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Apolipoprotein Mimetics in Cancer

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Abstract

Peptides have many advantages over traditional therapeutics, including small molecules and other biologics, because of their low toxicity and immunogenicity, while still exhibiting efficacy. This review discusses the benefits and mechanism of action of apolipoprotein mimetic peptides in tumor biology and their potential utility in treating various cancers. Among lipoproteins in the circulation, high-density lipoprotein (HDL) and its constituents including apolipoprotein A-I (apoA-I; the predominant protein in HDL), apoJ, and apoE, harbor anti-tumorigenic activities. Peptides that mimic apoA-I function have been developed through molecular mimicry of the amphipathic α-helices of apoA-I. Oral apoA-I mimetic peptides remodel HDL, promote cholesterol efflux, sequester oxidized lipids, and activate anti-inflammatory processes. ApoA-I and apoJ mimetic peptides ameliorate various metrics of cancer progression and have demonstrated efficacy in preclinical models in the inhibition of ovarian, colon, breast and metastatic, lung cancers. Apolipoprotein mimetic peptides are poorly absorbed when administered orally and

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6. **Conflict of Interest**

AMF and STR are principals in Bruin Pharma and AMF is an officer in Bruin Pharma. The other authors declare that there are no conflicts of interest.

rapidly degraded when injected into the circulation. The small intestine is the major site of action for apoA-I mimetic peptides and recent studies suggest that modulation of immune cells in the lamina propria of the small intestine is, in part, a potential mechanism of action. Finally, several recent studies underscore the use of reconstituted HDL as target-specific nanoparticles carrying poorly soluble or unstable therapeutics to tumors even across the blood-brain barrier. Preclinical studies suggest that these versatile recombinant lipoprotein based nanoparticles and apolipoprotein mimetics can serve as safe, novel drug delivery, and therapeutic agents for the treatment of a number of cancers.

Keywords

HDL; ApoA-I; Mimetic peptides; Nanoparticles; Cancer

1. Introduction

Physiological Functions of Lipoproteins and Apolipoproteins

Lipoproteins are the primary mediators of cholesterol and lipid transport, solubilizing their highly hydrophobic cargo for transit through aqueous environments. These multicomponent particles are composed of a hydrophobic core- where triglycerides (TG) and cholesterol esters are stored- and a hydrophilic shell composed of phospholipids, free cholesterol, and amphipathic apolipoproteins. Low density lipoproteins (LDL) and high-density lipoproteins (HDL) play opposing roles in cholesterol transport. LDL supplies cholesterol from the liver to peripheral cells, while HDL carries out reverse cholesterol transport, bringing excess cholesterol from the periphery to the liver for excretion. Chylomicrons and VLDL comprise the other major classes of lipoproteins participating in lipoprotein assembly and metabolism in the intestine and the circulation. Cholesterol uptake in cells is mediated by LDL receptors (LDLR) while the cellular efflux and excretory processes are primarily mediated by ABC transporters and hepatic scavenger receptors (e.g. SR-B1), respectively [1]. Lipoproteins are thus essential components of energy and lipid metabolism in the body and any imbalances in their physiology can lead to pathological manifestations.

Apolipoproteins are essential structural and functional components of lipoproteins. ApoB-100 is the primary protein component of LDL and very low density lipoprotein (VLDL), while apoB-48 is the primary component of chylomicrons. Apart from being solubilizers and carriers of lipids, apolipoproteins carry out a wide variety of physiological functions including antioxidant, anti-inflammatory, anti-infectious, and lipid homeostasis [2]. Apolipoproteins also serve as ligands for lipoprotein receptors (e.g. ABCA1). Apolipoprotein mutations cause an imbalance in plasma lipid homeostasis, which can lead to a number of diseases including hyperalphalipoproteinemia and atherosclerosis [3]. ApoA-I is one of the most studied among the apolipoproteins and the predominant protein component of HDL (~70% by mass), along with apoA-II, apoE, apoC, and apoJ, all of which are important contributors to HDL function [4].

LDL, HDL, and Cancer

The contribution of oxidized LDL (oxLDL) to atherogenesis and different cancers is well characterized [5–8]. Many cancer patients exhibit low serum activity of paraoxonase 1 (PON1), an HDL-associated protein reported to protect LDL from oxidation [9]. Recently, Cedó et al. [10] examined the literature on the implications of LDL in breast cancer (BCa) and suggested that large clinical trials show a direct association between LDL cholesterol (LDL-C) and BCa risk. Lu et al. [11] demonstrated that i) VLDL and LDL increased cell proliferation and migration of cultured BCa cells in whereas HDL did not and ii) VLDL promoted metastasis in nude mice.

Besides atherosclerosis, cancer is likely the most studied pathology associated with HDL. Using serum proteomics, Su et al. [12] were the first to report that several HDL constituents including apoA-I, transferrin, and transthyretin, are highly sensitive and specific biomarkers and better predictors than conventional CA-125 alone, for the detection of early stage ovarian cancer (OCa). Furberg et al. [13] examined whether low HDL cholesterol (HDL-C) levels are a potential biomarker for BCa and concluded that low HDL-C correlates with an unfavorable hormone profile and increased risk of BCa. Cedó et al. [10] also identified several reports showing an inverse association between HDL-C and apoA-I, and BCa risk. Epidemiological data have shown levels of HDL-C are significantly inversely correlated with risk for multiple cancers [14–16]. The relationship between HDL-C levels in the serum and cancer risk were examined in a large epidemiological study using data from the Atherosclerosis Risk in Communities (ARIC) cohort. The data revealed no association between low serum HDL-C and incidence of BCa in postmenopausal women, and only a modest association for premenopausal women [17]. Another study observed no link between aggressive prostate cancer (PCa) and total cholesterol, LDL-C, or HDL-C [18]. Thus, it is not entirely clear if HDL-C is implicated as beneficial for cancer risk.

The HDL receptor SR-B1 is reported to be overexpressed in many tumors [19,20]. SR-B1 is responsible for cholesterol uptake and metabolism in the tumor tissues, and thus has become an important biomarker and target for therapies. SR-B1 is upregulated in PCa, suggesting a potential role in tumor progression. Traughber et al. [21] reported that a SR-B1 knockout (KO) reduced HDL-associated proliferative responses in human and mouse PCa cell lines. The ability of HDL to reduce oxidative stress and reactive oxygen species (ROS) in PCa cell lines has also been demonstrated [22]. Synthetic HDL (sHDL) was able to recapitulate this antioxidant phenotype [22].

Recent publications have discussed the controversy surrounding HDL-C and cancer, noting that despite the myriad papers suggesting an inverse correlation between the two, the presence of confounding factors in much of the data may be skewing results [23,24]. Clinical or methodological differences in experimental design, variation in geographic regions, menopausal status, number of cases, and follow-up length may be a cause of discrepancy [10]. It has also been suggested that low HDL is actually a product, not a cause, of cancer-related inflammation and cell renewal [23]. Of critical importance is the idea that a rapidly proliferating population of tumor cells requires a lot of cholesterol and receives it. It is clear that a better mechanistic understanding of HDL function in cancer is required before the association can be fully understood.

Apolipoproteins and Cancer

Possible associations between apolipoproteins and various cancers have been explored through epidemiological data. A clinical case-control study examined over 500 patients with solid tumors, analyzing their levels of HDL-C, LDL-C, TGs, apoA-I, and other parameters to elucidate the relationship between serum lipoproteins and cancer progression [25]. Data revealed that apoA-I and HDL-C are significantly lower in cancer patients (n = 519) when compared to healthy, age-matched controls (n = 928) [25]. Zhou and Luo [26] recently explained that while some apolipoproteins (i.e. apoD, apoE, and apoA-I) have been shown to inhibit tumor growth in mammary tissues, apo D and apoE have also been implicated as pathogenic in BCa development. ApoA-I, apoB, apoC, apoH, apoJ, and apoM have been reported as potential clinical prognostic markers [27–30]. An inverse association between apoA-I and HDL-C levels and risk of colorectal cancer, lung, and breast cancers was demonstrated using data from the Malmö Diet and Cancer Study [31].

Several studies have reported that changes in apoA-I may cause various types of cancer and that serum apoA-I levels may be a useful biomarker [12,32]. Tuft-Stavnes et al. [33] reported apoA-I mRNA were significantly higher in OCa compared with BCa effusions, indicating its potential as a prognostic marker in metastatic serous carcinomas. High serum apoA-I was associated with better overall survival in metastatic colorectal cancer patients treated with bevacizumab as a first-line chemotherapy [34]. In addition to reporting on the immunomodulatory mechanism and utility of apoA-I in anti-tumor studies, one review has compiled the myriad clinical studies linking low levels of HDL-C or apoA-I to a higher risk for a variety of cancers [35]. Reduction of apoA-I transcription, intracellular and secreted apoA-I, and circulating HDL-C levels in hepatocellular carcinomas also suggest a tumor suppressor role [32]. Su et al. [12] demonstrated that apoA-I plays a critical role in halting tumorigenesis and improving overall survival in a mouse model of OCa. In a review, Mangaraj et al. [36] concluded that low concentrations of apoA-I are observed in many cancer types (e.g. acute lymphoblastic leukemia, pancreatic, and gastric), allowing more pro-inflammatory and pro-angiogenic activity from lysophosphatidic acid (LPA).

Zamanian-Daryoush et al. [37] questioned the effect of apoA-I on tumor growth and metastasis in a B16F10L murine malignant melanoma model. Mice overexpressing an apoA-I transgene had ten times less tumor growth and metastasis than apoA-I KO mice. Zamanian-Daryoush et al. [37] also demonstrated that pharmacological delivery of apoA-I was effective in reducing tumor burden and retarding metastasis. The experiments by Zamanian-Daryoush et al. [37] demonstrated that apoA-I expression causes a decrease in the recruitment of myeloid-derived suppressor cells (MDSC), a heterogeneous population of immature myeloid cells that multiply in response to tumor-driven factors. A preclinical study showed that agonism of liver X receptor (LXR) β reduced immunosuppression by MDSCs in mice and their abundance in patients treated in an ongoing multicenter human phase 1 trial [38]. It was further suggested that apoE, the transcriptional target of LXR, was responsible for mediating anti-tumorigenic effects of LXR agonist in mice [38].

2. Structure and Modifications of Apolipoproteins and Their Mimetics

Protein Structure

The function and distribution of amphipathic helices across the family of apolipoproteins was reviewed by Segrest et al. [39]. Since apoA-I is the most studied of the apolipoproteins, its structure specifically will be addressed below. ApoA-1 is 243 amino acids (AA) long and organized into 8 α-helical repeats separated by prolines. The amphipathic residues in the helix mediate lipid binding (in the core of the helix) while still interacting in an aqueous environment (outer face of helix) [40]. ApoA-I influences the discoidal and spherical HDL conformations in nascent HDL biogenesis, the first step in which is the binding of apoA-I to ABCA1, followed by translocation of free cholesterol and phospholipids [41]. Upon binding lipid cargo with its C-terminal domain, apoA-I becomes physically distanced from ABCA1 through exovesiculation followed by spontaneous solubilization, which results in discoidal nascent HDL, with 2–4 apoA-I proteins per particle [41].

The first mimetic peptides were developed by the Segrest group at the University of Alabama at Birmingham [42]. The peptides were 18 AA long and designed to resemble the repeating amphipathic helices of endogenous apoA-I. Since then, the monohelical peptide model has been expounded upon, substituting three to seven phenylalanine (F) residues on the nonpolar face of the helix. It is these substitutions that gave rise to the nomenclature for the apoA-I mimetic peptides; 2F, 3F, 4F, 5F, 6F, and 7F [43]. Mishra and Anantharamaiah [44] studied a series of peptides analyzing structural motifs of apoA-I allowing for mimicry of its anti-inflammatory and atheroprotective functions. Their meta-analysis suggested that aromatic residues at the center of the polar-nonpolar interface of the amphipathic helix were primarily responsible for interaction with inflammatory lipids. The review by Getz et al. [43] also contains a wealth of detailed structural information on aspects of the helix that is most essential for mimicking apoA-I lipid binding properties.

Novel Modifications

Similar to endogenous apoA-I, mimetic peptides stimulate cholesterol and phospholipid efflux through the ABCA1 transporter, forming discoidal HDL-like particles. Islam et al. [45] recently demonstrated that amphipathic “ELK” peptides containing only glutamic acid, leucine, lysine, or alanine, have a wide range of hydrophobicity and net charges and optimal ABCA1-dependent cholesterol efflux is achieved when ELKs have neutral net charges. As opposed to the antiparallel double belt around HDL formed by endogenous apoA-I, mimetics form a mostly antiparallel “picket fence” arrangement [45].

The amphipathic α-helices of apoA-I are the functional site of apoA-I mimetics. In order to minimize the non-specific cellular efflux of cholesterol by apoA-I mimetics, Kawahara et al. [46] designed a photo activatable mimetic peptide, 2F*. An internal photocleavable caging group assumes α-helical structure upon a UV light stimulus, consequently triggering cellular cholesterol efflux [46]. The authors suggest that their peptide can offer the maximum clinical benefit while reducing cholesterol efflux from non-targeted cells. The antiatherosclerosis effect of a novel apoA-I mimetic, FAMP, has been described previously [47]. Recently, this group published on an improved version of FAMP called i-FAMP, which

exhibits greater cholesterol efflux capacity and atheroprotective effects due to a stronger α-helical conformation [48].

Improvements to amphiphilicity or helicity seem to be effective methods for enhancing mimetic peptide function. Islam et al. [49] recently developed a new modification for increasing the cholesterol efflux potential of mimetic peptides. Since it is known that α-methylated alanine presents increased helicity, the authors proposed substituted with α-methylated AAs and demonstrated increased helicity and amphiphilicity. Furthermore, Islam et al. [49] showed that the newly modified peptides not only showed increased cholesterol efflux in ABCA1-transfected cells but also conferred protease-resistance. Table 1 highlights different features of the numerous apoA-I mimetic peptides.

It was demonstrated that D-amino acid containing apoA-I mimetic peptides (D-4F) were as effective as L-4F mimetic peptides [50]. D-4F mediated cholesterol efflux, reduced lipid hydroperoxides, promoted the formation of pre-ß HDL, increased PON activity, and mitigated atherosclerosis in apoE- and LDLR-null mice [50]. In another landmark paper, it was demonstrated that D-4F and L-4F bind pro-inflammatory oxidized lipids (e.g. PAPC [1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphatidylcholine] and its oxidized derivatives) with an affinity 4–6 orders of magnitude higher than endogenous apoA-I [51]. As will be explained in detail below, apoA-I mimetic peptides have been expressed as a transgene in tomatoes in an effort to increase the practical testing of oral apoA-I mimetic therapy in the treatment of dyslipidemia and cancer [52–53]. Apolipoprotein mimetics have been effective anti-inflammatory molecules, ameliorating various inflammation-based pathologies in both human trials and mouse models [54–63].

3. Mimetics as Therapeutics

Apolipoprotein mimetics have been demonstrated to be efficacious in several animal models of cancer, and the evidence for the mimetics as potential therapeutics continues to grow (Table 2).

Ovarian Cancer

Until 2010, the therapeutic focus for the apolipoprotein mimetics was primarily on inflammation and atherosclerosis. Su et al. [12] published the first paper on the utility of apoA-I mimetics in a mouse model of OCa. Mouse ovarian cancer cell line, ID8 cells were injected subcutaneously (SQ) or intraperitoneally (IP) into C57BL/6J mice, followed by oral or SQ treatment with apoA-I mimetic peptides L-4F, L-5F, or D-4F (the D enantiomer of the 4F peptide). Five to nine weeks of treatment resulted in a dramatic decrease in tumor burden. Furthermore, the peptides significantly decreased cell viability in ID8 cells and human cisplatin resistant OCa cell lines. Mice treated with L-4F or L-5F exhibited very low serum levels of unsaturated lysophosphatidic acid LPA (20:4 LPA) compared to untreated mice. The mimetics were also able to mitigate LPA-induced proliferation of ID8 cell lines [12]. Since unsaturated LPA species have been implicated in cancer development and progression, Su et al. [12] suggested that the mode of action of apoA-I mimetic peptides, may, in part, be due to their ability to inhibit LPA accumulation. In another study using a similar model

system, Ganapathy et al. [64] demonstrated that D-4F-mediated inhibition of oxidative stress, cell viability, and proliferation in ID8 cells is MnSOD-dependent.

Gao et al. [65] further examined the mechanisms by which apoA-I mimetic peptides inhibit tumor growth and studied the role of L-5F in angiogenesis. L-5F is ineffective in inhibiting proliferation of HUVEC cells under basal conditions, however, L-5F dose-dependently inhibited VEGF and bFGF-induced HUVEC cell proliferation, cell viability, migration, invasion, and tube formation. Moreover, the authors demonstrated that L-5F reduced LPA-induced proliferation and VEGF production in both mouse and human OCa cell lines. Female C57BL/6J mice given a SQ injection of ID8 cells and L-5F treatment exhibited significantly reduced tissue and circulatory VEGF levels when compared to control mice that received scrambled peptide treatment [65]. HIF-1α plays an important role in the production of angiogenic factors and has been shown to be associated with progression and metastasis. Gao et al. [66] demonstrated that L-4F inhibited the expression and activity of HIF-1α both in cell cultures and *in vivo*. The inhibition of HIF-1α may be a critical mechanism in the suppression of tumor progression by apoA-I mimetic peptides [66].

Neyen et al. [67] tested whether 4F peptide could antagonize the scavenger receptor A (SRA, Msr), which is expressed on M2 tumor-associated macrophages and is involved in tumor progression. This study demonstrated that 4F inhibited proliferation and metastatic spread of ID8 cells and pancreatic (Panc02) cancer cells and the results were very similar to Msr−/− mice [67]. The authors suggest that 4F may be acting as an inhibitor of SRA. A recent and important publication documented the effect of apoA-I and 4F on cell viability, invasiveness, and platinum-sensitivity in 3 human OCa cell lines [68]. At 100 μg/mL, both endogenous apoA-I and its mimetics decreased cell viability of SKOV3, CAOV3, and OVCAR3. The mimetics decreased invasiveness (assayed by transwell and spheroid experiments) of SKOV3 cells at 50 μg/mL, a concentration lower than that of endogenous apoA-I. Increasing concentrations of the mimetic peptides sensitized the 3 cell lines to cisplatin *in vitro* and *in vivo* [68].

Colon Cancer

Colon cancer (CCa) is another well-studied cancer in the field apolipoprotein mimetics. Su et al. [69] initially demonstrated HDL mimetics to inhibit both induced and spontaneous CCa development in mice. L-4F and G* (an apoJ mimetic) inhibited the proliferation of tumor cells, reduced pro-tumorigenic lipids, and inhibited angiogenesis. Oral administration of the D-4F peptide was shown to reduce IL-6 mRNA, a pro-inflammatory cytokine playing a major role in colitis and colitis-associated carcinogenesis [70].

In another study, adding 0.06% by weight of a concentrate of transgenic tomatoes expressing the 6F apoA-I mimetic peptide to a standard chow diet reduced tumor-associated neutrophils and reduced tumor burden in a mouse model of CCa metastatic to the lung [71]. Tumor burden was also decreased by peptide treatment in an OCa mouse model [71]. Interestingly, Tg6F decreased levels of LPA 20:4, and inhibited both colon and ovarian cancers. With Tg6F treatment, plasma TG levels decreased, plasma HDL-C levels increased, while plasma total cholesterol did not change. The authors suggested Tg6F may be reducing tumor burden through modulation of tumor-associated immune cells [71].

Chattopadhyay et al. [53] reported that Tg6F-supplemented diets significantly reduced tumor burden compared to a standard chow diet in a CCa metastatic to lung model using BALB/c mice. Gene expression analyses of jejunum & lung identified Notch pathway genes; Notch1, Notch2, DII1, and DII4 were significantly upregulated after Tg6F treatment while Spp1, TNFα, and iNOS were downregulated. IL-4, IL-10, IL-12, and TLR2 were also upregulated. Tg6F treatment also reduced oxidized phospholipid levels in the jejunum and 25-hydroxycholesterol (25-OHC) levels in the plasma and jejunum. 25-OHC and oxidized phospholipids are known to inhibit Notch1 and induce Spp1, respectively. A population of Ly6C monocytes (patrolling monocytes) recruited by the Notch pathway exhibited anti-tumorigenic effects. This cell population was increased in both jejunum and lung of the Tg6F-treated mice. Conversely, pro-tumorigenic MDSCs facilitated by Spp1 were decreased in the jejunum and lung of treated mice. The concluding hypothesis was that Tg6F alters levels of specific oxidized lipids and 25-OHC to modulate Spp1 and the Notch pathway. This ultimately leads to changes to immune cells in the lamina propria of the small intestine, resulting in lowering of the tumor burden [53].

Other Cancers

Apolipoprotein mimetics have also proven useful in cancers other than OCa or CCa. Overexpression of human apoA-I in a mouse model of BCa did not affect tumor onset or growth, even though HDL-C and oxLDL levels were increased and decreased, respectively [72]. By contrast, D-4F treatment increased tumor latency and inhibited tumor development independent of 27-OHC. D-4F reduced levels of 27-OHC in the serum but not the mammary gland, but LPA levels were not affected by D-4F [72]. Su et al. [12], reported a decrease in 20:4 LPA levels in a mouse model of OCa after treatment with L-4F or L-5F. Consistent with apoA-I's role to protect LDL from oxidation, D-4F treatment reduced plasma levels of oxLDL, preventing an oxLDL-mediated proliferative response in MCF-7 cells [72]. One recent paper reported the ability of L-4F treatment to induce differentiation, proliferation, and apoptosis in MDSCs in a murine model of pancreatic cancer [73]. Consistent with this immunomodulatory effect, L-4F suppressed the differentiation and accumulation of polymorphonuclear-MDSCs in mouse spleen and tumor tissue. Immunosuppression of MDSCs was inhibited while T cell activity was simultaneously increased [73]. This study also showed how L-4F reduced ROS production by MDSCs, a phenomenon similar to what was described by Ruscica et al. [22]. *Ex vivo* experiments and *in vivo* orthotopic implants in mice revealed a significant reduction in tumorigenicity of H7 cells [73,74]. However, L-4F was unable to induce apoptosis in H7 cells or attenuate their invasion *in vivo* [74].

Although apoA-I mimetics have been studied the most, peptides mimicking apoE have also been studied for anticancer utility. The COG112 and OP449 peptides have been studied in an attempt to recapitulate the anti-invasion effect of endogenous apoE on cancer cells [75]. Specifically, this study analyzed the ability of the mimetics to interfere with the SET-PPR complex in PCa, as chronic exposure to inflammatory stimuli is thought to play a role in this cancer. Data indicated that apoE mimetics decreased cell viability of androgen receptor (AR)-negative and AR-positive cells in a dose-dependent manner. Similarly, OP449 disrupted the cell cycle and thus progression of AR-negative PC3 cells [75]. ApoE mimetics are also effective in inhibiting the growth of U87 glioblastoma multiforme (GBM) cells [76].

One study reported on the anti-cancer activity of apoEdp, a dimer peptide derived from the receptor binding region of human apoE. In a rabbit model, apoEdp was effective against ocular angiogenesis while also reducing tumor growth in a mouse model and HUVEC cells [77].

4. Mimetics and Nanoparticles in the Clinic

Mimetics

Researchers at UCLA have been studying the therapeutic benefits of apoA-I mimetic peptides containing 18 amino acids [78,79] for more than fifteen years. These peptides have been shown to improve HDL function and atherosclerosis in mice and rabbits [80–82] and improve HDL function in normal monkeys [81,82]. The animal studies led to studies in humans that have been the subject of three reports [62,63,83]. Two of these reports demonstrated efficacy when the peptide was administered orally at high doses despite achieving extraordinarily low plasma levels [62,63]. A third report described studies in which low doses of peptide were administered intravenously or subcutaneously in order to achieve high plasma peptide levels with these low doses [83]. Despite achieving high plasma levels with these low doses, the third report was negative in terms of efficacy [83]. The low doses used in [83] had not been effective when they were given orally in the first two studies [62,63].

To understand the differing clinical trial results, UCLA researchers returned to mouse studies. In the first of these mouse studies the content of peptide in the feces predicted efficacy, but the plasma peptide levels did not [56]. In the next study the peptide concentration in the small intestine of LDLR null mice on a Western diet (WD) predicted efficacy, but the plasma levels again did not [84]. In these mouse studies [56,84] the dose required for efficacy was far above the highest dose tested in the human study that did not demonstrate efficacy [83]. Additionally, they noted that the lowest dose of these peptides tested in rabbits [80] and normal monkeys [81,82] that was effective was also higher than the doses used in the third human study [83]. While it is possible that mice, rabbits and monkeys are so different from humans that these peptides are efficacious in these species, but not in humans, the authors suggested that it is more likely that the failure to demonstrate efficacy with low doses in humans [83] was due to too little peptide reaching the small intestine. Even if all of the peptide administered in the low dose human study [83] had reached the small intestine, the dose would have been lower than any dose that was efficacious in mice, rabbits, monkeys, and humans.

There were two reasons that a low dose of peptide was chosen in the study that was not effective [83]. First, because of the need to chemically synthesize the peptide used in these studies (4F), the cost of production is very high. Second, there was a mistaken belief that the peptides act primarily in the plasma and that plasma peptide levels were the only critical success factor. The studies that were completed following the third clinical study report by Watson et al. [83], underscored the high therapeutic potential of this class of agents [56,84]. However, these studies [56,84] also demonstrated that high doses of peptide (40–100 mg/kg/day) must be delivered to the small intestine in order to achieve efficacy. The peptides used in the 3 reports of human clinical trials [62,63,83] contained blocked end groups, which can

only be added by chemical synthesis. The cost of producing such chemically synthesized peptides for use at these high doses is prohibitive. UCLA researchers searched and discovered that apoA-I mimetic peptide 6F is as effective without end blocked groups as is the 4F peptide with blocked end groups. Peptides that require end blocked groups for efficacy cannot be expressed as a transgene. The fact that 6F does not require blocked end groups for efficacy allowed UCLA researchers to express the 6F peptide in transgenic tomatoes (Tg6F) [85]. When freeze-dried and fed to LDLR null mice on WD at only 2.2% by weight of the diet, Tg6F was highly effective in ameliorating dyslipidemia and atherosclerosis [52]. Feeding control tomatoes that were either wild type (WT), or made transgenic with the same vector, but containing a sequence for the expression of a control marker protein (EV) instead of 6F were not effective [52]. Two hours after Tg6F was administered in the diet, intact 6F peptide was found in the small intestine, but at no time point was intact 6F peptide found in the plasma strongly suggesting that the peptide was indeed working in the small intestine, and not in the plasma.

Zhao et al. [86] used an apoA-I mimetic peptide with an amino acid sequence and structure completely different from UCLA peptides, found that oral doses of their peptide similar to what was used by UCLA group were equally effective compared to the same dose administered by injection in inhibiting aortic atherosclerosis in LDLR-null mice. Similar to the case with 6F, when this peptide was administered orally, it could not be detected in plasma, and when given by injection resulted in high plasma levels, but efficacy was the same as when administered orally [86]. The concordance of these studies with completely different apoA-I mimetic peptides strongly implicates the intestine as the site of action for apoA-I mimetic peptides.

In another trial, the use of an HDL mimetic containing apoA-I Milano (an endogenous Arg173Cys mutation) did not reduce coronary atherosclerosis in patients following an acute coronary syndrome (ACS) [87]. The HDL infusions showed an increase in cholesterol efflux capacity but failed to show favorable effects on coronary atherosclerosis [87]. This group then tested CER-001, a pre-ß HDL mimetic with sphingomyelin and recombinant WT apoA-I [88]. In a 10-week infusion of low-dose CER-001, the treatment did not reduce coronary atherosclerosis in statin-treated patients with ACS and high coronary plaque burden [88. Treatments in the Nicholls et al. studies [87,88] were both well tolerated, but join the growing list of clinical trials in which raising plasma HDL levels or apoA-I activity fails to have a protective or rescue effect, even though there is a wealth of data correlating low HDL levels and various pathologies (e.g. cancer and atherosclerosis).

The small intestine is responsible for the absorption of dietary bulk lipids (TGs, cholesterol, and phospholipids). It contains the largest number of immune cells in the body and is an important site where local lipid metabolism modulates inflammation [89]. Thus, the small intestine is an important site to investigate the development of cancer. The existence of many types of neutrophils in the intestine has been proposed, similar to the existence of pro-tumorigenic and antitumorigenic macrophages [90]. What mechanisms might be involved? This is an emerging field of study, but much promising data has been published in recent years. Chattopadhyay et al. [53,71] reported Tg6F acts through reduction of oxidized lipids, altering immune cells in the small intestine, resulting in similar immunomodulation in the

lungs, thereby reducing tumor burden. Both L-4F and COG1410 (an apoE mimetic) were shown to reduce airway neutrophilia through a reduction in CXCR-2-mediated chemotaxis [91]. CD36, SR-B1, SR-B2 have also been shown to interact with apoA-I mimetic peptides [92,93]. Interestingly, CD36 has been reported to interact with bacteria in the small intestine and also participate in the uptake of fatty acids and cholesterol in the proximal, but not distal, small intestine [94]. Considering this, another possible action of mechanism of apoA-1 mimetics may be through interaction with CD36 in the proximal small intestine, which alters immune cells in the lamina propria of the intestinal villi.

Nanoparticles

Tang et al. [95] explored the best routes of administering the 22A peptide, using a lipid-free form of the peptide or a phospholipid reconstituted 22A-sHDL. Treatments were administered to rats via intravenous (IV) or IP injection. For both routes, circulation half-life was longer for the 22A-sHDL complex (mean half-life = 6.27 h) than the lipid-free form (mean half-life = 3.81 h). Approximately 50% of 22A was absorbed by the vascular compartment for both free and reconstituted 22A. The strongest pharmacological response (assayed by plasma-free cholesterol) clearly came from the 22A-sHDL group injected IV, suggesting route of administration and formulation of the mimetic to both strongly influence the therapeutics and pharmacokinetics [95]. In 2019, the same group again used rats to show that the high stability of the egg sphingomyelin (eSM)-sHDL nanoparticle leads to slower kinetics of sHDL disassembly in blood when compared to 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)-sHDL [96]. AUC was increased two-fold in the eSM-sHDL-treated rats when compared to POPC-sHDL rats [96].

The utility of treating coronary atherosclerosis with reconstituted HDL (rHDL) was evaluated in a 2007 clinical trial, where percent change in atheroma volume was the primary metric of efficacy. Patients receiving the highest dose of rHDL CSL-111 (80 mg/kg) stopped receiving infusions because of liver abnormalities [97]. However, there was no significant difference in the overall frequency of adverse events between the treatment and placebo groups.

Mimetics and Nanoparticles

In recent years, based on the observation that SR-B1 is upregulated in cancer tissues, HDL-based nanoparticle therapies have been developed to deliver therapeutics specifically to tumor cells (Table 3) [19,98]. More specifically, nanoparticles of rHDL, some comprising of apolipoprotein mimetics, are designed to deliver highly lipophilic chemotherapeutics [99]. Zhang et al. [100] published the first major paper in the field of HDL-based nanoparticle therapy that has since exploded. This group assembled their nanoparticles from a series of phospholipids, an apoA-I mimetic peptide 18AA, and hydrophobic cargo, and demonstrated that the nanoparticles (<30 nm) exhibited not only a high diffusion of the therapeutic to tumors but also an improved half-life of 13.6 hours in nude mice [100].

The advantages of HDL and other lipoprotein-based delivery systems and rHDL as a chemotherapeutic platform for overcoming biological barriers (e.g. membrane transport, opsonization, and multidrug resistance proteins) have been extensively reviewed by Raut et

al. [99, 101]. Lipoprotein-based therapies can efficiently offload their therapeutic cargo while avoiding the off-target toxicity that has characteristically plagued traditional chemotherapeutics for decades [101]. One of the more notable biological barriers to the delivery of therapeutics to central nervous system (CNS) tumors is the blood-brain barrier (BBB). To combat this, many groups have explored the utility of treating CNS tumors with nanoparticle-based therapies, exploiting the biocompatible membranous structure. However, a current issue in this field is the poor specificity of nanoparticles to target tumors. Ye et al. [102] developed a methodology utilizing L-4F (not rHDL) to improve the association of extracellular vesicles (i.e. nanoparticles) and tumor cells, using methotrexate (MTX) and U87 glioma as a model system. Mice administered with this novel delivery system showed longer median survival compared to mice receiving free MTX [102].

Similarly, the 5A peptide was used in the synthesis of docetaxel (DTX)-loaded sHDL [103]. The cytotoxic and pharmacodynamic properties of sHDL nanoparticles were evaluated *in vitro* and in a BCa mouse model and exhibited a high payload of DTX, sustained drug release, high cytotoxicity against MCF-7 cells, and ultimately conferring a survival benefit to mice [103]. Adrenocortical carcinoma (ACC) is a rare endocrine malignancy that utilizes overexpression of SR-B1 and HDL to meet its cholesterol demands. One study recently utilized sHDL nanodisks to deliver the poorly soluble, natural compound withalongolide A - 4,19,27, triacetate (WGA-TA) [104]. The nanodisks used 22A to load WGA-TA and showed higher cytotoxicity than free WGA-TA, with a two-fold reduction in the IC_{50}. IP injection of WGA-TA-sHDL particles into H295R-bearing mice for 21 days significantly inhibited tumor growth *in vivo* compared to placebo [104]. Calcium carbonate (CC) nanoparticle shells have also been used to load doxorubicin (DOX), using HDL to stabilize and increase biocompatibility [105]. The HDL/CC/DOX complexes led to an increase in DOX uptake in MCF-7 cells compared to CC/DOX particles, validating HDL as an effective stabilizer and experiments in a nude mouse model of BCa confirmed *in vivo* efficacy [105].

HDL-based nanoparticles have also proved to be effective transporters for nucleic acid-based therapies. The utility of nucleic acids (e.g. siRNA, ncRNA, antisense oligomers [ASO]) as gene expression modulators is well documented. However, short serum half-lives due to nucleases have plagued their therapeutic potential. A comprehensive review by Lacko et al. [106] analyzes multiple studies documenting HDL-based nanoparticles as efficient carriers of siRNA and miRNA therapeutics. Lacko and collaborators have demonstrated targeted delivery of siRNA using rHDL nanoparticles, taking advantage of tumor overexpression of SR-B1 [107]. Orthotopic mouse models of OCa and CCa were used to exhibit the potential of delivering an siRNA *in vivo* via rHDL nanoparticles. An apoE3-based rHDL nanoparticle has exhibited efficacy in halting tumor progression of a Ras-driven glioblastoma (GBM) via siRNA delivery [108]. Encapsulating the therapeutic nucleic acids in the nanoparticle allowed for penetration of the BBB and a remarkable efficiency in silencing the targeted ATF5 transcript. Treatment with the nanoparticle increased GBM cell apoptosis and inhibited tumor cell growth *in vitro* and in murine xenograft models of GBM [108].

Structure and Auxiliary Functions

HDL-based nanoparticles, though only requiring a few major components, must be carefully designed in order to preserve optimum function and binding-capacity of apolipoprotein mimetics. For example, positively charged nanoparticles have been shown to reduce helical structure in apoA-I while neutral and negative surface charges induced more helical structure [109]. Many new and exciting structure-based HDL nanoparticles have been created in recent years. A recent paper from Raut et al. [110] reports on a novel apoA-I mimetic Myr5A, which is a myristic acid conjugated to the N-terminal aspartic acid residue of the 5A peptide. The novelty of the peptide is that it self-assembles into a nanomicellar structure with no lipid component needed. Payloads of drugs and fluorescent dyes were larger than those of free 5A nanoparticles. However, drug release from the nanoparticle was found to be slow [110]. Another important feature is that rHDL nanoparticles can deliver a payload of contrasting dyes and agents for clinical use in fluorescent and magnetic resonance imaging [111]. Because so many anticancer drugs indiscriminately kill normal and malignant tissues, there is a huge demand for more tumor-specific drugs. A key versatility of HDL-based nanoparticles is their ability to target specific cells. By attaching ligands to the lipid or protein component, therapeutic payloads that can be routed to a cell type of choice [111].

Porphyrin-HDL, an HDL nanoparticle with a high density of porphyrin has recently been developed for image-guided photodynamic therapy (PDT) [112]. The benefit of this novel system is its rapid dissociation upon tumor cell accumulation, thus becoming fluorescent and photoactive. *In vitro* uptake of porphyrin-HDL and PDT efficacy were evaluated and confirmed in SR-B1-positive and negative human lung cancer cell lines. After systemic administration to mice with orthotopic lung tumors, porphyrin-HDL induced apoptosis in 73.2% of tumor cells without toxicity to normal tissues [112]. Tumor-derived exosomes can transmit pro-malignant signals to distant cells, in a process dependent upon target cell cholesterol homeostasis. Henrich et al. [113] showed exosome communication from PCa cells to myeloid cells to be inhibited by HDL nanoparticles that reduce cholesterol in the latter. This effect was dependent upon SR-B1 expression in the myeloid cells.

5. Conclusion and Future Directions

A number of preclinical studies have demonstrated that apolipoprotein mimetics and rHDL nanoparticles are therapeutic in animal models of cancer (Table 2, Table 3). Although the clinical trials on the apoA-I mimetic peptide L-4F were unsuccessful [83], the pharmacokinetics data showed that the apolipoprotein mimetic peptides are safe and well tolerated in humans. Other clinical trials with D-4F and rHDL have shown mild success [62,63,97]. Given that one of the reasons behind the failed trials was the dosage of peptides [83], it is encouraging to note that recent developments in modality (expression of apolipoprotein mimetic peptides in transgenic plants) and delivery (recombinant and synthetic lipoprotein particles) have given promise and reason to initiate further clinical trials with apolipoprotein mimetic peptides and rHDL/sHDL nanoparticles.

Chattopadhyay et al. [53,71] developed transgenic tomatoes expressing the apolipoprotein mimetic Tg6F to overcome the dosage and cost factors associated with 4F clinical trials. Chattopadhyay et al. [53,71] have successfully completed preclinical studies in

atherosclerosis and cancer models, where Tg6F appears to be a promising therapy for treating ovarian and colon cancers. While the anti-inflammatory and consequent immunomodulatory properties of apolipoprotein mimetics seem to be the most well-supported mechanism (Figure 1), there are many outstanding questions. It is clear that mimetic peptides are effective at reducing tumor burden and inflammatory lipid signaling in animal models of cancer, but it remains to be seen if the latter is *causal* for the former. As highlighted by Chattopadhyay et al. [53], the precise sequence of events in the intestine-lung axis must be determined in order to identify the causative players in the anti-tumor mechanism. Another starting point may be to precisely characterize the interaction between apolipoprotein mimetics and the small intestine. Are CD36 and/or SR-B1 involved? If so, are they the *exclusive* mediators of the mimetic peptides' mode of action? It will also be necessary to collect more evidence that oxidized lipid traffic *directly* induces Notch signaling and subsequent immunomodulation, or whether there is an intermediate step. Finally, and more importantly, it is still unclear whether a similar mode of action is present in humans.

Recent advances in the development of rHDL- and sHDL-based delivery and therapeutic systems for cancer treatment are promising. The use of well-studied apolipoprotein mimetics to generate such macromolecules gives an additional advantage by maximizing delivery and therapy (Figure 2). It is further conceivable that apolipoprotein mimetic peptides, in addition to being used for delivery (rHDL/sHDL), can also be used as cargo for treating specific cancers.

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Abbreviations

ApoA-I	apolipoprotein A-I
BCa	breast cancer
CCa	colon cancer
HDL	high density lipoprotein
HDL-C	high density lipoprotein cholesterol
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
MDSC	myeloid-derived suppressor cell

OCa	ovarian cancer
oxLDL	oxidized low density lipoprotein
PCa	prostate cancer
rHDL	recombinant high density lipoprotein
sHDL	synthetic high density lipoprotein
Tg6F	transgenic tomatoes expressing the 6F peptide

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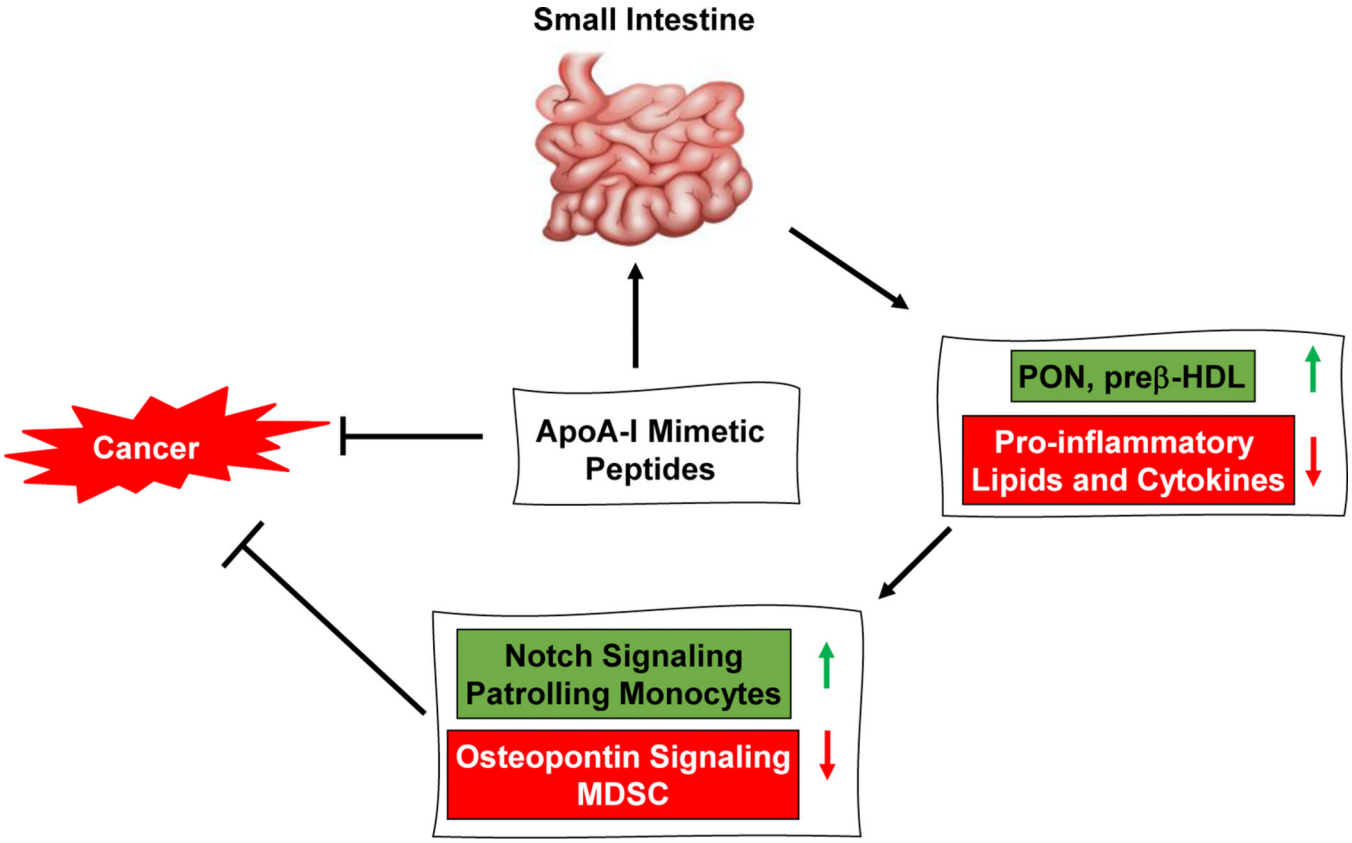

Fig. 1.
Proposed mechanism for the anti-tumorigenic activity of apoA-I mimetic peptides in cancer.

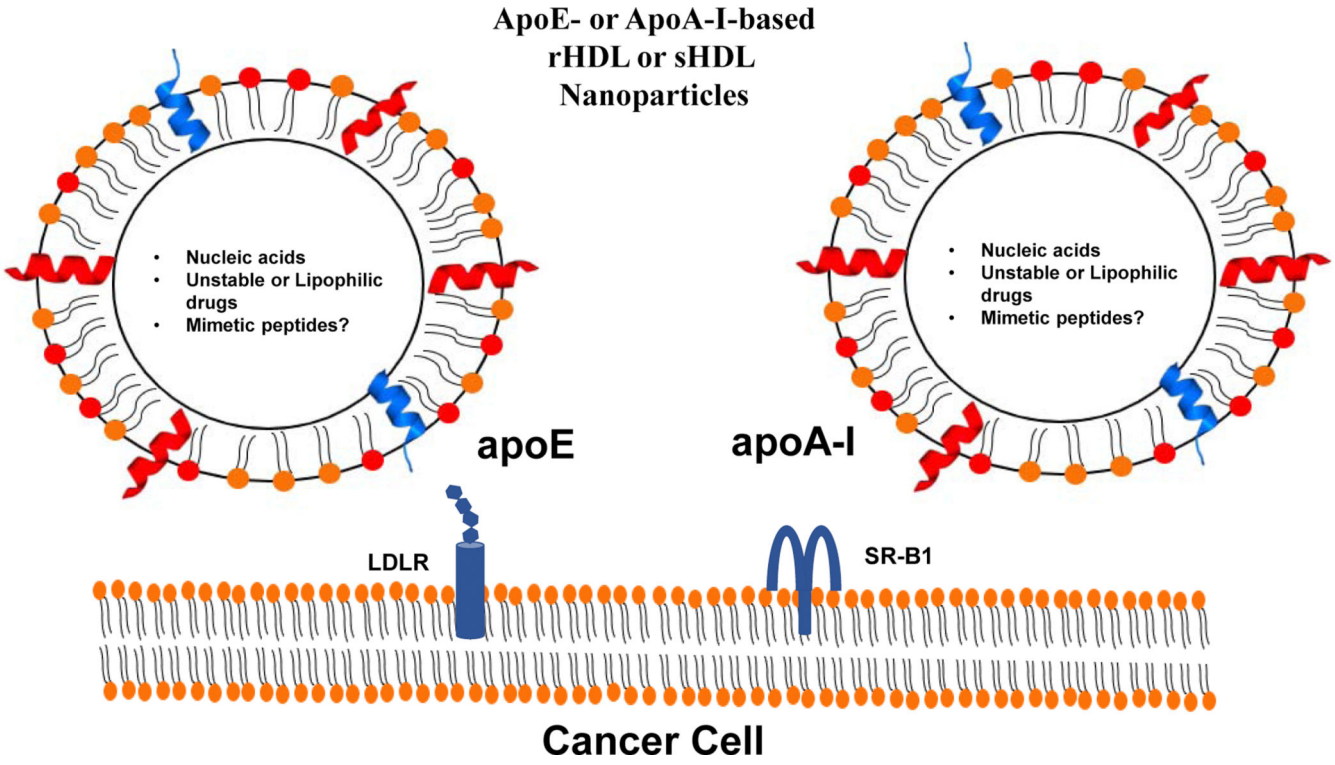

Fig. 2.

rHDL or sHDL nanoparticles utilize apolipoprotein mimetics to target tumor cells expressing SR-B1 or LDLR, delivering a payload of chemotherapeutics or potentially apolipoprotein mimetic peptides.

Table 1:

Structural features of different apoA-I mimetics.

Mimetic peptide	Features and function	Reference
37pA, 37aA	18 AA helical dimers, mimic endogenous apoA-I	[42]
2F, 3F, 4F, 5F, 6F and 7F	Phenylalanine substitutions, increase stability and helicity	[43]
ELK peptides	Optimize cholesterol efflux by using a select few AAs	[45]
2F*	UV stimulus triggers α-helix formation, increasing specificity of cholesterol efflux.	[46]
i-FAMP	Stronger α-helical conformation yields greater cholesterol efflux.	[48]
6α	α -methylated AAs confer protease resistance and increased her ity.	[49]

Table 2:

Utility of apolipoprotein mimetics in ameliorating preclinical models of cancer.

Mimetic peptide	Cancer model	Results	Reference(s)
D-4F (apoA-I)	OCa: ID8 cells in C57BL/6J mice	Decreased cell viability and proliferation, tumor burden, progression, and metastatic spread.	[12,65,66]
	OCa: SKOV3, CAOV3, and OVCAR3 human cell lines	Decreased cell viability and sensitized cells to cisplatin. Decreased invasiveness of SKOV3.	[68]
	Pancreatic: Panc02- bearing *Msr -/-* mice	Inhibited progression and metastatic spread in SRA-dependent manner.	[67]
	MCF-7 BCa cells and PyMT transgenic mice	Increased tumor latency and inhibited tumor development. Prevented proliferative response.	[72]
L-4F (apoA-I)	OCa: ID8 cells in C57BL/6J mice	Decreased cell viability, proliferation, and tumor burden.	[12]
	CCa: CT26-bearing BALB/c mice and $APC^{min/+}$ mice	Removed pro-tumorigenic lipids and decreased tumor cell proliferation.	[70]
	Pancreatic: H7 cells and H7-bearing C57BL/6 mice	Induced differentiation and apoptosis of MDSCs. Increased T cell activity. Decreased tumorigenicity of H7 cells.	[73,74]
L-5F (apoA-I)	OCa: ID8 cells in C57BL/6J mice; HUVEC cells	Decreased cell viability, proliferation, and tumor burden. Halted angiogenesis, and VEGF-induced proliferation, invasion, and cell viability.	[12,65]
G* (apoJ)	CCa: CT26-bearing BALB/c mice and $APC^{min/+}$ mice	Removed pro-tumorigenic lipids and decreased tumor cell proliferation.	[70]
Tg6F (apoA-I)	CCa: CT26 cells metastatic to lung of BALB/c mice	Decreased MDSCs and increased patrolling monocytes in jejunum and lung, lowering tumor burden.	[53,71]
	OCa: ID8 cells in C57BL/6J mice		
COG112 & OP449 (apoE)	PCa: AR+ & AR- cells	Dose-dependently decreased cell viability. Disrupted cell cycle and progression.	[75]
	GBM: U87 cells	Inhibited cell growth.	[76]

Table 3:

Uses of HDL- or apolipoprotein-associated nanoparticles in cancer.

Nanoparticle type	Cancer model	Results	Reference
HDL-mimicking phospholipids, apoA-I mimetic	Nude mice bearing EGFR+ tumors	13.6 h half-life *in vivo*, high rate of therapeutic diffusion to tumors.	[100]
Extracellular vesicle containing L-4F	GBM: U87-bearing BALB/c nude mice	Improved association between tumors and MTX-loaded vesicles. Conferred survival benefit.	[102]
DTX-loaded sHDL, 5A mimetic	BCa: MCF-7 cell line and 4T1-bearing KM mice	Delivered high payload of DTX, resulting in high cytotoxicity. Targeted to cells overexpressing to SR-B1.	[103]
Nanodisk containing 22A mimetic	ACC: H295R-bearing nude mice	Inhibited tumor growth *in vivo*.	[104]
CC nanoparticles with HDL stabilizer	BCa: MCF-7-bearing nude mice	Increased DOX delivery to tumor *in vivo* compared to free DOX.	[105]
rHDL containing siRNA	OCa: Orthotopic SKOV3-bearing nude mice Metastatic colorectal: HCT116-bearing nude mice	Targeted to cells overexpressing SR-B1. Treatment effectively silenced target transcript.	[107]
apoE3-based rHDL nanoparticle containing siRNA	GBM: Ras-driven C6 cell xenografts to nude mice	Efficiently silenced target transcript. Induced GBM cell apoptosis and inhibited tumor growth *in vitro* and *in vivo*.	[108]
Myr5A	n/a	Novel peptide self-assembles into nanomicellar structure. Improved drug payload compared to free 5A nanoparticles.	[110]
Porphyrin HDL	Lung: SR-B1+ & SR-B1-cell lines, and orthotopic lung tumors in nude mice	Induced apoptosis in >70% of tumor cells without toxicity to normal tissue.	[112]