeneous, with particles varying in composition, size, and structure, which can be altered under different circumstances, such as inflammation, aging, and certain diseases. It has also been proposed that HDL functionality might have a bearing on the breast cancer. Owing to the potential role of cholesterol in cancer, its reduction using statins, and particularly as an adjuvant during chemotherapy may be useful in the anticancer treatment, and may also be related to the decline in cancer mortality. Reconstituted HDLs have the ability to release chemotherapeutic drugs inside the cell. As a consequence, this may be a novel way to improve therapeutic targeting for the breast cancer on the basis of detrimental impacts of oxidized HDL on cancer development.

KEYWORDS

breast cancer, high-density lipoprotein function, high-density lipoprotein transporter, reconstituted high-density lipoprotein, therapy

1 | INTRODUCTION

The high-density lipoproteins (HDLs) are a family of lipoprotein particles involved in reverse cholesterol transport, away from the arterial wall,[1] and HDL may partially exert its cardiovascular protective effects through reverse cholesterol transport (RCT).[2] HDL is also involved in the efflux of cholesterol from macrophage-derived foam cells and this process can occur through passive diffusion, or by the effects of specific transporters located on the blood vessel wall, including: ATP-binding cassette transporter A1 (ABCA1) that

recruits lipid-poor apolipoprotein A-I (apoA-I) as a lipid acceptor, and ATP-binding cassette transporter G1 (ABCG1) that mediates cholesterol efflux to spherical large HDLs.[1,3] Another cholesterol efflux mechanism is related to the scavenger receptor class B type I (SR-BI).[3] HDL has several other pleiotropic activities including antioxidant effects, protecting low-density lipoprotein (LDL) from oxidative modification, preventing the release of proinflammatory cytokines, downregulating the expression of cell adhesion molecules, and promoting the formation of nitric oxide, as well as inhibiting aggregation of platelet molecules, antithrombotic, and as a result has a particular impact on the atherosclerosis.[4,5] Although it has been shown that serum HDL-cholesterol (HDL-C) concentrations are inversely related to cardiovascular disease (CVD) risk, most recent studies aiming at increasing plasma HDL-C by means of niacin or CETP inhibitors have failed to show protection against CVD risk.[6] Data derived from multiple cohort studies using new techniques to evaluate HDL functionality rather than HDL-C level have consistently demonstrated that HDL function represents a better biomarker for predicting CVD risk compared to HDL-C level.[7] There have also been some reports relating to HDL functionality and some types of cancer.[8] The HDL particles' composition, size, and structure could be altered under various circumstances, such as inflammation, aging, and diseases (HIV, psoriasis, and so forth). Owing to the changes in HDL functionality, the measurement of HDL function rather than HDL-C concentration may be a better marker for determining the risk of breast cancer.[9] There is emerging data showing that high levels of HDL-C are associated with a lower risk of breast cancer.[10]

In the current study, we have reviewed the recent evidence in relation to the role of HDL and its association with breast cancer, and the utility of methods for assessing HDL function as a potential measure of disease risk.

2 | HDL-C LEVELS VERSUS HDL FUNCTION

It has been shown that plasma HDL-C concentrations are inversely associated with the risk of cardiovascular events.[11] This has been shown at all levels of LDL-cholesterol.[3,5] The protective effect of HDL is based on the capacity of this lipoprotein (as lipid acceptor) to promote cholesterol efflux from macrophages and transfer cholesterol to the liver and bile in a process called reverse cholesterol transport (RCT). To reduce CVD risk, efforts have been made to increase HDL concentration using drugs such as niacin, but while this increases serum HDL-C levels by 30% it does not enhance the HDL function.[12] Despite increasing serum HDL-C substantially, niacin and cholesteryl ester transfer protein inhibitors fail to improve CVD risk in randomized controlled trials.[4] Moreover, Mendelian randomization (MR) studies using variants (eg, P376L) that related with high serum HDL-C concentrations revealed no association between these variants and decreased the risk of atherosclerosis.[3,13] Hence it is believed that the anti-atherogenic role of HDL in predicting cardiovascular events risk cannot be attributed to serum HDL-C levels alone.[12] HDL promotes the cholesterol efflux from macrophage foam cells to HDL[14] and the prevention of CVD is mostly affected by cholesterol efflux capacity in animal models rather than serum HDL-C concentrations.[15] Studies with an aim of investigating the cholesterol efflux assessment, a measure of HDL functionality, in low- and high-HDL serum specimens (HDL $\leq$ 10th and HDL $\geq$ 90th age/sex-specific percentile) have indicated attenuated ability of cholesterol acceptor in serum derived from low-HDL samples.[3] It is believed that HDL function, rather than serum HDL-C concentrations, may be a more reliable biomarker for CVD risk. Although evaluating HDL-C level provides some information about the number of HDL particles, its composition and function are not accurately assessed. Therefore, development of standardized assays for HDL function measurement seems to be necessary along with HDL-C concentration for clinical applications.[14] A high throughput, the cell-free assay has been developed as a surrogate for HDL function, based on HDL lipid peroxidation and this has been found to be consistent with the development of cardiovascular events.[16-19] As previously reported, several epidemiological and clinical studies with a large number of population (Dallas Heart Study) assessed HDL-C efflux capacity as a measure of HDL function using cell-based methods including radiolabeled cholesterol and fluorescent reagents, such as bodipy (boron dipyrromethene difluoride). A 67% reduction in CVD risk was found at the highest quartile in contrast to the lowest quartile of cholesterol efflux capacity. Hence, cholesterol efflux capacity combined with other risk factors may better predict the risk of cardiovascular events.[15] Controlled trial studies have shown that human immunodeficiency virus (HIV) infection is associated with HDL-C reduction and consequently increased the risk of CVD. Cholesterol efflux capacity was evaluated in acute HIV patients who were randomized to antiretroviral therapy (ART). As a result of ART for HIV patients and a decrease in the viral load, ATP-binding cassette transporter A1 was overexpressed and promoted increased efflux capacity of cholesterol by HDL.[20] In the EPIC-Norfolk study, cholesterol efflux capacity was measured and results

supporting the use of cholesterol efflux as an accurate and independent measure to determine the protective effects of HDL.[21,22] With respect to circulating HDL-C, a number of studies have indicated an inverse relationship between serum HDL-C and risk of breast cancer[23-25] and considered high serum HDL levels as a protective biomarker in patients with premenopausal breast cancer.[26] However, several studies have found no relationship between serum HDL-C and breast cancer risk,[27,28] and a few studies even reported a positive association between high HDL-C level and breast cancer risk.[29,30] Since serum HDL concentrations are not directly related to its functionality, it would seem to be important to assess HDL function rather than the HDL-C level in case of determining the risk of breast cancer.

3 | METABOLISM OF CHOLESTEROL IN BREAST CANCER

Breast cancer is an important cause of death globally, especially in developed countries. Population studies examining the migration of individuals with low risk of breast cancer to regions with high prevalence of disease show a significant effect of environmental factors on the development and progression of the tumors.[31] Among the environmental factors involved, many studies have suggested diet and obesity as two important risk factors that affect the development of breast cancer.[32,33] The evaluation of cholesterol metabolism and breast cancer has indicated a relationship between concentrations of estrogen and HDL-C. Indeed, there is an increased risk of tumor development and progression associated with serum estrogen concentrations. Using mouse models for studying cholesterol function in breast cancer development, plasma cholesterol was shown to be involved in the tumor progression.[34,35] The SCARB1 gene encodes for the scavenger receptor class B type I, and mediates the balance of cholesterol exchange among HDL and cells. In addition, reverse cholesterol transport uses hepatic SR-BI to excrete excess cholesterol into the bile and remove it from the body. SR-BI contributes to the tumor development and malignant processes and studies have proposed a role for SR-BI in breast cancer and as novel therapeutic aim.[36] HDL particles are an important carrier of circulating plasma cholesterol and promote mitogen-activated protein kinase (MAPK) and AKT signaling pathways through binding of HDL to the SR-BI receptor.[37-39] The level of SR-BI receptor expression in aggressive tumors has been found to be increased compared with the normal cells. Data extracted from studies based on the function of HDL and SR-BI receptor in two human cell lines of breast cancer, MDA-MB-231 and MCF7, and growth of tumors have shown the ability of HDL to promote migration and induce various signaling pathways.[39] Moreover, tumor progression was shown to be attenuated, by altering the activity of SR-BI and its expression.[40]

To maintain the integrity of cell membrane structures, cholesterol plays a pivotal function and, therefore, cholesterol metabolism may have a role in the development of cancer. Cholesterol production in cells, absorption of cholesterol from the diet, and cholesterol transportation in the circulation are all factors that may affect the development of cancer. High levels of cholesterol can stimulate tumor growth and migration.[41] Cancer cell development and metastasis are influenced by cholesterol membrane contents, via signaling pathways that are involved in modulating growth, cell adhesion, and migration. Steroid hormones, are derived from cholesterol and are able to control differentiation and proliferation of the cells. Thus, they play a key role in the pathogenesis of breast cancer.[42] Oxidative stress, glycation, and inflammation may also promote the formation of dysfunctional HDL, clarifying the relationship between lipoprotein abnormalities and breast cancer.[7,43] There are multiple mechanisms thought to be involved in the altered serum cholesterol concentrations in cancer, including the upregulation of LDL receptors in metastatic cells as a result of enhanced cholesterol catabolism,[44-46] heightened storage of esterified cholesterol in cancer cells, and increased usage of cholesterol in case of newly synthesized membranes.[47]

4 | ROLE OF HDL IN BREAST CANCER

Breast cancer is an important cause of mortality and morbidity in women and is affected by several risk factors, such as hormones, radiation exposure, chemicals, and obesity. The protective potential of HDL-C in breast cancer has previously been shown in several studies.[9] Apolipoprotein A1, the main protein of HDL, appears to be associated with tumor aggressiveness and malignancy.[48,49] Results from systematic review and meta-analysis evaluating the relationship between lipid levels including HDL-C, LDL-cholesterol, total cholesterol, and triglycerides, and incidence of breast cancer, indicated a significant inverse relationship between serum HDL-C and breast cancer risk.[12] This was especially in women with a high LDL:HDL ratio, and which are intrinsically related to a high rate of estradiol synthesis.[50,51]

In African American women there was a significant reduction of breast cancer prevalence in women with a high total cholesterol (odds ratio [OR], 0.46; 95% confidence interval [CI], 0.25–0.85) and an elevation in the risk of breast cancer associated with lower HDL-C level (OR, 1.99; 95% CI, 1.06–3.74).[52]

Obesity has recently been investigated as a risk factor for breast cancer, which may be a consequence of inadequate physical activity and poor dietary intake and this would also lead to an abnormal lipid profile.[53-55] A case-control study conducted on women in Taiwan reported that although no correlation was found between serum triglyceride, LDL, or total cholesterol level and breast cancer, there was a significant inverse relationship with serum HDL (OR, 2.59; 95% CI, 1.41–4.77). Overall, a low serum HDL was associated with a three-fold increase in the risk of breast cancer.[56] A meta-analysis of premenopausal and postmenopausal patients with breast cancer has shown that serum triglyceride level was higher in comparison with controls, as well as an inverse relationship between plasma HDL-C and breast cancer was demonstrated in the postmenopausal group.[57]

It is often assumed that high levels of HDL-C associated with breast cancer because of the correlation between tumor cell propagation and HDL concentration.[42,58] Moreover, carcinogenesis may be affected by HDL-C, especially by its effects on apoptosis or activation of protein kinase pathway.[59,60] In vitro studies have shown that HDL-C may independently cause the development of cell lines of breast cancer.[61] Prospective studies, have investigated the association between breast cancer risk and lipid profile and investigated the effects of a low serum HDL-C in women with established breast cancer, providing strong evidence supporting an inverse association between circulating HDL-C and breast cancer risk.[23]

Patients with breast cancer who are estrogen receptor-negative (ER^-) and progesterone receptor-negative (PR^-) have an association between serum HDL-C and triglyceride with breast cancer, supporting an interaction between receptor status in relation to the circulating HDL-C.[26] Some reports have shown an association between high levels of serum VLDL-cholesterol and triglycerides and also low levels of HDL-C in breast cancer in stage IV compared with patients in stage I disease. Verifying the correlation between serum HDL-C and breast cancer risk, the Atherosclerosis Risk in Communities Cohort Study comprising 7,575 females during a 13 years follow-up, showed a positive association between low plasma HDL-C in premenopausal women and increased incidence of breast cancer.[62] In vitro studies have indicated breast cancer progression and aggressiveness of tumor cells by adding exogenous HDL.[63-65]

5 | PATHWAYS INFLUENCING THE RELATIONSHIP BETWEEN SERUM HDL-C AND BREAST CANCER

A high serum cholesterol may enhance cancer cell growth and hence a raised serum cholesterol may have a potential role in breast cancer malignancy.[66] For instance, in vivo and in vitro studies have revealed that a precursor of cholesterol synthesis, mevalonate, could induce the proliferation of breast cancer cells[67,68] and a high concentration of a metabolite of cholesterol, 27 hydroxyl cholesterol, might be observed in estrogen receptor-positive in breast cancer.[69-71]

The ABCG1 transporter might be involved in tumor immunity and be an example that might explain the association between cholesterol metabolism and breast cancer. ABCG1 mediated cholesterol transport from the cells to HDL particle[72,73] and also played a role in regulating cholesterol in the cell, which is essential for normal cell functioning and its survival.[74,75] A prominent function of ABCG1 is in promoting immunity of a tumor, which has been shown in some preclinical studies using $Abcg1^{-/-}$ mice. Hence, it is possible that cancer cell proliferation might be suppressed in case of the absence of ABCG1, and this might occur via a change in macrophage function in the cancer cell. The ABCG1 transporter affected the immune system by altering T-cell function. In vivo studies using $Abcg1^{-/-}$ mice have demonstrated that ABCG1 deficiency might lead to an enhanced proliferation of CD4 T cells.[76-78]

The ABCA1 transporter played a key role in the efflux of intracellular cholesterol to apolipoprotein A-I and on the contrary, high concentrations of cellular cholesterol might be found in breast cancer. In support of this idea, some studies have attempted to suppress the expression of ABCA1 by creating loss-of-function mutations in the ABCA1 gene and have demonstrated the potential anticancer function of ABCA1. In the absence of ABCA1, mitochondrial cholesterol concentrations were found to be elevated and consequently inhibited mitochondrial cell death factors leading to the survival of breast cancer cells. Several pathways might be involved in the accumulation of cellular cholesterol in tumors: a high expression of HMG-CoA reductase, which is required for cholesterol synthesis,[79,80] deficient feedback control of HMG-CoA reductase that would normally be controlled by the cholesterol,[81] and a reduced expression of the ABCA1 transporter.[82,83] Hence, serum cholesterol concentrations are influenced by these various pathways. A high expression of ABCA1 might lead to a reduced

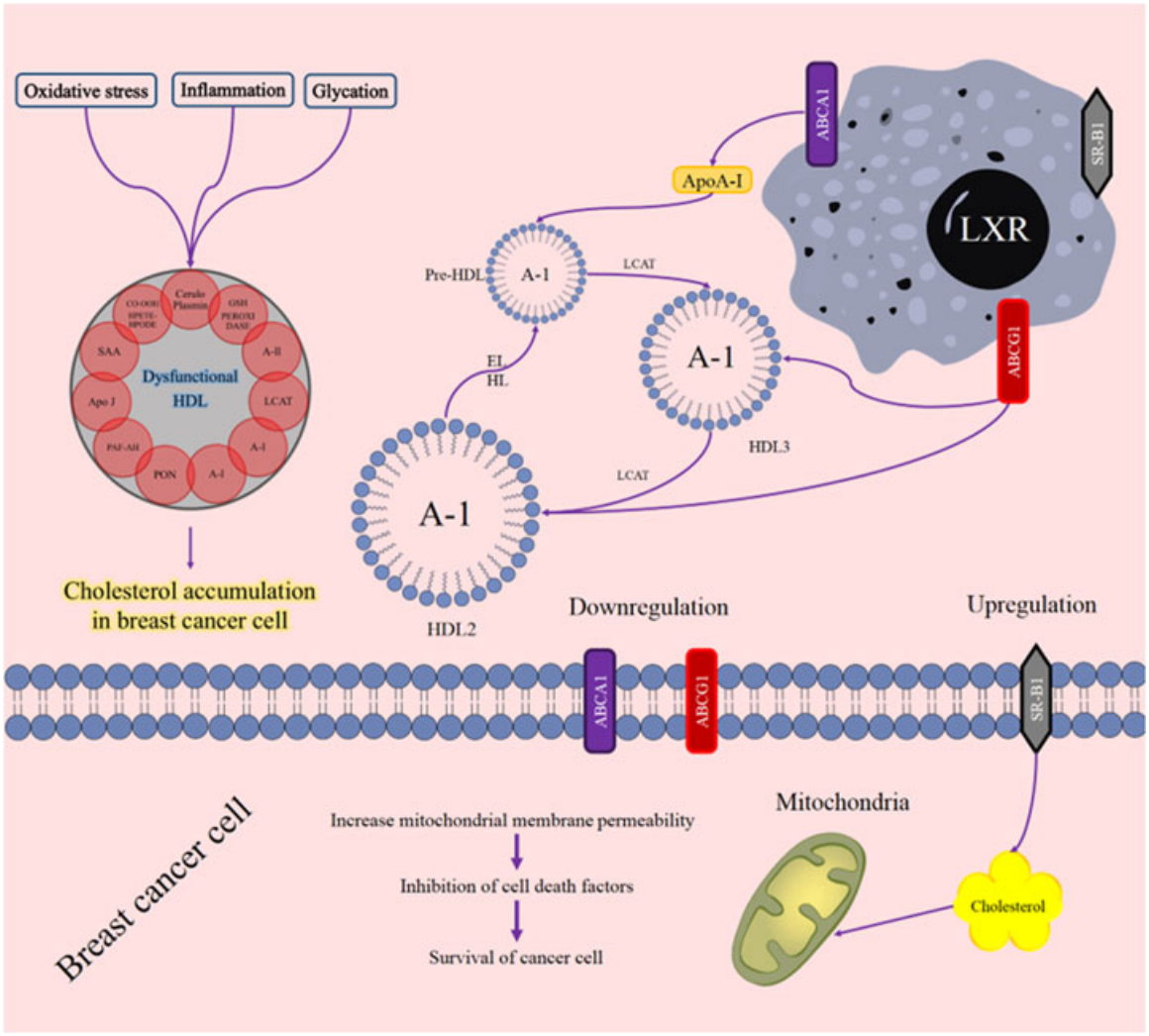

FIGURE 1 The effects of HDL on the development of breast cancer. (1) Dysfunctional HDL that may result as a consequence of inflammation, may increase the accumulation of cholesterol inside the cells by reducing cholesterol uptake via HDL from the cells. Increased mitochondrial cholesterol mediate heightened mitochondrial membrane permeability, prohibition of cell death factors and survival of cancer cell. In addition, the plasma membrane of cancer cells contains high levels of lipid rafts with increased cholesterol that affects signaling pathways in the cell. (2) Upregulation of SR-B1, a HDL receptor, promotes the MAPK and AKT signaling pathways and finally lead to the immigration of endothelial cells. (3) ABCA1 and ABCG1 transporters of HDL play a pivotal role in regulating cholesterol within the cells, which is essential to normal cell function and its survival

cholesterol content in tumors, suggesting that elevated mitochondrial membrane permeability in stress conditions, and as a consequence of diminished mitochondrial cholesterol content, and a reduction in the activity of the AKT pathway has been reported to be correlated with ABCA1-induced tumor suppression[84] (Figure 1).

Oxidized cholesterol could be formed by the direct reaction of cholesterol with reactive oxygen species (ROS) or by enzymatic interactions. Oxysterols that are derived from oxidized cholesterol, have been found to be involved in some process including effects on steroid hormones that play a fundamental role in breast cell growth and progression.[85] An inflammatory process that may occur following cholesterol oxidation, might also be associated with the breast cancer.[86] Since cholesterol played a prominent role in promoting carcinogenesis through oxidized cholesterol and cholesterol accumulation, and also lipoproteins have been recognized as cholesterol carriers, suggesting that lipoproteins might in part contribute to breast cell proliferation by providing cholesterol for cancer cells.[87]

The possibility that lipoproteins might be involved in the development of breast cancer is supported by various evidence.[88] Determining circulating cholesterol reduction in patients with malignant cancer might be used for screening goals.[89] Assessing the lipid profile of breast cancer patients have shown that HDL can be influenced

by tumor malignancy compared to LDL.[90] Although epidemiological findings indicated that plasma HDL concentrations are negatively related to the breast cancer development, there is some data showing the direct and positive association between circulating cholesterol and cyclinD1 overexpression as a molecule involved in tumor promotion.[34]

In vitro analysis has shown that there is a role of lipoproteins in inducing the development of breast cancer and also in increasing the aggressive features of the tumor.[64] It has been previously indicated that in cell culture studies, the growth of breast cancer cells would occur as a result of HDL addition.[63]

Several studies have shown a high expression of the SR-B1 receptor in breast cancer cells that recruit HDL to remove excess cholesterol and enhance required intracellular cholesterol.[42] Enhanced intracellular cholesterol is directly related to an increase in carcinogenesis risk.[91,92]

The plasma membrane in cancer cells contains an increased concentration of lipid rafts, which are cholesterol-rich and that influence signaling transduction.[93] However, by removing cholesterol from these lipid rafts, apoptosis is enhanced and may lead to cancer cell death.[94] Studies have shown that microcalcification develops in malignant tumors. Lipid rafts that are comprised of a high cholesterol content and contain GPI-anchored alkaline phosphatase, contribute to the formation of cell surface vesicles. Calcium hydroxy crystals could be precipitated into these vesicles extracellularly and may participate in microcalcification in breast cancer. It has been proposed that there is a positive association between a high cholesterol content within lipid rafts and tumor aggressiveness by enhancement of microcalcification. There is evidence that 27-hydroxy cholesterol, which could be derived from cholesterol in tumor tissues, binds to the estrogen receptor alpha-subunit to promote the oncogenic estrogen-dependent signaling pathway and lead to breast cancer cell proliferation and metastasis.[95] Furthermore, cytochrome p450 CYP27A1, the enzyme that catalyzes the conversion of cholesterol to 27-hydroxy cholesterol, is highly expressed in breast cancer cells and there is a direct relationship with the stage of the tumor.[70] This mechanism may account for the concept that cholesterol contributes to enhanced breast cancer cell proliferation based on the clinical implications, while studies show that statins are protective against CVD; their inhibition of cholesterol synthesis by blocking 3-hydroxy 3-methylglutaryl COA reductase (HMGCR) may also inhibit the proliferation of breast cancer cells.[96-98]

6 | HDL AS A POTENTIAL TARGET FOR TREATING BREAST CANCER

HDL nanoparticles could be manufactured to contain phospholipids and the major apolipoprotein of HDL (apoA-I). These nanoparticles exhibit specific properties that may be useful for drug-delivery. If they are manufactured at a size of <30 nanometers, they could penetrate into cells, remain for a long duration in the circulation, and stabilize hydrophobic drugs in the HDL core. Therapies involving the administration of HDL-nanomimetic particles increase the level of HDL even up to 30-fold and could be tolerated by cells. The nanoparticles could bind to the HDL receptor (SR-BI) to exert their metabolic functions favorable for drug-delivery.[99] The cholesteryl esters contained within the HDL could translocate through the SR-BI receptor into the cells of the liver and therefore the drug that is being carried via these vehicles are preserved against destruction within the lysosomes.[100] The increased affinity, and the ability of HDL to accumulate within cancer cells make HDL an appropriate candidate for loading anticancer drugs for their delivery into the target cells.[101,102] In addition, experimental evidence has shown that the physical properties of drugs loaded into the HDL particle could be preserved as indicated by high-performance liquid chromatography and electron microscopy. Therefore, the size and characteristics of HDLs have not been influenced by loading drug in HDL particles.[102] Side effects of chemotherapy might also be reduced by administration of HDL-anticancer drug complexes.[101,103] Reconstituted HDLs have a key role in releasing chemotherapeutic drugs inside the cell. Because of the affinity of tumor cells to uptake core components of HDL particles and the suitable size of HDLs for translocation of drugs, means that rHDLs may be desirable molecules for the delivery of anticancer drugs.[104,105]

Rapid dividing cancer cells require additional cholesterol for membrane formation and the receptor-mediated uptake of HDL core components might support this cholesterol requirement. Several studies have shown an association between cell proliferation and HDL component uptake[106] and the high expression of HDL receptors in breast cancer cell lines.[107] Overall, data from these investigations indicate that the desirable features of HDL particles mean that these particles could be used as vehicles for transporting drugs.[105] A reduced expression of the HDL receptor in the peripheral cells as a result of delivering drug-HDL complex[108] might lead to a reduction in the toxic side effects of anticancer drugs.[101]

The SR-BI is overexpressed and it has been suggested that it could be used as a biomarker of cancer, especially

as a therapeutic agent delivery. Furthermore, several studies have recently reported an association between the expression of SR-BI receptor and tumor progression.[109-111]

Anticancer therapies based on hormonal treatment have a negative impact on the lipid profile, including the lowering of serum HDL-C and raised serum triglyceride levels in patients with malignancies, the importance of these effects need to be clarified. Pitavastatin reduces LDL-cholesterol and enhances the delivery of cholesterol to the cell inside as well as increase the HDL-C and antioxidative effect of HDL. As a result, pitavastatin elevates the level of HDL by improving its competence without altering HDL quality.[11] Recent studies indicated that oxidative stress is associated with breast cancer development. Under oxidative stress conditions, such as breast cancer, HDL predispose to oxidative modifications and these alterations can affect the HDLs functionality.[112–114]

7 | CONCLUSION

It now appears that dysfunctional and low serum HDL levels, affect the key pathways involved in carcinogenesis. A high serum HDL-C is associated with a lower risk of breast cancer and plasma HDL-C concentration does not accurately reflect its functionality, and therefore it may be important to develop assays to quantify HDL function. rHDLs have a potential role in targeting chemotherapeutic drugs to cells and there is good evidence to support the use of treatments that improve cholesterol efflux capacity, and as a measure of HDL function, may be beneficial to patients with breast cancer.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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