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REVIEWS

Review

High-Density Lipoprotein Components and Functionality in Cancer: State-of-the-Art

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Cancer is the second leading cause of death in western countries, and thus represents a major global public health issue. Whilst it is well-recognized that diet, obesity, and smoking are risk factors for cancer, the role of low levels of high-density lipoprotein cholesterol (HDL-C) in cancer is less well appreciated. Conflicting evidence suggests that serum HDL-C levels may be either positively or negatively associated with cancer incidence and mortality. Such disparate associations are supported in part by the multitude of high-density lipoprotein (HDL) functions that can all have an impact on cancer cell biology. The aim of this review is to provide a comprehensive overview of the crosstalk between HDLs and cancer, focusing on the molecular mechanisms underlying this association.

Highlights

Controversy exists about whether low HDL levels are associated with an increased cancer risk.

Tumor cells require increased cholesterol and are able to accumulate it.

Complex alterations in lipid and cholesterol metabolism occur in tumor cells.

Plasma lipid levels may change in patients with cancer, reflecting altered lipid metabolism.

Available evidence supports an association between HDL-C levels and cancer incidence/survival, though the mechanism is unclear.

HDL-C levels could serve as a prognostic marker in cancer patients, and may identify patients at increased risk of cancer.

Introduction

Cancer is the second leading cause of death in the USA, and thus represents a major public health issue [1]. The identification of subsets of subjects at increased risk of cancer may represent one of the most important prevention strategies for reduction of cancer incidence and progression [1]. In addition, whilst cancer therapeutics are rapidly evolving, chemotherapy and radiotherapy remain the mainstay for treatment options. However, such approaches are often limited by side effects [2], and in other cases, by treatment resistance of cancer cells [3]. Thus, additional therapeutic targets and treatment strategies for cancer are urgently required [1].

A growing body of evidence suggests that tumor cells require an increased cholesterol supply and are able to accumulate cholesterol [4]; additionally, complex alterations in lipid and cholesterol metabolism are encountered in tumor cells, and as a possible result, plasma lipid levels may also change in patients with cancer. Thus, hypocholesterolemia or hypercholesterolemia, hypertriglyceridemia or hypotriglyceridemia, and decreased HDLs, especially the HDL2 subfraction, have been reported in a number of human cancers [5,6]. Importantly, blood lipid levels may be variably associated with oncogenesis and cancer progression [7]. Thus, for instance, total cholesterol (TC) levels were inversely associated with nonmelanoma skin cancer or carcinoma *in situ* risk [8], whereas higher serum levels of TC have been reported in patients with colorectal cancer [9]. An inverse relationship between plasma HDL-C levels and the risk of developing cancer has been reported [10]. Also, in a large meta-analysis, decreased levels of plasma HDL-C have been found to correlate with an increased cancer risk. Thus, for every 10 mg/dL increase in plasma levels of HDL-C, the risk of cancer incidence was significantly decreased (by 36%) [11]. However, opposing results have also been reported, with some studies concluding that low plasma HDL-C levels can be considered as an epiphenomenon of the presence of cancer [12].

As an additional link between cancer and HDLs, chemotherapy-induced reductions in HDL-C levels have been seen [13], further complicating the link between HDLs and cancer. In addition, several variables (e.g., type of cancer, age, tobacco exposure, obesity) may exert a

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confounding influence on the association between HDL-C levels and cancer [8]. Among these confounders, HDL composition and functionality may play a key role.

HDLs, Apolipoproteins and Cancer

HDL and its related lipids and proteins have broad activities. The main atheroprotective function of HDLs is their role in reverse cholesterol transport (RCT), in which apolipoprotein AI (apoA-I) interacts with ATP-binding cassette transporters A1 (ABCA1) at the cell membrane and extracts cholesterol and phospholipids (PLs) from cells to deliver them to the liver for excretion [10,14]. In addition, there are several non-RCT atheroprotective activities of apoA-I/HDLs, including antioxidant, anti-inflammatory, antiapoptotic, and immune modulatory activities [15]. In light of the recognized association between oxidative stress, inflammation, immunity, and tumorigenesis, it was proposed that HDLs may also be protective against cancer (Table 1). Oxidation, inflammation, and dyslipidemic states in cancer can, however, alter the anticarcinogenic properties of HDL through remodeling and interconversion via addition and removal of neutral lipids, PLs, and apolipoprotein components. Therefore, compositional changes in HDL have been related to the concept of 'dysfunctional HDL', and identification of specific biomarkers in different experimental models will provide important information for the evaluation of patients with cancer and for the development of new antitumor therapies.

The relationship between HDLs, HDL-C, and cancer incidence and mortality is still controversial, and may be tumor-type-dependent, with some studies reporting a negative, and other studies a positive association [16]. This dual effect of HDLs in cancer also emerges in *in vitro* studies. For instance, the HDL antioxidant activity has been found to limit prostate cancer cell proliferation [17], whereas HDLs can stimulate cell migration in breast cancer (BC) cell lines [18], possibly due to oxidative modification of HDL in the oxidative condition of BC. In this regard, it has been revealed that hypochlorite-oxidized HDL stimulated migration and invasion of breast cancer cells [19], and also, glycated and oxidized HDL from diabetic patients stimulated adhesion of tumor cells to the human umbilical vein endothelial cell (HUVEC) and extracellular matrix (ECM) [20], and consequently, breast cancer metastasis was promoted. Furthermore, HDLs also carry nonlipid cargo, including proteins, enzymes, microRNA, hormones, vitamins and metabolites, which could play an important functional role in tumor cell survival [21]. In particular, a controversial association between apoA-I, the main apolipoprotein of HDL, and different types of cancer has been reported. Accordingly, some *in vitro* studies reported a cancer-promoting effect of ApoA-I [22], whilst other *in vivo* studies reported either increased or decreased apoA-I levels in cancer patients [23,24], and an unfavorable prognostic impact of lower plasma apoA-I levels [25]. However, other studies demonstrated that apoA-I promoted antitumor effects, and an increase in apoA-I expression and levels markedly decreased both tumor growth and metastasis through removal of lysophosphatidic acid [26], or redirection of elicited immune cells towards tumors [15] in multiple animal models. Also, while apolipoprotein L1 (apoL1) might serve as a protective agent against renal cell carcinoma (RCC) [27], preliminary data suggests a direct correlation between apolipoprotein E (apoE) levels and cancer, both *in vitro* and *in vivo* [24,28].

Overall, this data indicates that HDLs and their apolipoproteins may have different roles in cancer that may be tumor specific, which might explain, at least in part, the conflicting data observed in the clinical setting.

Cholesterol Efflux Capacity in Cancer

Tumor cells are characterized by abnormal cholesterol metabolism, which primarily leads to an increase of intracellular cholesterol esters. An increase in influx and synthesis of cholesterol, as well as a decrease in cholesterol efflux and more active free cholesterol formation from

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Table 1. Compositional Changes of HDL in Cancer[a]

	Conditions	Status	Refs	Type of study
ApoA-I	BC patients, compared with healthy controls	Decreased serum level	[23]	Clinical trials
	Astrocytoma brain tumors from glioma carcinoma	Upregulation in tumor tissue	[22]	
	Benign, low-grade malignant, and high-grade malignant patients with bladder cancer, compared with healthy controls	Increased in urine	[103]	
	In patients with various cancers, compared with healthy controls	Decreased plasma level	[104]	
	In Uighur women with stage I-IIA and IIB-IV CSCC compared to chronic cervicitis patients	Decreased plasma level	[24]	
ApoE	In HSIL, early and late stage CSCC patients, compared to chronic cervicitis group	Increased plasma level	[24]	
	In papillary and follicular carcinomas, compared to normal thyroid	Downregulation of mRNA level	[28]	
	In anaplastic carcinoma, compared to papillary and follicular carcinomas as well as normal thyroid	Upregulation of mRNA level	[28]	
ABCA1	In HCC tissue, compared to the adjacent normal tissues	Decrease in protein levels	[33]	
	In primary tumors from serous OC patients	High expression levels	[49]	
	In colon cancer tissues, compared to the adjacent normal tissues	Decreased protein levels	[30]	
	In pancreatic tumor, compared to non-neoplastic pancreatic tissues	Upregulation in tumor tissue	[50]	
	In LNCaP prostate cancer cells	Downregulation of mRNA and decreased protein levels	[32,36]	*In vitro*
	In androgen-dependent, compared with androgen-independent LNCaP human prostate cancer cells	High expression levels	[47]	
	In A2780 and CP70 ovarian carcinoma cells	Downregulation of mRNA levels	[34]	
	In the differentiated GBM cells, compared to initiating cells	High expression level	[52]	
SR-BI	In prostate cancer tumor, compared to nontumor tissues	Upregulation in tumor tissue	[54,105]	Clinical trial
	In C4-2 and LNCap prostate cancer cell lines	Downregulation	[56]	*In vitro*
PLTP	In the pCR patients who had no invasive tumors in the final surgical breast and axillary lymph node, when compared with those in the non-pCR patients	High expression level	[60]	Clinical trial
Lp-PLA2	In tumor tissues from patients with colon cancer, than in tissues from healthy donors	Increased activity and mRNA level	[63]	Clinical trial
PON1	In patients with endometrial, laryngeal, bladder, pancreatic, papillary thyroid, breast, colorectal, lung, gastroesophageal, epithelial ovarian, metastatic gastric cancers, benign ovarian tumor, brain tumors, multiple myeloma, esophageal squamous cell carcinoma, and oral squamous cell carcinoma, compared to controls	Decreased serum levels and PON activity	[64,66–75]	Clinical trial
	In patients with pancreatic, papillary thyroid, breast, colorectal, lung, epithelial ovarian, multiple myeloma, esophageal squamous cell carcinoma, and oral squamous cell carcinoma, compared to controls	Decreased ARE activity	[69,71,74,86]	
LCAT	In BC patients, compared to healthy subjects before and after radiotherapy	Decreased plasma level	[2]	Clinical trial

Table 1. (continued)

	Conditions	Status	Refs	Type of study
	In BC patients, compared to the age-matched controls	Decreased Plasma activity	[87]	
SAA	In dogs with lymphoma before chemotherapy, compared to healthy and chemotherapy control dogs	Increased serum level	[90]	*In vivo*
	In patients with head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, pancreatic adenocarcinoma, lung, gastric, nasopharyngeal, endometrial, uterine serous papillary, breast, ovarian, and colorectal cancers, compared to control subjects	High expression levels	[91,92,94,98,106]	Clinical trial
	In patients with advanced tumor of RCC, compared with those with localized tumors	High expression levels	[95]	Clinical trial
	In stage II, III, and IV patients with BC, compared to those of the healthy, benign breast diseases, and stage I groups	High expression levels	[96]	Clinical trial
	BC patients with lymph node metastasis or distant metastasis, compared to those without metastases	High expression levels	[96]	Clinical trial

[a]ARE, arylesterase; CSCC, cervical squamous cell carcinoma; HSIL, high-grade squamous intraepithelial lesions.

cholesterol ester stores, have been reported during cancer progression [29]. Since cholesterol efflux capacity is crucial for cancer cell survival, and HDLs are strictly involved in this activity, mainly through the activities of ATP-binding cassette (ABC) transporters and Scavenger receptor of the B class (SR-BI), the mechanisms underlying the regulation of HDL-mediated cholesterol efflux are thought to be determinant for cancer cell biology.

ABC Transporters

The ABCA1 protein, a protein encoded by the ABCA1 gene in humans (Abca1 in rodents), mediates the transfer of cellular cholesterol across the plasma membrane to apoA-I, which then form nascent HDL by further lipidation [30,31]. It has been shown that ABCA1 expression levels are lower in prostate cancer [32], hepatocellular carcinoma (HCC) [33], and colon cancer tissues [34]. Of note, ABCA1 overexpression was found to reduce the proliferation rate of colon cancer HCT116 cells, while silencing of ABCA1 promoted the proliferation and inhibited the apoptosis of colon cancer LDL1 cells [25]. Low levels of ABCA1 have also been reported in ovarian cancer (OC) patients, and were associated with shorter progression-free survival [34]. ABCA1 deficiency was previously shown to allow for mitochondrial cholesterol accumulation, to inhibit the release of mitochondrial cell death-promoting molecules, and thus to facilitate cancer cell survival [35]. Moreover, Lee et al. have demonstrated that ABCA1 is strongly downregulated in prostate cancers, and expression levels are inversely correlated with Gleason grade. This study suggests that cancer-specific ABCA1 hypermethylation and loss of protein expression increase intracellular cholesterol levels, thus contributing to tumor progression [36]. Accordingly, Chou et al. showed that a reduced expression of ABCA1 in A2780 and CP70 ovarian cancer cell lines was associated with promoter hypermethylation. The same study demonstrated that higher ABCA1 methylation in OC patient samples was associated with higher stage and grade, and shorter overall survival [34].

A growing body of evidence suggests a potential protective role of liver X receptor α (LXRα) in cancer [37], which may be explained, at least in part, by LXRα-mediated upregulation of ABCA1

expression [38–41]. Not surprisingly, treatment of both LNCaP and PC-3 prostate cancer cell lines with T0901317, a potent LXRα agonist, increased ABCA1 and ABC transporter G1 (ABCG1) mRNA expression [38]. Also, the liver X receptor (LXR) agonist GW3965 has been reported to degrade the low-density lipoprotein receptor (LDLR) and to increase the expression of ABCA1, thus promoting glioblastoma (GBM) cell death *in vivo* [42]. In this regard, it was shown that 3-deoxyschweinfurthin B (3dSB), an analog of the natural anticancer product schweinfurthin B, reduced the levels of intracellular cholesterol in GBM cell lines through LXR activation, and increased ABCA1 expression [43]. In addition, the antitumor doxorubicin reduced the expression of peroxisome proliferator-activated receptor γ (PPARγ), LXRα, and ABCA1 in the HepG2 cell line [13]. Furthermore, lycopene exerted antiproliferative effects on LNCaP prostate cancer cells, mediated by the activation of the PPARγ-LXRα-ABCA1 pathways, thus resulting in reduced cellular total cholesterol levels [44]. Finally, DNA topoisomerase II inhibitors, such as etoposide and teniposide, were found to induce macrophage ABCA1 expression and cholesterol efflux through LXR signaling [45].

In apparent contrast with the above-mentioned results, the level of cholesterol uptake was similar in both normal and malignant human kidney cells in culture, although the release of cholesterol plateaued early in normal cells, whereas it continued at a linear rate in malignant cells, indicating that the regulation of cholesterol efflux is defective in malignant cells [46]. Moreover, it has been found that ABCA1 expression was 15–20-fold higher in androgen-dependent, compared with androgen-independent LNCaP human prostate cancer cells [36,47,48]. In addition, high expression levels of ABCA1 were reported in primary serous OCs, and were associated with a decreased survival rate [49]. Furthermore, an impairment of cellular cholesterol homeostasis in pancreatic ductal adenocarcinoma (PDAC) has also been reported, possibly as a consequence of ABCA1 upregulation [50]. ABCA1 overexpression may account for the increased resistance of M14 melanoma cells to the anticancer effects of curcumin [51]. Overexpression of ABCA1 was also demonstrated in GBM cells, and such overexpression might be responsible, at least in part, for the chemoresistance observed in the GBM cell line [52]. Deficiency in ABCG1, another ABC transporter, which acts synergistically with ABCA1, was reported to result in a reduced tumor burden in a mouse model, through modulation of macrophage function [53].

Scavenger Receptor of the B Class

SR-BI, also known as SCARB1 or CLA-1 (CD-36 and LIMPII analogous 1), facilitates the cellular uptake of cholesterol from LDLs and HDLs, thus providing an advantage in terms of cell growth and proliferation [4]; it exerts its effects via mitogen-activated protein kinase (MAPK) and protein kinase B (Akt) signaling pathway activation, and subsequent CE and lipid transfer to the cell, which mechanistically favors cancer cell survival [18]. In this regard, SR-BI upregulation has been reported in Leydig cell tumors, nasopharyngeal carcinoma, and especially prostate and BC [4,16,54]. Higher expression levels of SR-BI have been found to correlate with an advanced pathologic stage of disease, with larger tumor size, lymph node metastasis, and the absence of estrogen receptors in human BC tissues. Moreover, patients with high SR-BI expression had significantly shorter overall survival (OS) [55]. Enhanced cholesterol influx through the increased expression of SR-BI has been observed in human metastatic prostate tissue compared to primary tumor tissue [54]. It has also been reported that the proliferation of MCF-7 cells transfected with mutant CLA-1 was significantly inhibited compared to those with full length of CLA-1 (a receptor with high amino acid identity with SR-BI). A further study has shown that knockdown of SR-BI reduced HDL-induced activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which led to a reduction in cellular proliferation and migration in both MDA-MB-231 and MCF7 cell lines. In addition, the authors observed a significant decrease in tumor

growth *in vivo* [18]. SR-BI downregulation has been shown to cause a deficiency in cholesterol availability for the androgen synthesis pathway in C4-2 and LNCap prostate cancer cell lines, leading to a significant decrease in cellular viability and prostate specific antigen (PSA) secretion [56]. SR-BI overexpression has been observed in patients with nasopharyngeal carcinoma (NPC). *In vitro*, SR-BI upregulation was associated with increased cell motility, which was significantly inhibited by downregulation of SR-BI via the HDL-mimicking peptide-phospholipid scaffold (HPPS) nanocarrier [57]. However, downregulation of SR-BI has also been reported in other types of tumors, including adrenocortical carcinomas [58] and testicular seminoma [48], which might be due to several mechanisms, including cholesterol levels, not representing a rate-limiting factor for tumor growth, other isoforms of SR-BI being upregulated, or alternative cholesterol uptake pathways being constitutively active.

HDL-Associated Enzymes in Cancer

Phospholipid Transfer Protein

Phospholipid transfer protein (PLTP) mediates the transfer of phospholipids from apoB-containing triglyceride-rich lipoproteins to HDLs, and participates in phospholipid exchanges between lipoproteins and HDL conversion and remodeling. While PLTP can act like a fusion factor enlarging HDLs, the role of PLTP in RCT is still controversial [59].

A recent study has revealed that PLTP, which is involved in the PPAR pathway, was significantly overexpressed in end-stage BC patients with a pathological complete response (pCR) following neoadjuvant chemotherapy, when compared with those who did not obtain a pCR. This study suggests that the PLTP-PPAR pathway may be an important predictor of chemotherapy response [60].

Lipoprotein-Associated Phospholipase A2

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase (PAF-AH), and encoded by the PLA2G7 gene [61], is a Ca^{2+}-dependent enzyme [62] that has recently been suggested as a potential biomarker for cancer due to its role in promoting cancer cell migration and invasion. Abnormal expression of different human secreted PLAs has been reported in several types of malignancy, including colon cancer, prostate cancer, and BC [62]. Increased plasma levels of Lp-PLA2 have been found in patients with colon cancer [63] and prostate cancer [61]. In addition, increased enzymatic activity, as well as mRNA levels of Lp-PLA2, have been detected in samples from patients with colon cancer compared to healthy donors [63]. Phospholipase A2 Group 7 deficiency decreases intestinal polyposis and colon tumorigenesis in the $Apc^{Min/+}$ mice model, thus providing evidence for the future potential therapeutic application of Lp-PLA2 inhibitors against cancer [63].

Paraoxonase-1

Paraoxonase-1 (PON1) is a Ca^{++}-dependent esterase synthesized by the liver, and is one of the most important antioxidant HDL-related enzymes [64]. This lipolactonase could eliminate carcinogenic free radicals and restore oxidative balance [65]. Serum PON1 activity is lower in patients with endometrial cancer [64], metastatic gastric cancer [66], benign ovarian tumors [67], BC [68], colorectal cancer [69], lung cancer [70], epithelial ovarian cancer [71], multiple myeloma [69], brain tumors (high grade gliomas and meningiomas) [72], laryngeal cancer [73], bladder cancer [69], and other cancer types [74,75], which suggests an impaired antioxidant defense during carcinogenesis [64]. Consistent with this, the association between cancer and reduced serum PON1 activity has been reported [65,107]. It has been reported that the arylesterase activity of PON1 is negatively and independently associated with early death in

BC patients [76]. As noted previously, low levels of HDL-C have been increasingly identified in cancer patients, and these indirectly reflect the low level of PON1 enzyme activity [77]. The PON1/HDL ratio is significantly lower in patients with multiple myeloma and lung cancer [70], when compared to controls. However, PON activity may be tumor dependent, as one study showed that serum PON1 activity was significantly higher in patients with ovarian cancer [67] and esophageal cancer, compared to healthy controls. However, in agreement with the negative association of PON1 with cancer, the PON1 values were significantly decreased in stage III and stage IV esophageal cancer patients, compared with patients in stage $\leq$2 [78]. A second study demonstrated an enhanced HDL-cholesterol-associated antioxidant PON-1 activity in prostate cancer patients, but the number of subjects enrolled in this study was very low, thus leading to inconclusive results [79]. Of note, the PON1 polymorphisms have been associated with an increased risk of BC, prostate cancer, and ovarian cancer. PON1 192 AA genotype was proposed as a risk factor for BC and ovarian cancer [68]. In addition, it has been demonstrated that individuals carrying the QQ genotype of PON1 are at increased risk for RCC and lung cancer, as compared with those individuals carrying the QR or RR genotype [80]. Conversely, the heterogeneous AB genotype of PON1 p.Q192R variation has been recognized as a low-risk parameter for the development of uterine leiomyomas in Turkish women [81]. Consistent with this study, the PON1 Q192R polymorphism is associated with a reduced risk of overall cancers [82]. However, one study showed that the Q192R polymorphism was not predictive of BC development [83]. Among potential protective PON1 variants, subjects with PON1 rs662 AA genotype have a significantly lower risk of lung cancer, when compared to the GG genotype [84]. Conversely, other studies have suggested that no significant difference in genotype distributions or allele frequencies for polymorphisms in the PON1 genes exist between colorectal cancer patients [85], or pancreatic cancer [86], and matched controls.

Lecithin-Cholesterol Acyltransferase

Lecithin-cholesterol acyltransferase (LCAT) promotes discoidal HDL maturation, converting free cholesterol into cholesteryl ester, and large quantities of lysolecithin are generated on HDL. It is recognized that LCAT activity strongly contributes to the antioxidant properties of HDL. Plasma LCAT levels tend to be lower in BC patients, compared to healthy subjects. Interestingly, LCAT levels have also been reported to decrease after radiotherapy in BC patients, indicating that LCAT activity correlates with the treatment effects of radiotherapy [2]. In addition, the cholesterol-esterifying activity of LCAT was found to be significantly lower in BC patients, whether assayed with endogenous substrates, or with an exogenous substrate, suggesting an impaired esterification in plasma in patients with BC [87]. From a therapeutic perspective, a recent study showed the feasibility of using monocholesterylsuccinate (CHS)-modified paclitaxel-loaded discoidal reconstituted high-density lipoproteins (cP-d-rHDL) as novel biomimetic nanocarriers for cancer therapy [88] that are resistant to LCAT-mediated remodeling and consequent reduced cancer cell drug uptake.

Serum Amyloid A and Cancer

Serum amyloid A (SAA), a family of apolipoproteins, is an acute phase protein principally released by the liver and transported by lipoproteins, including HDLs. Accumulation of SAA can modify biological properties of HDLs and reduce their anti-inflammatory activity in cancer. It has been suggested that delivery of HDL-mediated cholesterol, which is a major determinant for the proliferation of cancer cells, is impaired due to the alteration of SAA content of HDL that mediates HDL binding to the cell surface [89]. SAA may be also synthesized by cancer cell lines *in vitro*. High levels of SAA have been observed in preclinical models of lymphoma [90], in patients with lung cancer [91], RCC [92,93], nasopharyngeal cancer [94], and many other cancer types.

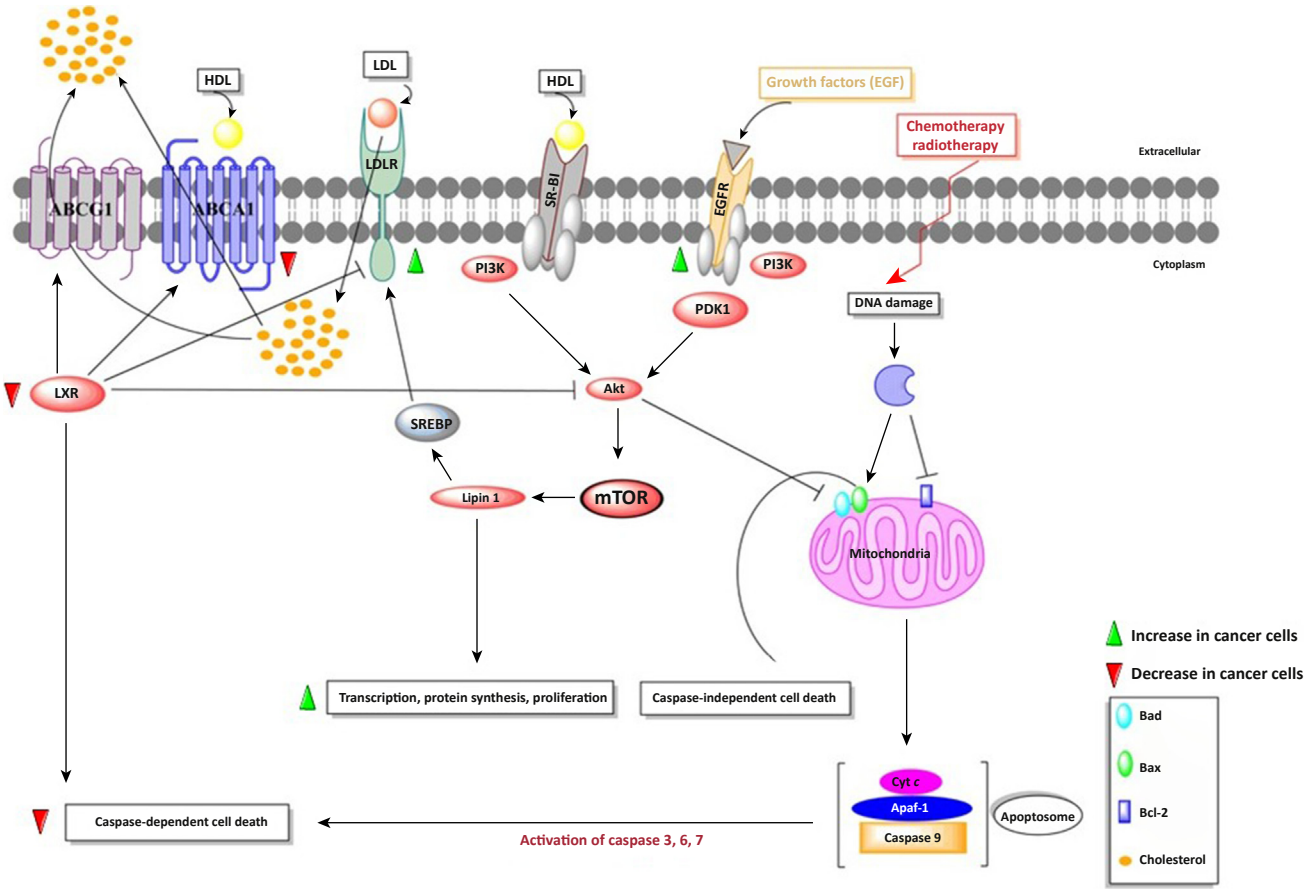

Figure 1. Cancer Cells Require Surplus Cholesterol to Retain Proliferation at High Level. This excess cholesterol is supplied through upregulation of cholesterol biosynthesis, Low-density lipoprotein cholesterol (LDL-C) uptake pathways, inhibition of cholesterol catabolism, and lipoprotein-associated cholesterol export at the same time. So, liver X receptor (LXR)-driven cholesterol depletion through inducing the expression of the ATP-binding cassette (ABC) transporters (ABCA1 and ABCG1) and degradation of low-density lipoprotein receptor (LDLR), and also through increased caspase-dependent apoptosis, can cause the cell proliferation, inhibition, and apoptosis stimulation in tumor cells. In addition, LXR activation suppresses cancer cell proliferation by disrupting key growth pathways, such as epidermal growth factor receptor (EGFR), as well as downregulating protein kinase B (Akt) survival signaling and inducing apoptosis of cancer cells.

Intriguingly, SAA levels directly correlated with the stage of the disease in patients with RCC [95], non-small cell lung cancer, and BC [96]. Baseline SAA levels below 22 mg/L were associated with a prolonged OS in patients with advanced pancreatic cancer [97]. Also, patients with esophageal squamous cell carcinoma who had SAA levels ≥8.0 mg/L had a reduced survival rate, compared to those with SAA <8.0 mg/L [98]. Increased SAA levels were also associated with higher risk of gastric cancer [99]. Furthermore, esophageal squamous cell carcinoma patients with lower preoperative levels of SAA experienced significantly longer OS than those with high SAA levels [100]. Mechanistically, it has been proposed that SAA may have a role in cancer progression through the increase of plasminogen activation [101]. In addition, because a higher SAA protein expression level has been reported in tumor-associated macrophages compared with tumor cells, it has been suggested that tumor-associated macrophages may be an important source of SAA production in the tumor microenvironment [102].

Table 2. Association of HDL-Cholesterol and HDL Components with the Risk of Cancer in Clinical Studies[a]

Type of cancer	Design of study	Results of studies	OR or RR or Dif	Refs
Various cancers	Prospective cohort	High levels of HDL-C were associated with the low risk of cancer	RR: 0.89	[8]
	Meta-analysis of randomized controlled trials	High plasma levels of HDL-C were inversely related to the incidence of cancer development	Every 10 mg/dL increase in plasma levels of HDL-C, decreased the risk of cancer incidence by 36%	[11]
NPC	Cohort	Patients with high pretreatment HDL-C levels exhibited decreased OS, compared to patients with low HDL-C levels	HR: 1.369	[16]
BC	Retrospective cohort	Patients with high SR-BI expression had shorter OS	HR: 2.312	[55]
		ARE activity was negatively associated with early death in BC patients, compared to patients surviving more than one year after the analysis, and those who died within one year	OR: 0.10	[76]
		ARE activity was independently associated with early death in BC patients, compared to patients surviving more than one year after the analysis, and those who died within one year	OR: 0.12	[76]
	Meta-analysis	The M allele of PON1 gene was significantly associated with an increased risk of BC	OR: 1.34	[83]
RCC	Retrospective cohort	Preoperative low level of apoA-I (<1.04) had lower OS	HR: 0.57	[25]
		Low apoA-I was associated with shortened DFS time in nonmetastatic patients	HR: 0.65	
OC	Prospective cohort	Patients with higher levels of methylation of ABCA1 have shorter OS	HR: 1.106	[34]
	Case–control	High expression level of ABCA1 in primary tumors was associated with decreased survival, compared to those expressing low levels of ABCA1	Dif: −25.8%	[49]
Lung cancer	Case–control	The PON1 rs662 AA genotype showed a significantly lower risk of lung cancer, compared to the GG genotype in nonsmoking subjects	OR: 0.60	[84]
Gastric cancer	Prospective cohort	Patients with increased SAA levels were associated with high risk of gastric cancer	OR: 1.93	[99]
Esophageal squamous cell carcinoma	Retrospective cohort	Esophageal squamous cell carcinoma patients with preoperative lower levels of SAA had longer OS compared to those with high SAA levels	OR: 11.752	[100]

[a]ARE, arylesterase; DFS, disease-free survival; Dif, difference; HR, hazard ratio; OR, odds ratio; RR, relative risk.

Concluding Remarks and Future Perspectives

Early prediction and detection of cancer is a priority to reduce the morbidity, mortality, and health care costs. A biomarker panel that can be used on easily accessible biological body fluids would be a step forward for the early diagnosis of cancer and for screening purposes. Accordingly, researchers are turning their attention to the development of novel approaches to investigate molecular markers based on serum and plasma by using metabolomics, proteomic, and epigenetic techniques, in order to improve the diagnosis of early stage cancers and predict the outcome of patients with known tumors. Cholesterol is known to serve as a precursor for steroid hormone synthesis, promote cell migration, and mediate inflammatory processes, all of which play a key role in carcinogenesis. As a consequence, targeting cholesterol supplying of cancer cells by interfering with lipoprotein pathways might be an intriguing strategy for both cancer therapy and for preventing or delaying the development and progression of cancer (Figure 1).

Whilst the relationship between HDL-C levels and cancer incidence and survival are still debated [108], there is increasing evidence of this association, though whether this is mechanistically causal remains largely unanswered. Evidence is accumulating that serum HDL-C levels could serve as a prognostic marker in patients with cancer, and might help to identify a subset of patients at increased risk of cancer (Table 2).

In addition to the HDL-C levels that may be influenced by several confounding factors and cancer covariates, it has been proposed that the variable HDL composition and functionality might better explain the association between HDLs and cancer. The latter hypothesis, which is suggested by the multitude of HDL-associated proteins and enzymes involved in cancer cell biology, might provide novel and unexpected targets for anticancer therapy. In this regard, ABCA1 has garnered attention as a potential anticancer target. ABCA1 inactivation impairs the cholesterol efflux pathway, and thus cholesterol is accumulated in cancer cells, which partially accounts for the biological aggressiveness of cancer cells. Along with ABCA1, SR-BI is emerging as a potential diagnostic and prognostic indicator of cancer, as it has been found to be upregulated in virtually all cancers. Of note, SR-BI is increasingly gaining interest, as it might also represent a potential gateway for the delivery of therapeutic agents when reconstituted with HDL nanoparticles.

In light of the expanding knowledge about HDL function in the tumor microenvironment, an appealing therapeutic strategy to reduce cancer risk and progression might be through lifestyle modifications that alter HDL levels, or by direct therapeutic intervention to raise HDL levels. This may be of particular relevance due to the increasing prevalence of low HDL-cholesterol levels and impaired HDL functionality.

Outstanding Questions

What is the mechanism underlying the association of HDL-C with cancer?

Could circulating HDL-C levels, generally or subtype specifically, serve as a biomarker to predict risk and/or prognosis of cancer?

Could a therapeutic increase in HDL-C levels augment cancer treatment?

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