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Chapter 26

Lipoproteins and Cancer

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1. Introduction

Circulating lipoproteins perform vital functions, including the transport of fatty acids and cholesterol from intestine and liver throughout the body. However, in well-fed Western societies, elevated concentrations of lipoproteins in blood have long been recognized to convey increased risk for cardiovascular disease. High fat diets, obesity, and heredity can all contribute to hyperlipidemia. More recently, there has been concern for the possible effects of hyperlipidemia on risk for or progression of cancers, which have a far greater demand for lipids than normal tissues. For example, obesity is now an established risk factor for certain types of cancer and is also found to affect the prognosis for cancer patients (Calle and Kaaks 2004; Cleary and Grossmann 2009). While the association of obesity with cancer is complex, higher circulating lipids may be a contributing element. Similarly type 2 diabetes, a condition of multiple co-morbidities including hyperlipidemia, is associated with the incidence of and mortality from cancer (Faulds and Dahlman-Wright 2012).

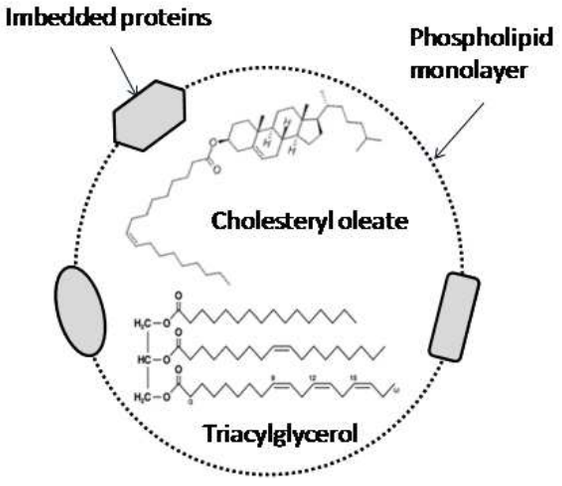

Figure 1. Cytoplasmic lipid droplets consist of an oily core of TAG and CE surrounded by a phospholipid monolayer, specific coat proteins, and other proteins.

The association of hyperlipidemia with cancer began with early observations of an accumulation of cholesterol in tumors (reviewed, (Mulas, Abete et al. 2011)). Higher levels of cholesterol and cholesteryl esters (CE) in malignant compared to less malignant tumors and normal tissues were first measured chemically (Yasuda and Bloor 1932). The accumulation of lipids in tumors was subsequently noted in tumor sections through histological examination and staining for lipid droplets (also called lipid bodies) (Freitas, Pontiggia et al. 1990). Lipid droplets are cellular organelles that store neutral lipids triacylglycerol (TAG) and CE (**Fig. 1**). Adipocytes store lipids in a single, large lipid droplet. Most other cell types have fewer, smaller lipid droplets except under pathological conditions when increased numbers and amounts of lipid may be present (Bozza and Viola 2010). Lipid droplets were detected *in vivo* in tumors with proton magnetic resonance (Delikatny, Chawla et al. 2011), and more recently, *in vivo* and *in vitro* with coherent anti-Stokes Raman scattering microscopy (Le, Huff et al. 2009). Unlike adipocyte lipid droplets, tumor cell lipid droplets contain significant quantities of CE (Tosi and Tugnoli 2005); therefore as these tumors grow and accumulate cholesterol, they may be expected to affect whole body cholesterol homeostasis and circulating cholesterol levels.

The observation of changes in plasma cholesterol in cancer patients constitutes the second line of evidence in the association of lipoproteins with cancer. It appeared in multiple studies over many years that lower plasma cholesterol was associated with a higher risk of cancer (Rose and Shipley 1980). This was a concern because lowering plasma cholesterol is a goal in cardiovascular disease prevention. The relationship between plasma cholesterol and cancer was examined in many population-based studies. Although total plasma cholesterol (total-C) measurements were used in many studies, determinations of individual lipoprotein cholesterol fractions were increasingly included. Plasma cholesterol resides primarily in low density lipoproteins (LDL) and high density lipoproteins (HDL), the lipoproteins that transport cholesterol to cells and collect excess cholesterol from cells, respectively. High HDL-C is a protective factor against atherosclerosis, while high LDL-C is positively associated with risk of atherosclerosis.

Two trends ultimately emerged from the data. First, total-C concentrations were lower two to six years prior to a cancer diagnosis, suggesting reverse causation: i.e., the early stages of the tumor led to lower circulating cholesterol (Sharp and Pocock 1997). Second, the plasma cholesterol fraction associated with tumor-caused decreases was primarily HDL-C, although the trend was detectable in total-C values also (Ahn, Lim et al. 2009). These conclusions were supported by data showing an increase in HDL-C when the patient was in remission (Dessi, Batetta et al. 1995).

The observations above suggest that in some types of cancer, tumor cells accumulate cholesterol as CE in lipid droplets and efflux less cholesterol to HDL, resulting in lower circulating HDL-C, detectable even before the tumor can be diagnosed. There is also some indication that low HDL-C levels may contribute to the development of cancer (Mondul, Weinstein et al. 2011). HDL has antioxidant and anti-inflammatory properties in addition to its role in reverse cholesterol transport (Kwiterovich 2000), and low HDL-C is a defining

characteristic of the metabolic syndrome which has already been linked to cancer risk (Faulds and Dahlman-Wright 2012). Although lower HDL-C can have multiple etiologies, it can be one indicator of the presence of a tumor. If some tumors accumulate cholesterol, then it might be reasonable to ask if LDL-C fuels the development of this type of tumor.

In this chapter, we will review the evidence that LDL-C, which is usually highly correlated to total-C, is positively associated with the risk of some types of cancer. We will also review the growing body of data on what mechanisms may be involved in tumor cholesterol accumulation and what markers may be useful to identify tumors that are stimulated by cholesterol. We will address the questions: does higher circulating cholesterol increase the risk of or prognosis for certain cancers, and should lowering LDL-C be a goal in the prevention or management of some types of cancer?

2. Clinical and epidemiological evidence for an association of LDL with cancer

The presence of cancer can affect whole body cholesterol homeostasis, leading to the observation of low plasma HDL-C in cancer patients as described above. Plasma LDL-C levels in cancer may be confounded by the increased catabolism of LDL by a known or undiagnosed tumor, leading to an apparent association of low LDL-C with some types of cancer (Vitols, Gahrton et al. 1985). These apparent interactions of synchronous lipoprotein levels with cancer make it difficult to distinguish a tumor-promoting effect of lipoproteins from a tumor-induced effect on lipoproteins. Prospective studies that include a baseline measurement of blood cholesterol levels and a sufficient follow-up period could reveal if there was a positive association of hypercholesterolemia with the incidence of cancer, or in cancer patients, with prognosis or survival. Such studies have been conducted and the results have been somewhat inconsistent, which may be partially explained by the fact that tumors vary greatly by tissue of origin and even by sub-types of tumor arising from the same tissue.

Additional insight has been gained from studies of statins and statin users. Statins (inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR)), the rate limiting step in cholesterol biosynthesis) are considered to have pleiotropic effects against cancer due to the multiple biosynthetic products downstream of HMGCR (Gazzerro, Proto et al. 2012). However, pharmacokinetic data suggests that the peripheral tissues do not have access to high enough concentrations of therapeutic statins to effect other pathways and that the major effect of statins is through the reduction of cholesterol biosynthesis in the liver (Solomon and Freeman 2008). Statins lower plasma total-C, which reflects a large reduction in LDL-C (up to 50% or more), a lesser reduction of VLDL-C and minor effects on HDL-C. The reduction of circulating LDL-C, a major consequence of statin use, is likely the primary anti-cancer action of statins.

The largest prospective study to date on cholesterol and cancer was done in Korean adults enrolled in the Korean National Health Insurance Corporation (NHIC); participants (n = > one million) underwent biennial medical evaluations where a baseline fasting total-C

measurement was obtained and follow-up data was collected for up to 14 years (Kitahara, Berrington de Gonzalez et al. 2011). The study identified cancer types that had a positive trend with quintiles of total-C in men (prostate, P = 0.002, and colon, P = 0.05) and women (breast, P = 0.003, and colon, P = 0.004), as well as those that had a negative trend in men (esophageal, stomach, liver, and lung) and women (liver). The results were adjusted for multiple factors including BMI, and excluded cancers diagnosed in the first 5 years of follow-up. This study identified the hormone-related cancers and colon cancer as having the greatest association with total-C. These cancers are also the most heavily studied with respect to the effects of total-C, statins, or dietary fat.

Prostate cancer. Early stage prostate cancer (PrC) is stimulated by circulating testosterone through over-expression of the androgen receptor (AR). AR signaling regulates the expression of the PrC marker prostate specific antigen (PSA); androgen-deprivation (castration) therapies block AR signaling, providing an effective treatment and reducing PSA levels. However, over time advanced PrC emerges which is resistant to castration therapies (androgen-independent), although the AR may still play a role in tumor progression (Taplin and Balk 2004). Testosterone is synthesized from cholesterol in the testes, but also in advanced prostate tumor cells, providing a rationale for an effect of cholesterol availability on prostate tumorigenesis (Mostaghel, Solomon et al. 2012).

Several large prospective studies in the USA showed an association between higher baseline plasma total-C and the development of high-grade (Gleason sum ≥ 7), but not total or low-grade PrC. In the Health Professionals Follow-Up Study, 18,018 men provided a baseline blood sample and were followed for up to 7 years (Platz, Clinton et al. 2008). Men with low total-C had a reduced incidence of high-grade PrC (odds ratio (OR) = 0.61, 95% CI, 0.39-0.98), and the association persisted after excluding men who were diagnosed within 2 years of blood draw. In the Prostate Cancer Prevention Trial (7 years), 5586 men in the placebo arm with a lower baseline total-C measurement had a reduced incidence of Gleason 8-10 PrC (OR = 0.41, 95% CI, 0.22-0.77) (Platz, Till et al. 2009). In the CLUE II study, 6816 men in Washington County, Maryland were followed for a mean of 12 years (Mondul, Clipp et al. 2010). Those with a baseline total-C in the desirable or borderline range had a reduced incidence of high grade PrC (hazard ratio (HR) = 0.68, 95% CI, 0.40-1.18), which was more pronounced in men with a higher BMI (HR = 0.36, 95% CI, 0.16-0.79). Excluding users of cholesterol-lowering drugs or cases diagnosed within two years of follow-up did not change the results.

The differential effects of total-C on high-grade PrC were supported in several studies conducted outside the USA. In the Alpha Tocopherol, Beta Carotene Cancer Prevention Study cohort, baseline fasting total-C and HDL-C were obtained for >29,000 Finnish male smokers who were enrolled between 1985 and 1988. After long-term follow-up (still ongoing) in 2006, and excluding the first 10 years from baseline, it was found that men with higher total-C had increased risk of overall (HR = 1.22, 95% CI, 1.03-1.44) and advanced (HR = 1.85, 95% CI, 1.13-3.03) PrC (Mondul, Weinstein et al. 2011). The Midspan studies (begun in the 1960s and 1970s in Scotland, UK) had a median follow-up period of 24 years after a

baseline plasma total-C measurement (Shafique, McLoone et al. 2012). In 12,926 men diagnosed with PrC >5 years after entry into the study (n = 650), the HR for the risk of high-grade disease (Gleason score ≥ 8) in those with cholesterol levels in the second highest quintile or the highest two quintiles combined compared to the lowest quintile was 1.75 (95% CI, 1.03-2.97) and 1.88 (95% CI, 1.08-3.27), respectively. The use of statins was not available. The Nijmegen Biomedical Study in the Netherlands reported that among 2118 men followed for a median period of 6.7 years who had never used cholesterol-lowering drugs (and excluding those diagnosed in the first year), those with higher baseline total-C had increased risk for PrC (HR = 1.39, 95% CI, 1.03–1.88) and aggressive PrC (HR = 1.65, 95% CI, 1.10–2.47 (Kok, van Roermund et al. 2011). An even stronger association was seen for LDL-C levels and PrC (HR = 1.42, 95% CI, 1.00–2.02) and aggressive PrC (HR = 1.83, 95% CI, 1.15–2.90).

Some studies did not support a role for cholesterol in PrC. No association of baseline plasma total-C or HDL-C with incident, advanced, or fatal PrC was found in the HUNT 2 study where a cohort of 29,364 Norwegian men were followed for a mean 9.3 years (Martin, Vatten et al. 2009). A stated limitation of the study was the small number of advanced or fatal cases. Similarly, no association of total-C with incidence of PrC was found in the Apolipoprotein MOrtality RISk (AMORIS) study, which followed 200,660 Swedish men for a mean of 8 years (Van Hemelrijck, Garmo et al. 2011). In this study no information was available on tumor severity, precluding a finding of a differential effect based on tumor grade.

Other types of studies have contributed evidence for the effects of blood cholesterol on PrC. In a cross-sectional cohort study of 531 American men, the incidence of benign prostate hyperplasia was 4-fold greater in those with diabetes who were in the highest compared to the lowest quartile of LDL-C; this effect was not seen in those without diabetes (Parsons, Bergstrom et al. 2008). A positive diagnosis of PrC in African-American (AA) men (n = 521), but not non-AA men (n = 451), undergoing biopsy was >3-fold higher for those in the highest quartile of LDL-C compared to the lowest (Moses, Abd et al. 2009). In a case-control study in 1294 Italian men <75 years of age with incident PrC compared to 1451 men hospitalized with acute, non-neoplastic conditions, the odd ratio (OR) for prostate cancer was 1.54 (95% CI, 1.26-1.89) for those with hypercholesterolemia (Pelucchi, Serraino et al. 2011). A post hoc analysis of the REDUCE study (which evaluated the anti-testosterone dutasteride in men with high prostate specific antigen (PSA) values but no PrC) examined the association of coronary artery disease (CAD) with PrC risk (Thomas, Gerber et al. 2012). In 6729 men who underwent at least one biopsy, those with CAD had an increased risk of PrC diagnosis (OR = 1.35, 95% CI, 1.08–1.67), suggesting common risk factors.

The benefit of statins in PrC prevention or treatment is still under evaluation, but observational studies have demonstrated reduced risk of PrC in statin users (reviewed, (Solomon and Freeman 2008; Marcella, David et al. 2011)). Statin use was recently shown to reduce the risk if death from PrC in a case-control study; cases were residents of New Jersey, USA ages 55 to 79 years who died from PrC between 1997 and 2000 (n = 380) and controls from the population were matched by 5-year age group and race. The unadjusted OR for

death from PrC was 0.49 (95% CI, 0.34-0.70) for any exposure to statins and decreased to 0.37 (P < .0001) after multivariate adjustment (Marcella, David et al. 2011). Users of high-potency statins had about 2.5 times more protection compared with users of low-potency statins; the authors suggest that this points to cholesterol-lowering as the mechanism of protection. A positive association between LDL-C and PSA was demonstrated in a longitudinal study of 1214 American veterans undergoing statin treatment between 1990 and 2006 (Hamilton, Goldberg et al. 2008). After a relatively short period of statin use (< 1 year), there was a near-linear relationship between changes in LDL-C and changes in PSA values. After adjustment for multiple factors, for every 10% change in LDL-C, PSA changed by 1.64% (95% CI, 0.64% to 2.65%, P = .001). This relationship held over increases or decreases in the values, although the mean and median changes in LDL and PSA were -26% and -4.1%, respectively (Hamilton, Goldberg et al. 2008). A subsequent study showed that statin use dose-dependently lowered the risk of a PSA recurrence in men who underwent a radical prostectomy (n = 1319) (30% lower risk of PSA recurrence (HR = 0.70, 95% CI, 0.50-0.97) (Hamilton, Banez et al. 2010). Median follow-up time was 24 months for statin users (n = 236, 18%), 36 months for non-users.

Breast cancer. Epidemiological studies showing a higher incidence of breast cancer (BrC) in Westernized countries led to a focus on the role of dietary fat in BrC risk (Kelsey 1993). Although dietary fat may affect circulating cholesterol levels, the specific contribution of plasma lipoproteins to BrC has received less attention. In addition, the relationship between circulating cholesterol and BrC risk may be complicated by the fact that, as for testosterone, cholesterol is a biosynthetic estrogen precursor and structurally similar to estrogen. Estrogen lowers plasma LDL by increasing the expression of the LDLR (Kovanen, Brown et al. 1979; Hulley, Grady et al. 1998), but stimulates breast tumor growth through over-expression of estrogen receptor alpha (herein referred to as ER). Obesity and menopausal status can affect circulating lipids, estrogen levels, and BrC risk.

The Nurses' Health Study of >70,000 female, married, American nurses used self-reported serum cholesterol levels to analyze the association of blood cholesterol with risk of invasive BrC during up to 12 years of follow-up (Eliassen, Colditz et al. 2005). In that study, BrC incidence was not affected by cholesterol levels or use of statins or other lipid-lowering drugs. In a 10-year follow-up of postmenopausal Korean women (n = 170,374), a positive trend for quartiles of baseline fasting serum total-C and BrC incidence was found (HR = 1.31, 95% CI, 1.06-1.61); however, after adjustment for BMI the trend was no longer significant (Ha, Sung et al. 2009). In contrast, 157 of 5865 peri/postmenopausal Swedish women in the Malmö Preventive Project developed BrC over a mean of 6.6 years; relative risk was increased by quartiles of baseline fasting total-C (P for trend, 0.05) (Manjer, Kaaks et al. 2001). This effect was not seen among the 112/3873 premenopausal women who developed BrC over a mean of 9.6 yrs. BMI was not a factor in the risk of BrC in either group.

Because BrC has multiple types with distinct and recognizable patterns of gene expression, different treatments and prognoses, it may be more useful to examine BrC types separately

(Hu, Fan et al. 2006). Expression of the ER is an important discriminating factor among BrC types, with ER- BrC having fewer treatment options and a worse prognosis. A number of studies have shown differences in cholesterol metabolism between ER+ and ER- BrC. LDLR and ER content were determined (by ligand binding) in tumors from 72 Swedish patients who had undergone mastectomy (Rudling, Stahle et al. 1986). Interesting, LDLR content was negatively, while ER content was positively correlated with survival in months. LDLR content strongly and independently predicted a worse prognosis in these patients (Rudling, Stahle et al. 1986). This finding is consistent with more recent data on tumor gene expression, where LDLR mRNA expression was generally higher in ER- as compared to ER+ human breast tumors in multiple studies ($P < 0.05$, oncomine.org).

Circulating cholesterol may affect severity, recurrence, or outcome of BrC. In a prospective study of Canadian women diagnosed with early stage BrC (n = 520) and followed for a median period of 8.7 years, a trend toward higher risk of recurrence was seen in women with a higher fasting baseline total-C or LDL-C (Bahl, Ennis et al. 2005). Unfortunately, women with preexisting hyperlipidemia were excluded from the study, leaving a population with a smaller range of cholesterol levels in the evaluation. In 24,329 Norwegian women, a higher baseline non-fasting total-C level was not associated with BrC incidence (Vatten and Foss 1990), but those in the highest quartile did have an increased the risk of death from BrC (HR = 2.0, 95% CI, 1.1 – 3.7) (Vatten, Foss et al. 1991). In the Women's Intervention Nutrition Study (WINS), women with BrC counseled for a low-fat diet (20% of calories) and followed for a median period of 5 years had a 24% lower risk of recurrence (n = 96/975, HR = 0.76, 95% CI, 0.60 to 0.98) as compared to the control group (n = 181/1462); interestingly, the effect was even stronger in those whose tumor was ER- (n = 28/205, HR = 0.58, 95% CI, 0.37 to 0.91) as compared to those whose tumor was ER+ (n = 59/273) (Chlebowski, Blackburn et al. 2006). Although neither total-C nor LDL-C were reported, serum fatty acid analysis showed a reduction in saturated fats in the diet group, and saturated fats are known to increase circulating cholesterol levels (Blackburn and Wang 2007).

A number of clinical trials are underway to evaluate statins for the prevention or treatment of breast cancer. Large scale prospective studies on the association of statin use with risk of breast cancer have had mixed results (Cauley, McTiernan et al. 2006; Jacobs, Newton et al. 2011), but beneficial effects of statins on disease recurrence have been documented. In a prospective cohort study of all female residents in Denmark diagnosed with stage I-III invasive BrC between 1996 and 2003 (n = 18,769), users of simvastatin (a lipophilic statin) had a 10% lower risk of recurrence (95% CI, -11% to -8%) as compared with nonusers of statins (Ahern, Pedersen et al. 2011). No reduced risk was observed in users of hydrophilic statins. In 703 American women treated for stage II/III breast cancer between 1999 and 2005 and followed until 2008, users of statins (n = 156) had a reduced risk of recurrence in multivariate analysis (HR = 0.40, 95% CI, 0.24–0.67) (Chae, Valsecchi et al. 2011). No effect was seen on overall survival. Interestingly, a retrospective analysis of BrC patients in the Kaiser Permanente Cancer Registry in California (n = 2141) found that those who had used statins for one year or more had fewer aggressive ER-/PR- tumors and were more likely to have low grade and less invasive tumors (Kumar, Benz et al. 2008).

In a small study of women with newly diagnosed BrC (chemotherapy and radiotherapy naïve, n = 17) who were postmenopausal and normal weight, it was found that oxidized LDL (oxLDL) ($P < 0.001$), total-C ($P = 0.001$) and LDL-C ($P = 0.001$) were higher compared to a matched control group (n = 30) (Delimaris, Faviou et al. 2007). While LDL-C may contribute to cancer risk or prognosis, as in cardiovascular disease oxLDL may also play a role. OxLDL is present as a small percentage of total LDL in normal individuals, but the percentage of oxLDL may increase in pathological states (Holvoet, Lee et al. 2008; Mello, da Silva et al. 2011). An oxLDL receptor (OLR1) and was recently identified experimentally as part of gene signature responsible for transformation, tumor growth, and proliferation in multiple cancer cell lines (Hirsch, Iliopoulos et al. 2010). There is evidence that oxLDL is higher in hypercholesterolemic subjects, and that lowering total LDL with statins will result in lower oxLDL (Stojakovic, Claudel et al. 2010; Tavridou, Efthimiadis et al. 2010).

Ovarian cancer. Ovarian cancer (OvC) has a much lower incidence than BrC, but is more deadly as most tumors are highly advanced at diagnosis. OvC is not stimulated by estrogen, but there is some evidence that circulating cholesterol affects outcomes. In a prospective study of 132 American women with stage III or IV OvC, serum banked at the time of diagnostic surgery was analyzed for total-C, HDL-C, and TAG (LDL was calculated; statin users were excluded) (Li, Elmore et al. 2010). Disease-specific survival was longer in patients with normal LDL as compared to those with elevated LDL-C (59 and 51 months, respectively, $P = 0.04$). In another study at the same site, statin use was found to be an independent positive prognostic factor in 126 women with stage III/IV OvC, 17 of whom were taking statins at the time of initial surgery (Elmore, Ioffe et al. 2008). Mean progression-free survival, as well as overall survival, was longer for statin users (24 months compared to 16 months, $P = 0.007$) as compared to statin non-users (62 months compared to 46 months, $P = 0.04$). Serum was not available to determine actual levels of lipoproteins. In a small study, women with OvC (n = 15) compared to a matched control group (n = 30) had higher oxLDL ($P = 0.006$) and there was a trend toward higher LDL-C ($P = 0.076$) (Delimaris, Faviou et al. 2007). The women had not yet received any chemotherapy or radiotherapy at the time of blood collection.

Colorectal cancer. Colon cancer risk was associated with baseline total-C in the Korean NHIC data (Kitahara, Berrington de Gonzalez et al. 2011). Other studies have had mixed results. In the European Prospective Investigation into Cancer and Nutrition, 1238 incident cases of colorectal cancer (CRC) and matched controls were analyzed for an association of CRC risk with serum lipoproteins (van Duijnhoven, Bueno-De-Mesquita et al. 2011). No significant trend for quintiles of total-C or LDL-C with CRC incidence was detected; a negative trend for HDL-C with colon cancer was seen, even when excluding the first two years of follow-up. No correction for the use of statins, aspirin or other medications was possible in this study. In the Japan Collaborative Cohort Study for Evaluation of Cancer Risk, the association of oxLDL and autoantibodies to oxLDL (oLAB) with the incidence of CRC was examined (Suzuki, Ito et al. 2004). A positive trend was found for oxLDL and CRC, even after multiple adjustments ($P = 0.038$, n = 119 cases, 316 controls); the trend for oLAB was not significant. The adjusted OR for the highest compared to the lowest quartile

of oxLDL was 3.10, 95% CI, 1.04-9.23. Although total-C was not different between cases and controls, oxLDL was strongly associated with total-C ($P < 0.001$, $n = 304$).

Plasma cholesterol may affect the progression of colon cancer to a more aggressive disease. The fasting lipid profiles of Italian men and women with metastatic CRC (n = 22) had higher synchronous total cholesterol, LDL-cholesterol and LDL/HDL ratios compared to those without metastases (n = 62) ($P = 0.03$, 0.01, and 0.002, respectively) (Notarnicola, Altomare et al. 2005). These results were independent of BMI. The authors hypothesized that LDL is beneficial for the proliferation and invasion steps of tumor progression. The effect of statin use on CRC incidence is unsettled due to mixed results from several retrospective analyses (Poynter, Gruber et al. 2005; Flick, Habel et al. 2009; Singh, Mahmud et al. 2009). There is hopeful data that statins may lower the recurrence rate of CRC , and a large-scale clinical trial is currently examining the potential of statin therapy to reduce the relapse rate in colon cancer in patients who have had surgery for early stage colon cancer (Hede 2011).

Other cancers. There is little consistent evidence to date from large prospective studies for the positive association of total-C or LDL-C with the incidence of other cancers. However, retrospective case control and observational studies showing a reduced risk of cancer in statin users are suggestive that lowering LDL-C may be an effective preventative strategy for a wider range of cancer types. For example, renal clear cell carcinoma (the most prevalent renal cell carcinoma) is known to accumulate large amounts of CE (Gebhard, Clayman et al. 1987), and a large case control study in American veterans (n = 1446 cases) found a 48% reduction in risk for this cancer in statin users (Khurana, Caldito et al. 2008). In the same population, a 55% reduction in the incidence of lung cancer in statin users compared to nonusers was found (n = 7280 cases) (Khurana, Bejjanki et al. 2007).

The evidence cited in this section suggests that higher circulating cholesterol can have the strongest effects on more advanced tumors. The question of whether more advanced or aggressive tumors accumulate more cholesterol as compared to early stage tumors *in vivo* has not been specifically addressed, although there is some evidence to suggest that this is the case (Tosi and Tugnoli 2005). Experimental data in the next section provide more support for the association of exogenous cholesterol with more aggressive cancer, as well as insight into how and why cancer cells accumulate cholesterol against normal homeostatic mechanisms.

3. Experimental and mechanistic evidence for role of LDL in cancer

Cholesterol homeostasis. If cholesterol homeostasis is altered in cancer cells to meet a greater demand for cholesterol, an understanding of the mechanisms involved will open up new targets against cancer. In normal cells, free cholesterol in cells is closely regulated to maintain adequate membrane cholesterol but prevent free cholesterol toxicity. Excess cholesterol is stored in the form of neutral cholesteryl esters (CE) that are available to the cell through the CE cycle (Brown, Ho et al. 1980), or is effluxed to circulating HDL for transport back to the liver (Fielding and Fielding 2001). In cholesterol-accumulating tumors, there is more CE storage and less efflux of cholesterol to HDL. Is this cholesterol newly synthesized

Study (Country)	Years of follow-up	n (n for cases)	Sex	Type of cancer	Association with risk of cancer for:			Reference
					Total-C	LDL-C	HDL-C	
National Health Insurance Corp. enrollees (South Korea)	Up to 14	1,189,719 (M:53,944 F: 24,475)	M,F	All	Positive for PrC (M), BrC (F), CRC (M,F); negative for stomach, liver (M,F), lung (M)	Not measured	Not measured	{Kitahara, 2011}
Health Professionals Follow-Up (USA)	Up to 7	18,018 (698)	M	PrC	Positive for high-grade PrC	Not measured	Not measured	{Platz, 2008}
Prostate Cancer Prevention Trial (USA)	Up to 7	5,586 (1,251)	M	PrC	Positive for high-grade PrC			{Platz, 2009}
CLUE II (USA)	Mean of 11.9	6,816 (438)	M	PrC	Positive for high-grade PrC	Not measured	Not measured	{Mondul, 2010}
Alpha-Tocopherol, Beta-Carotene Cancer Prevention (smokers, Finland)	>10	29,093 (2,041)	M	PrC	Positive for aggressive and advanced PrC	Not measured	Negative trend	{Mondul, 2011}
Midspan (Scotland, UK)	Up to 37	12,926 (650)	M	PrC	Positive for high-grade PrC	Not measured	Not measured	{Shafique, 2012}
Nijmegen Biomedical (Netherlands)	Mean of 6.6	2,118 (43)	M	PrC	Positive for total and aggressive PrC	Positive for total and aggressive PrC	Positive for non-aggressive PrC	{Kok, 2011}
HUNT 2 (Norway)	Mean of 9.3	29,364 (687)	M	PrC	None	Not measured	None	{Martin, 2009}
Apolipoprotein MOrtality RISk (Sweden)	Mean of 7.0 - 8.3	200,660 (5,112)	M	PrC	None			{Van Hemelrijck, 2011}
Nurses' Health (self-reported serum chol-esterol) (USA)	6 - 12	79,994 (3177)	F	BrC	None	Not measured	Not measured	{Eliassen, 2005}
Postmenopausal public servants (South Korea)	Up to 10	170,374 (714)	F	BrC	Positive trend	Not measured	Not measured	{Ha, 2009}
Malmö Preventive Project (Sweden)	Up to 20	9,738 (269)	F	BrC	Positive for postmenopausal; none for premenopausal	Not measured	Not measured	{Manjer, 2001}
National Health Screening Service (Norway)	11 - 14	24,329 (242)	F	BrC	Negative (pre-menopausal); none (post-menopausal)	Not measured	Not measured	{Vatten, 1990}
EPIC and Nutrition (nested case-control)	Mean of 3.8	521,448 (1238)	M,F	CRC	None	Not measured	Positive for colon cancer	{van Duijn-hoven, 2011}

Table 1. Large, prospective studies with a baseline total cholesterol measurement and long-term follow-up for cancer incidence. M, male; F, female; PrC, prostate cancer; BrC, breast cancer; CRC, colorectal cancer.

or obtained from LDL, and what determines this? Normal cells obtain cholesterol primarily through endocytosis of circulating LDL through the LDLR, but have the capacity for endogenous synthesis via the mevalonate pathway; both mechanisms are tightly controlled for cholesterol homeostasis (Goldstein, DeBose-Boyd et al. 2006). The expressions of both LDLR and HMGCR are regulated by the transcription factors sterol response element binding proteins (SREBP1/2), whose processing and maturation proceed in response to decreased intracellular cholesterol (Brown and Goldstein 1997). The observed accumulation of CE in some tumors, the positive association of total-C with the risk of some types of cancer, and the demand for cholesterol for membrane building in growing cells, all suggest that the expression of these proteins and other components of the cholesterol homeostatic response system are altered in cancer.

Cholesterol biosynthesis in cancer. In order to obtain sufficient cholesterol, proliferating cells may accelerate the rate of cholesterol biosynthesis. Oncogenes that transform cells and dysregulate growth activate anabolic and biosynthetic pathways leading to *de novo* cholesterol and fatty acid synthesis. This is accomplished by a greatly increased flux of glucose into cells and through the glycolytic pathway to produce energy, and transport of TCA cycle citrate from the mitochondria to the cytosol for lipid biosynthesis (Vander Heiden, Cantley et al. 2009). The cytosolic enzyme ATP citrate lyase converts citrate to acetyl-CoA, the basic building block for both fatty acids and cholesterol. Growth factor activation of tyrosine kinase receptors and downstream PI3K/AKT and MAP-kinase signaling pathways increase expression and activation of the SREBPs (Kotzka, Muller-Wieland et al. 2000; Porstmann, Griffiths et al. 2005; Krycer, Sharpe et al. 2010), which control many lipid biosynthetic enzymes. Interesting, it was recently demonstrated that a mutated form of the cell cycle regulator p53, common in many tumors, bound to the promoter regions of the SREBPs and increased the expression of mevalonate pathway genes in BrC cells (Freed-Pastor, Mizuno et al. 2012).

A high enough rate of *de novo* biosynthesis may not always be possible; for example in solid tumors, expansion and insufficient vascularization may limit the delivery of glucose and oxygen. If oxygen is limited, activation of the hypoxia inducible factor 1 (HIF1) pathway can increase survival but divert pyruvate to lactate, reducing production of citrate (Gordan, Thompson et al. 2007). If glucose is limited, reducing ATP production, the AMP activated protein kinase (AMPK) pathway can inactivate key biosynthetic enzymes by phosphorylation (Shackelford and Shaw 2009). If biosynthesis becomes constrained, cells would have an advantage by being able to obtain lipids exogenously from circulating lipoproteins.

Cholesterol uptake in cancer. Uptake of cholesterol from LDL is primarily through the LDLR, although several scavenger receptors may also contribute. Over-expression of LDLR without feedback regulation by cholesterol has been observed in many types of cancer cells (Chen, Li et al. 1988; Hirakawa, Maruyama et al. 1991; Chen and Hughes-Fulford 2001; Antalis, Uchida et al. 2011). Although the role of SREBPs in feedback regulation of LDLR expression is well understood (Goldstein, DeBose-Boyd et al. 2006), there is evidence that

cell signaling pathways also contribute to LDLR up-regulation in cancer. In BrC cells, LDLR mRNA expression was 3-5-fold higher in ER- as compared to ER+ cell lines; PKC activation was strongly associated with increased LDLR expression in ER+ BrC cells, and to a lesser extent, even in ER- cells (Stranzl, Schmidt et al. 1997). Activation of the p42/44 (MAPK) cascade was sufficient to induce LDLR transcription in human hepatoma HepG2 cells expressing oncogenic Raf-1 kinase (Kapoor, Atkins et al. 2002). In glioblastoma cells, chronic activation of the EGF receptor tyrosine kinase, or other mechanisms which ultimately activated the PI3K/AKT pathway, led to increased expression of SREBP1 and the LDLR and to LDL-responsive proliferation (Guo, Reinitz et al. 2011).

Increased dietary cholesterol has been shown to promote tumorigenesis in animal models. A Western-type high cholesterol diet compared to a chow diet increased tumor incidence and metastasis in a mouse model of PrC (Llaverias, Danilo et al. 2010). The same group, using similar diets, showed an increase in tumor formation and more aggressive tumors in a mouse model of BrC (Llaverias, Danilo et al. 2011). In both studies, plasma total-C was reduced following tumor development, suggesting utilization of circulating cholesterol by the tumor and similarity to what is observed in people with cancer.

Role of cholesterol esterification. Whether tumor cells obtain the needed cholesterol endogenously or exogenously, it would be imperative to have a way to manage the increased flux of cholesterol so as to meet the dual goals of ensuring a ready supply and avoiding toxicity. Cholesterol toxicity is prevented by effluxing the excess free cholesterol to an extracellular acceptor or converting free cholesterol to non-toxic esters of fatty acids. The observed low HDL-C in cancer patients, combined with the observed increased cholesterol content in tumors suggest that efflux mechanisms are reduced and esterification is increased. Synthesis and storage of CE in lipid droplets not only reduces toxicity but provides an accessible depot of cholesterol for future cell needs.

The enzyme responsible for cholesterol esterification is acyl-CoA:cholesterol acyltransferase 1 (ACAT1/SOAT1), a constitutive resident of the endoplasmic reticulum. ACAT1 esterifies cholesterol obtained from LDL and also from endogenous synthesis (Chang, Li et al. 2009). ACAT1 is frequently found to be over-expressed in cancer vs. normal tissues in human tumor gene expression analyses, including cancers of brain, breast, cervix, esophagus, head and neck, kidney, and testis ($P < 0.05$, oncomine.org). Over-expression of ACAT1 has been specifically associated with cholesterol accumulation in renal clear cell carcinoma, a tumor type characterized by 35-fold more CE as compared to normal kidney (Gebhard, Clayman et al. 1987).

ACAT activity has been associated with proliferation in cancer cells. The CE content of lymphocytes from patients with acute or chronic lymphocytic leukemia ($n = 30$) was 6-fold higher as compared to lymphocytes from healthy age-matched controls ($n = 15$), and plasma HDL was >40% reduced in the leukemia patients compared to the controls (Mulas, Abete et al. 2011). Phytohemaglutinin (PHA)-stimulated proliferation of the isolated leukemic cells was positively correlated to esterification of oleate to cholesterol, and inhibition of ACAT greatly reduced PHA-induced proliferation (Mulas, Abete et al. 2011). Cholesterol

esterification and ACAT1 expression were also studied in leukemia cell lines. Cells with a greater ability to esterify cholesterol and with lower cholesterol efflux (CEM) had a higher rate of proliferation as compared to cells with a greater ability to synthesize cholesterol *de novo* (MOLT4) (Dessi, Batetta et al. 1997). Further work demonstrated that the faster-growing CEM cells expressed more ACAT1 and less HMGCR mRNA as compared to the slower-growing MOLT4 cells (Batetta, Pani et al. 1999).

In BrC, we showed that more aggressive basal-like ER- BrC cells had more lipid droplets and a much higher ratio of CE to TAG in stored neutral lipids as compared to less aggressive ER+ BrC cells; this was associated with higher expression of ACAT1 (Antalis, Arnold et al. 2010). The cell line differences were mirrored in gene expression analyses of human breast tumors, where higher expression of ACAT1/SOAT1 is characteristic of basal-like ER- tumors (Antalis, Arnold et al. 2010). We further showed that ER- cells took up more LDL as compared to ER+ cells, and that LDL dose-responsively increased proliferation only of ER- cells and in an ACAT-sensitive manner. In a follow-up study, we examined the effect of lipoprotein deprivation on chemotactic migration of the highly motile basal-like ER- cell line MDA-MB-231. We showed that lipid droplets were depleted and migration was reduced 85% when cells were grown in medium without lipoproteins, and that adding back LDL or fatty acids restored migration in an ACAT-sensitive manner (Antalis, Uchida et al. 2011). In addition, LDLR expression in these cells was not affected by exogenous LDL but was reduced 75% in the presence of an ACAT inhibitor, suggesting that high ACAT1 expression permitted continued high expression of the LDLR.

What mediates the over-expression of ACAT1 in cancer is not completely understood. Although ACAT1 is a critical component of intracellular cholesterol homeostasis, its expression is not known to be regulated by the SREBPs (Goldstein, DeBose-Boyd et al. 2006). In monocytes and macrophages, ACAT1 expression was up-regulated by interferon γ and all-*trans*-retinoic acid via STAT1 (Yang, Duan et al. 2001) and by dexamethasone via a glucocorticoid response element in its promoter (Yang, Yang et al. 2004). ACAT1 has also been shown to have an NFκB binding element in its proximal promoter and to be up-regulated in response to TNFα signaling through NFκB (Lei, Xiong et al. 2009). Cholesterol acts as an allosteric activator of ACAT1 activity (Liu, Chang et al. 2005).

The LXR pathway. The transcription factor LXR is a major regulator of fatty acid and cholesterol metabolism in cells. When cellular free cholesterol levels are high, some cholesterol is oxidized to form oxysterols, which act as endogenous ligands for LXR; thus LXRs are considered "cholesterol sensors"(Tontonoz 2011). LXR has an absolute requirement for RXRα as a dimerization partner. RXRα expression is highly regulated by both transcription and protein degradation (Boudjelal, Wang et al. 2000; Lefebvre, Benomar et al. 2010). RXRα availability is also affected by competition with its other binding partners, including PPAR, RAR, VDR, TR and FXR. LXR/RXRα is a permissive heterodimer, being stimulated by agonists of either partner (Tontonoz 2011).

LXR signaling is known to have dual roles: up-regulation of genes of fatty acid biosynthesis (including fatty acid synthase and stearoyl-CoA desaturase 1/2) and repression of NFκB

controlled inflammatory genes (including IL-6, COX-2, and nitric oxide synthase) (Joseph, Castrillo et al. 2003). In addition, LXR/RXRα controls the transcription of key genes in cholesterol homeostasis: MYLIP/IDOL, the E3-ligase that ubiquitinates the LDLR leading to its degradation, ABCA1 and ABCG1, transporters involved in cholesterol efflux to APOA1 and HDL, and others (Tontonoz 2011). The demonstrated control of ACAT1 by NFκB suggests that its transcription could be antagonized by LXR activity. LXR signaling may have the ability to mediate the balance between lipid biosynthesis/efflux mechanisms and uptake/storage mechanisms. **Fig. 2** and **Fig. 3** illustrate how key factors in cellular cholesterol homeostasis may be affected by the activity of LXR and its target genes.

The uptake of exogenous LDL through LDLR leads to increased cellular free cholesterol, reduced maturation of SREBPs and reduced transcription of LDLR. When LXR/RXRα is active (**Fig. 2**), LDLR protein is degraded by MYLIP and cholesterol efflux mechanisms are increased (Beltowski 2008). ACAT1 transcription may be reduced by the inhibitory effect of LXR/RXRα on NFκB transactivation activity, blocking cholesterol accumulation. Similarly ApoA1, the apolipoprotein acceptor for cholesterol efflux, which under some conditions is repressed by NFκB, could be increased (Mogilenko, Dizhe et al. 2009). As a result, normal cellular cholesterol homeostasis is enforced.

When LXR/RXRα is less active (**Fig. 3**), and under the influence of cytokines, a different pattern of gene expression predominates. Cholesterol efflux is reduced and thus free cholesterol is maintained at a high enough level in bilayer membranes that maturation of SREBPs is not triggered. More free cholesterol is esterified and stored in lipid droplets, due to a possible induction of ACAT1. LDLR protein degradation is reduced, allowing the cell to maintain high LDLR expression and unrestrained uptake of LDL. In this way, cellular cholesterol homeostasis is perturbed in the direction of LDL uptake and cholesterol accumulation.

The pathways described in **Figs. 2 and 3** are hypothesized to explain the observed cholesterol accumulation in some tumors and cancer cell lines. LDLR is placed at the center of the process of LDL uptake and accumulation, with LXR pathway inactivation being the key factor allowing cholesterol accumulation. No doubt the situation is more complicated than shown, as it does not account for scavenger receptor participation. However, the central role of LXR makes it a potential target in cancer.

LXR agonists have been tested in experimental models of cancer. In glioblastoma cells over-expressing the EGFR, EGF stimulated PI3K/Akt-driven up-regulation of SREBP1 and LDLR (Guo, Reinitz et al. 2011). An LXR agonist induced MYLIP/IDOL-mediated degradation of LDLR, ABCA1-mediated cholesterol efflux, and cell death both *in vitro* and in an animal model. In OvC cells, oxLDL stimulated proliferation and secretion of the cytokine cardiotrophin 1 (Scoles, Xu et al. 2010). An LXR agonist blocked both the cytokine secretion and the proliferation induced by oxLDL; the authors attribute the response to increased cholesterol efflux and decreased inflammatory effects of the LXR agonist. In an athymic model of PrC, progression of androgen-dependent tumors to androgen-independent tumors after castration was accompanied by decreases in expression of LXR target genes in the

tumor, and treatment with an LXR agonist delayed the progression for about 4 weeks (Chuu, Hiipakka et al. 2006).

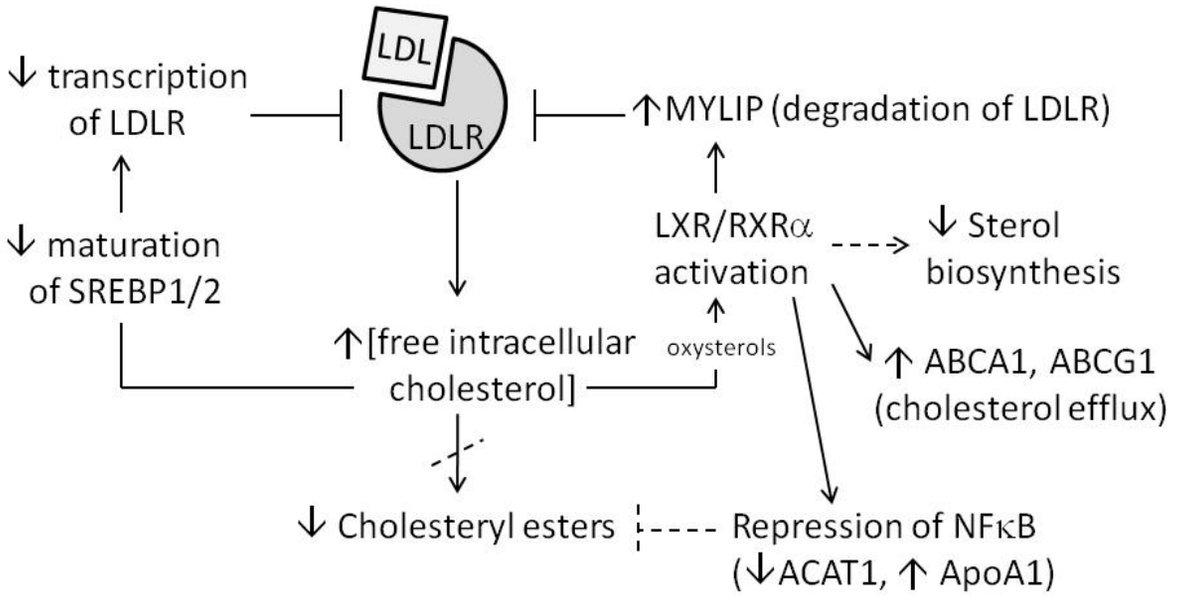

Figure 2. LXR transcriptional targets control intracellular cholesterol concentrations. Dotted line indicates pathways not proven.

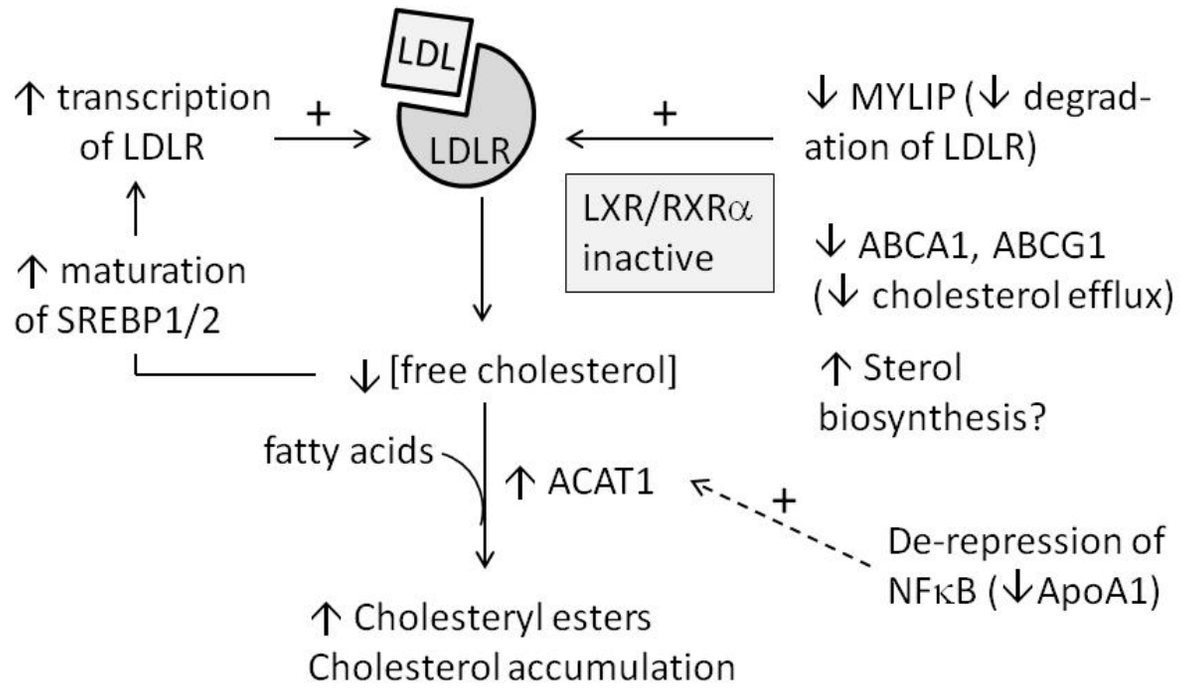

Figure 3. Reduced LXR signaling allows increased LDL uptake and intracellular cholesterol accumulation. Dotted line indicates pathways not proven.

Cholesterol and tumorigenesis. The question remains as to the role that CEs may play in the survival, proliferation and metastasis of cancer cells. We and others have proposed that accumulation of CE spares energy needed for *de novo* sterol synthesis, allowing greater

proliferation and migration and perhaps a quicker return to growth after a period of stasis (Batetta, Pani et al. 1999; Antalis, Arnold et al. 2010; Antalis, Uchida et al. 2011). The process of cholesterol esterification was linked to proliferation in multiple studies in different cancer cell lines (Batetta, Pani et al. 1999; Peiretti, Dessi et al. 2007; Paillasse, de Medina et al. 2009; Antalis, Arnold et al. 2010; Mulas, Abete et al. 2011), implying a complex network of signaling pathways and gene expression that ties cholesterol accretion to tumorigenesis. However, the exact role of CE in tumorigenesis remains to be determined.

PrC is a unique case considering the slow growth characteristics of this malignancy. The lipid raft concept has been proposed to account for the tumorigenic effects of cholesterol (Freeman, Cinar et al. 2007), and a higher level of cholesterol in PrC cells has been linked to membrane lipid raft-induced oncogenic cell signaling (Hager, Solomon et al. 2006). A connection between LXR signaling and lipid raft-associated signaling was demonstrated in androgen-responsive LnCAP cells, where an LXR agonist down-regulated Akt signaling in a cholesterol- and lipid raft-dependent manner, resulting in apoptosis of cells and xenograft tumors (Pommier, Alves et al. 2010). In addition, a relationship between androgens and cholesterol metabolism was demonstrated in PrC cells. It was first noted that androgen stimulation caused a dramatic increase in lipid droplets in LNCap cells. The induced neutral lipids included both TAG (33-fold) and CE (7-fold increase), most of which originated from new lipid synthesis (Swinnen, Van Veldhoven et al. 1996). This was later found to be due to an up-regulation of the SREBPs and lipid biosynthetic genes (Nelson, Clegg et al. 2002). The androgen-independent PC-3 cells had a higher content of CE and but not higher ACAT1 activity or expression as compared to LNCap cells (Locke, Wasan et al. 2008). In both an androgen-independent cell line and a mouse xenograft model of PrC progression, changes in cholesterol metabolism and homeostasis were associated with initiation of tumoral androgen production and expression of the AR and PSA (Locke, Wasan et al. 2008; Leon, Locke et al. 2010). These data, along with the clinical data cited in **Section 2,** suggest that in PrC cholesterol accumulation may be important for androgen synthesis, which is closely involved with PrC progression even under castration therapy.

Another function of LDL and other lipoproteins is the provision of essential fatty acids. Mammalian cells are not able to make polyunsaturated fatty acids; the essential n-6 and n-3 fatty acids are derived from the diet and carried to cells by lipoproteins. Human glioma, one of the deadliest types of cancer, was found to contain up to 100-fold more CE compared to control tissue, and the fatty acid composition of the tumor CEs indicated an LDL origin (Nygren, von Holst et al. 1997). The n-6 fatty acid arachidonic acid is necessary for synthesis of second messengers such as the prostaglandin PGE_2, a tumor promoter (Wang and Dubois 2006). In androgen-independent PrC PC-3 cells, PGE_2 production increased >3-fold in response to LDL (Chen and Hughes-Fulford 2001). Thus the fatty acids esterified to cholesterol and other lipids may be important for the effect of LDL on cancer cells.

Finally, although lower plasma HDL-C in cancer patients may be due to reduced efflux of cholesterol to HDL from the tumor, there is evidence that some cancer cells can take up CE from circulating HDL, providing another explanation for low HDL. Recent investigations with the CEM-CCRF lymphoblastic cell line into the source of intracellular CE showed that

HDL-CE were taken up and stored without hydrolysis and re-esterification, while LDL-CE were hydrolyzed and re-esterified (Uda, Accossu et al. 2012). Although the mechanism was not clear, the data implied that HDL as well as LDL could be a source of CE for leukemic cells. A previous study in BrC cells showed that either HDL or LDL dose-dependently stimulated proliferation of ER- cell lines, but only HDL had the effect on ER+ cells lines (Rotheneder and Kostner 1989). In an animal model of PrC, a diet high in fat and cholesterol resulted in increased tumor incidence and increased tumor expression of scavenger receptor B1, the receptor responsible for selective uptake of HDL-C (the major form of circulating cholesterol in mice) by cells (Llaverias, Danilo et al. 2010). The question of whether HDL can supply cholesterol to tumor cells *in vivo* in humans remains open.

4. Conclusions and future directions

The heterogeneous nature of cancer and the changes that accompany tumor progression make it very difficult to draw overall conclusions about the effects of circulating cholesterol on cancer incidence or progression. However, large scale prospective studies have shown that higher plasma total-C and LDL-C can increase the risk for some cancers, with the hormone-related cancers in men and women being especially affected. Data also point to a more potent effect of exogenous cholesterol on more aggressive cancers. These conclusions are supported by data on the effect of statins, which have been shown to reduce both the risk and the progression of some cancers. As more clinical trial data emerges, we will have a clearer picture of the usefulness of cholesterol reduction and statins in cancer and what types of cancer respond to these therapies.

Individualized approaches are the future for cancer therapy. Gene and protein expressions may serve as biomarkers to identify tumors that are stimulated by LDL. The genes/proteins expected to be more expressed as a result of LXR/RXRα pathway activation, i.e. MYLIP and ABCA1, and those expected to be more expressed as a result of LXR/RXRα pathway inactivation, i.e. ACAT1/SOAT1 and LDLR, may be used to distinguish tumors that are cholesterol-accumulating. The cholesterol and CE content of tumor biopsies determined by chemical or enzymatic methods could also be used as biomarkers. Imaging methods such as magnetic resonance (Delikatny, Chawla et al. 2011) and coherent anti-Stokes Raman scattering (Le, Huff et al. 2009) have the potential to allow *in vivo* visualization of lipids in tumors. These kinds of data will help to substantiate and clarify the association of CE accumulation with types of cancer.

If it can be shown that a tumor has the markers of higher cholesterol uptake and accumulation, treatments to lower circulating lipids and affect intracellular cholesterol homeostasis are available. Existing drugs developed for prevention or treatment of cardiovascular disease or metabolic syndrome, such as statins and metformin (an AMPK activator), are being "repurposed" for the treatment of cancer. ACAT inhibitors that did not have the expected result of reducing atherosclerotic plaques in clinical trials may find a new use in cholesterol-accumulating cancers. A new ACAT1-specific inhibitor was effective in killing glioma cells in *in vitro* studies (Bemlih, Poirier et al. 2010). LXR pathway modulators

that can increase cholesterol efflux and HDL-C levels without stimulating lipid biosynthesis in the liver, needed to treat cardiovascular disease and metabolic syndrome, may also be useful in cancer (Ratni, Blum-Kaelin et al. 2009). Dietary regimens targeting fat and cholesterol reduction in those with hyperlipidemia, with known benefits in preventing and treating heart disease, may be recommended to decrease the risk or recurrence of some types of cancer.

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