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Synthetic high-density lipoprotein-like nanoparticles for cancer therapy

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Summary

High-density lipoproteins (HDLs) are a diverse group of natural nanoparticles that are most well-known for their role in cholesterol transport. However, HDLs have diverse functions that provide significant opportunities for cancer therapy. Presented is a focused review of the ways that synthetic versions of HDL have been used as targeted therapies for cancer, and as vehicles for the delivery of diverse therapeutic cargo to cancer cells. As such, synthetic HDLs are likely to play a central role in the development of next generation cancer therapies.

Keywords

High-density lipoprotein; cholesterol; cancer, drug delivery; nucleic acids; scavenger receptor

Cholesterol Metabolism and Cancer

Cholesterol metabolism and cancer are tightly linked: A sustained and increased supply of cholesterol is essential for cancer cell proliferation and tumor progression. Cancer-related anomalies of cholesterol metabolism have been implicated in angiogenesis, metastasis, and drug resistance [1]. On a cellular level, cholesterol is a crucial component of membranes and

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modulates their fluidity, stability, and overall architecture [2]. Additionally, cholesterol is known to accumulate in discrete regions of the membrane, endowing these areas with unique properties. These so-called lipid rafts serve as assembly platforms for molecules involved in signaling cascades, including those associated with development [3–5]. Finally, cholesterol serves as a precursor for steroid hormones, which are known regulators of cell proliferation and differentiation, and are critical players in the progression of breast and prostate cancer [1,4].

In a healthy organism, cholesterol homeostasis is achieved by joint regulation of cellular synthesis, influx, and efflux [4]. Cholesterol synthesis is usually limited to the liver, adipose and lactating breast tissues, but it is also up-regulated in cancer cells [6,7]. Since cholesterol is minimally soluble in water, its transport within the human body is mediated by lipoproteins – highly organized, yet very dynamic emulsions composed of lipids, proteins and additional components. Low density lipoprotein (LDL) is the major lipoprotein that delivers cholesterol from the liver to healthy peripheral cells [1,8,9]. Cholesterol from LDLs is taken up through LDL receptor-mediated endocytosis and transported to the lysosome [1]. By contrast, high density lipoprotein (HDL) both delivers and removes cholesterol from cells. One of the main functions of HDL is to remove excess cholesterol from peripheral cells and deliver it to the liver for excretion in the bile, a process called reverse cholesterol transport [10]. HDL further delivers cholesterol to steroidogenic tissues [10]. Lipoproteins also play a critical role in cancer progression through delivery of cholesterol to malignant cells. Consistently, many cancer patients exhibit reduced levels of cholesterol in the blood [11–13], which are restored to normal values upon successful remission [14]. Malignant cells overexpress the HDL-specific high-affinity scavenger receptor B1 (SR-B1) [2,13,15–18]. Consistently, exogenously added HDL has been shown to promote growth of breast cancer cells *in vitro* and promote aggressiveness of tumors *in vivo* [19–21]. Finally, and vastly extending the functional role that HDL may play in cancer, HDLs also exhibit anti-inflammatory, anti-oxidant, anti-microbial and pro-immunity properties [22,23] and carry non-lipid components including microRNA, hormones, vitamins and metabolites [24,25].

HDLs possess a core of cholesteryl esters (CE) and triglycerides surrounded by a monolayer of phospholipids and unesterified cholesterol. These 5–12 nm large nanoparticles (NP) are stabilized by Apolipoprotein [26], which influences the lipoprotein's shape and specific interactions with cellular receptors and transporters including SR-B1, ATP-binding cassette transporter (ABC) A1[1] and ABC-G1 [27]. All three receptors facilitate HDL-mediated cholesterol efflux from cells, but only SR-B1 is known to mediate cholesterol influx. Due to engagement with cholesterol-rich HDLs, the ability to mediate bi-directional cholesterol flux, and its overexpression in multiple cancer types [2,13,15–18], SR-B1 has been the most studied HDL receptor in cancer. Also, HDL binding to SR-B1 can trigger downstream signaling cascades, such as through Akt, that promote cancer progression and migration [18]. Apolipoprotein AI (ApoA-I) is the most important and most abundant protein component of HDLs [28]. Due to constant remodeling and maturation through interactions between HDL and other lipoproteins, lipid-modifying enzymes or target cells, HDLs display significant particle heterogeneity with respect to size, density, shape (spherical versus discoidal), associated molecules, chemical composition and surface properties [28]. As such,

HDL subclasses belong to a continuous metabolic cascade, which serves a multitude of different functions.

Targeted Drug Delivery to Cancer Cells

Despite significant recent progress, enormous room and need for improvement of current anti-cancer therapeutic options remain [29]. Most standard anti-cancer drugs are inherently non-specific, both in their bio-distribution (diffusing both into healthy and cancer tissues), as well as in their mechanism of action (affecting all rapidly dividing cells rather than cancer cells specifically). About 40% of new anti-cancer drugs in the pipeline are characterized by poor water-solubility [30]. Targeted drug delivery has the great potential to overcome these disadvantages: A preferential accumulation of the therapeutic agent in malignant rather than healthy cells significantly improves the therapeutic index of a drug.

Reconstituted HDL nanoparticles have in general been shown to be very biocompatible, and are – due to their targeting of cancer cells – an attractive vehicle for the delivery of antineoplastic substances. In this review we summarize recent scientific advancements in using synthetic, Apolipoprotein or Apo-peptide containing, biomimetic HDL-like nanoparticles (NP) both as efficient delivery vehicles for anticancer drugs, nucleic acids and phototherapeutic compounds, as well as agents that are intrinsically therapeutic.

The preferential accumulation of HDL-like NPs in cancer cells is achieved by passive and active targeting. Tumor tissues are characterized by a leaky vasculature and low lymphatic drainage, leading to differences in interstitial pressure between the center of a tumor and its periphery. This pressure difference allows for the preferential retention of particles between 10–100 nm in the tumor, a passive targeting phenomenon known as the enhanced permeability and retention effect [31,32]. HDL-like NPs can also be actively targeted to cancer cells by specific interaction with SR-B1, which is highly expressed by many different types of cancer [2,13,15–18]. Importantly, SR-B1 facilitates the uptake of cholesterol esters and anticancer drugs from spherical HDL-like NPs to the cytosol via a non-endocytic pathway [33,34], avoiding lysosomal degradation of HDL-like NP payload.

Synthetic HDL-like NPs are highly customizable, therefore providing researchers with the unique opportunity to control many of the particles' structural and compositional features and to endow these particles with tailored and unique functions. For instance, NP can differ in the composition of their core (e.g. cholesterol esters [16] versus inorganic scaffolds [35]), in their shape (discoidal [36] versus spherical [35]), their protein content (full-length Apolipoprotein [37] versus Apo-mimetic peptide[38]), their phospholipid composition [39] and in the nature of the surrounding lipid layer (bilayer [35] versus monolayer [40]). Further, drug-conjugated particles can differ in the mechanism of the drug loading (covalent attachment [41], encapsulation [42] or integration in lipid layer [43]) and the presence or absence of additional targeting moieties [39]. Many HDL-like NPs have been shown to mimic their natural spherical or discoidal counterparts in many characteristics like composition, surface properties and size. Further, many constructs have been found to be non-immunogenic, to avoid clearance by the reticuloendothelial system, and to have relatively long circulation times in the blood stream [31]. In summary, HDL-like NPs may be an effective and biocompatible platform for targeted delivery to cancer cells [44].

Spherical HDL-like NP for Drug Delivery

Delivery of hydrophobic antineoplastic agents by HDL-like NPs is often achieved by encapsulation of the drug in the hydrophobic core. Recently, Lacko and coworkers showed that inclusion of highly water-insoluble drugs like valrubicin in spherical HDL-like NPs composed of phosphatidyl choline, Apo-AI, free cholesterol and cholesteryl oleate led to increased toxicity in SR-B1 expressing, malignant prostate and ovarian cell lines as compared to the free drug [34,45]. Off-target cytotoxic effects in non-malignant epithelial prostate and ovarian cell lines with low SR-B1 expression were decreased for the drug-containing particle compared to the free drug [34,45]. Encapsulation of valrubicin into HDL-like NP therefore has the potential to significantly expand the therapeutic spectrum of the drug, which had previously exclusively been used for treatment of bladder cancer [34]. The authors also used a similar NP construct to target the therapeutic agent fenretinide to two different neuroblastoma cells lines *in vitro* [45]. Compared to the free drug, cytotoxicity in the malignant cells lines was significantly increased, while cytotoxicity in retinal pigment epithelial cells, a control cells line for off-target fenretinide toxicity, was reduced [34,45]. Feng and coworkers used a similar strategy of drug encapsulation to target doxorubicin to hepatocellular carcinoma and hepatoma cells lines [42,46]. Their particles composed of egg phospholipids, Apo-AI and doxorubicin showed increased cytotoxicity, apoptosis rates, and cellular accumulation in target cells compared with the free or liposome encapsulated drug [42]. The drug-loaded HDL-like NPs also decreased tumor growth in a metastatic model of human hepatocellular carcinoma (HCC) in nude mice more effectively while reducing hemolysis-related side effects [46].

To better understand the uptake of lipophilic components from HDL-like NPs through SR-B1, Lin et al. developed multifluorophore-labeled, HDL-mimicking peptide phospholipid scaffold (HPPS) nanoparticles [47]. Although ApoA-I is critical for determining the shape of HDLs and allowing for specific interactions with cellular receptors, the protein can be replaced by short (<20 amino acids) peptides that show no sequence similarity to the full-length protein [48]. These peptides mimic the amphipathic helical structure of ApoA-I and receptor and lipid binding abilities [48]. Lin et al. [47] generated a variety of different cholesteryl oleate/phosphocholine HDL-like NPs with either fluorescent compounds in the particle core, fluorescently labeled Apo-peptides and phospholipids on the surface, or combinations thereof. Through sequential inhibition studies, they found that after initial interaction of the NP with SR-B1, the particle bound to a specific sub-domain of the receptor, leading to particle dissociation and internalization of the hydrophobic, fluorescent particle payload into the cytosol by a lipid-raft/caveolae-like mechanism. Phospholipids and Apo-mimetic peptides were mainly retained on the cell surface. For natural, mature HDL, selective influx of the CE payload does not require the catabolism of the particle [49,50], suggesting that the cellular fate of specific HDL-like NPs might be dependent on their specific composition and determined by additional factors that warrant further investigation.

Alternative Targeting Ligands

HDL-like NPs can also serve as scaffolds for the attachment of alternative targeting ligands. Corbin et al. [39,51] exploited the fact that over 90% of non-mucinous ovarian cancers overexpress the folate receptor- α (FR- α) [52]. Covalent linkage of folate to the lysine

residues of ApoA-I abolished the particle's ability to interact with SR-B1, therefore rerouting the HDL-like NP to FR- α . The researchers used this technique to specifically deliver an NP-encapsulated near-infrared fluorescent dye to ovarian tumors in mice, therefore enhancing optical imaging *in vivo* [39,51]. Current studies are underway to utilize these particles not only for delivery of optical dyes, but for therapeutic antineoplastic agents as well [39].

Discoidal HDL-like NP for Drug Delivery

Both discoidal and spherical HDL-like NPs have been used successfully for the delivery of a large variety of antineoplastic agents. Discoidal HDLs lack a core composed of triglycerides and CE, and it has been suggested that they bind to the SR-B1 receptor with higher affinity than spherical HDLs [53]. However, discoidal species have the disadvantage of being prone to undergo maturation in the blood stream due to interaction with lecithin-cholesterol-acyltransferase (LCAT). LCAT converts the cholesterol present in discoidal HDL into CE, which moves into the center of the particle, increasing the particle's size and remodeling it into a sphere [54]. This can lead to unwanted leakage of drug cargo [55]. To address this problem, researchers used monocholesteryl succinate (CHS) instead of cholesterol to prevent particle interaction with LCAT, and further anchored ApoA-I in the particle by covalently linking it to CHS [56,57]. CHS-modified discoidal HDL-like NPs loaded with paclitaxel, a mitotic inhibitor used to treat a variety of cancers, showed improved pharmacokinetics in rats [57], as well as improved targeting, cytotoxicity and limitation of tumor growth in breast cancer tumors compared to the unmodified particle [56]. Ultimately, the choice of whether to use spherical or discoidal HDL-like NPs for drug delivery will depend on the nature of the payload and the type of cancer to be targeted.

Delivery of Nucleic Acids

It has recently been demonstrated that natural HDLs not only associate with small, regulatory nucleic acids like microRNA (miRNA), but are further capable of delivering these molecules to cells in a SR-B1-dependent fashion and of down-regulating gene expression of corresponding miRNA targets [24,58]. Notably, the HDL-miRNA profiles of patients with diseases like familial hypercholesterolemia differ substantially from those of healthy volunteers [24], and miRNA in the serum has been found to be a good indicator for a variety of disease states including cancer [59–61], although with some limitations [62]. It has further been suggested that serum miRNA could serve as a mean of cell-cell communication. While the exact biological function of HDL-associated nucleic acids remains to be elucidated, several research groups have already exploited the nucleic acid binding properties of HDL to design HDL-like NPs to target both RNA and DNA to the cytosol of cancer cells. Ding et al. used reconstituted HDL composed of phospholipids, cholesterol, CE and ApoA-I to deliver double stranded, cholesterylated short interfering RNA (chol-siRNA) to hepatocellular carcinoma. These siRNA-NPs were specifically targeted to tumor sites, where they effectively decreased the expression of the oncogenes *POKEMON* and *BCL-2* and inhibited cellular growth [63]. Accumulation of these HDL-like NPs in the target tissues could further be confirmed by using fluorescently labeled chol-siRNA. Rui et al. constructed a HDL-like NP composed of phospholipids, ApoA-I and cholesterol that harbored un-modified siRNA complexed with a cationic polymer in its core

[40]. Mediated by an SR-B1-dependent mechanism and with minimal cytotoxicity [40], the construct efficiently silenced the luciferase gene expressed by hepatoma target cells. Similarly, Shahzad et al. used oligolysine peptides to neutralize and complex siRNA, allowing its formulation with a HDL-like NP with similar composition of that of Rui et al. [16,40]. The particle was successfully used to silence the genes for the signal transducer and activator of transcription 3, as well as focal adhesion kinase, two proteins involved in malignant cell survival and progression [16,40]. Using multiple tumor mouse models of ovarian cancer and colorectal cancer, the authors showed decreased tumor growth, angiogenesis and cell survival upon siRNA-HDL-like NP treatment [16]. Zheng and coworkers also used their above mentioned HPPS particle [47] to deliver chol-siRNA to cancer cells. Their chol-siRNA-particles successfully down-regulated the *BCL-2* gene in mice bearing KB (SR-B1+) tumor xenografts, resulting in increased apoptosis and decreased tumor growth without significant side effects [64]. Further, the additional encapsulation of fluorescent dyes in the core of the HDL-like NP, or the use of dye-labeled siRNA, could serve as valuable tools not only to track the constructs in the body, but also to evaluate different treatment regimens and allow for treatment planning of siRNA delivery to orthotopic tumors [65]. In one of the first demonstrations of a synthetic, biomimetic HDL nanoparticle used for nucleic acid delivery, our research lab has previously developed HDL-like NPs that are based on a core gold nanoparticle scaffold, covered by a lipid bilayer, and stabilized by ApoA-I. Size, shape, cholesterol binding and efflux properties of the HDL-like NP have been shown to be comparable to the ones of natural HDL [35]. We demonstrated that cholesterylated ssDNA (chol-ssDNA) not only adsorbs to the HDL-like NP and is protected from nuclease degradation, but is also effectively delivered to prostate cancer cells, which exhibit a particularly high demand for cholesterol [66]. Our DNA-HDL-like NPs further bypassed endolysosomal sequestration, regulated target gene expression, and could be tracked using transmission electron microscopy [67]. Using a similar HDL-like NP construct, we were also able to deliver ssRNAi to vascular endothelial cells, leading to attenuation of *in vivo* neovascularization and remarkable reduction in the growth of hypervascular lung tumor allografts [68].

Apolipoproteins

In addition to ApoA-I, ApoE has been used as a targeting moiety for HDL-like NPs. Dong et al. generated an entire library of NPs composed of phospholipids, cholesterol, polyethylene glycol-lipid, siRNA and different lipopeptides – lipids whose tails were conjugated to a diversity of different amino acids, peptides, and polypeptide head groups [69]. When assessing the different particles for their potential to knock down a variety of genes in different tissues, the authors found that their lead construct's ability to silence the luciferase gene in dual-luciferase-expressing HeLa cells was significantly increased by incubation of the particle with ApoE [69]. ApoE plays a key role in HDL-like NP uptake by the liver through the LDL receptor and the low-density lipoprotein receptor-related protein 1 [70,71]. This Apolipoprotein has also been used by other groups to systematically deliver chol-siRNA conjugated to discoidal HDL-like NP to liver cells with the goal of silencing a number of different genes [37]. These ApoE-conjugated HDL-like NP more efficiently delivered chol-siRNA to hepatocytes compared to ApoA-I-conjugated particles, presumably

due to the employment of a different uptake mechanism (LDL receptor for ApoE vs. SR-B1 for ApoA-I) [37].

A systematic approach to understand the bio-distribution, toxicity and potential of ApoE containing NPs to deliver a variety of different compounds was undertaken by Fischer et al. [41]. The authors used three main approaches to conjugate different compounds to their ApoE-containing discoidal HDL-like NPs. Namely, lipids with functionalized head groups (like Ni-chelating lipids for the binding of His-tagged proteins), highly hydrophobic groups like cholesterol that could be covalently linked to the cargo molecule (like chol-ssDNA), and click-chemistry-based covalent conjugation of proteins to a lipophilic moiety embedded in the lipid bilayer. The resulting suite of HDL-like NPs was stable in complex biological fluids and non-cytotoxic *in vitro* in concentrations up to 320 mg/ml. Administration of the particles *in vivo* did not cause weight loss, organ specific toxicity or overt immunogenicity. Biodistribution of the particles varied by route of administration, with preferred accumulation of the particles in kidney and liver after i.v., i.p., i.m. and s.c. administration [41].

Photothermal Agents

HDL-like NPs have also been used to for the delivery of photothermal agents. These compounds facilitate infrared light-induced temperature changes in tumor tissues leading to tissue necrosis. Mathew et al. generated an HDL-like NP composed of phosphocholine, ApoA-I fused to a trans-activating transcriptional activator peptide for enhanced cell internalization and a water-insoluble gadolinium bis(naphthalocyanine) sandwich complex as a photothermal compound [72]. Using this particle, the authors achieved photothermal killing of human lung cancer cells in a near infrared light-irradiation-dependent manner. By conjugating pyropheophorbide, a reduced porphyrin, to lysophospholipids, Ng and al created a phototherapeutic, fluorescent pyro-lipid, which self-assembled with ApoA-I into nanodiscs [36]. While fluorescence of the photosensitizer was quenched in intact particles, particle uptake by SR-B1 transfected Chinese hamster ovary cells led to un-quenching of the fluorescence, likely due to disruption of particle structure. Importantly, the transfected, SR-B1 positive cells exhibited a dose-dependent decrease in survival when treated with 660 nm light, whereas untransfected SR-B1 negative cells neither took up the particles nor were affected by light treatment [36].

Scale up

A challenge for many, but not all, of the HDL-like NPs is the ability to produce particles at the scale required for more extensive studies. Kim et al. [43] presented a microfluidics-based method for the large-scale production of NPs. By manipulating mixing speeds and lipid to protein ratios, the authors were able to fine-tune the production of a variety of HDL-like NPs that differ in shape (discoidal and spherical) and encapsulated compound (such as the drug simvastatin and fluorophores or inorganic cores such as gold, iron oxides and quantum dots for imaging purposes) [43]. This work illustrates how versatile HDL-like NPs are in terms of their range of deliverable compounds. For the use of HDL-like NP as therapeutic agents, cost of the individual components needs to be considered. The most costly component of many of the HDL-like NPs may be the ApoA-I protein; however, significant

past work has demonstrated the scale-up and use of ApoA-I in human clinical trials [73–75]. In addition, alternative approaches, like the use of ApoA-I-mimetic peptides, have been explored as well [31].

Nanoparticles as Intrinsically Therapeutic Agents

Some HDL-like NP constructs are intrinsically therapeutic without requiring a cargo. Zheng et al. found that their SR-B1-targeted HDL-like NP named HPPS, which the authors had previously loaded with various compounds like antineoplastic agents, siRNA and photosensitizers [47,64,65,76] also inhibited motility and colony formation of nasopharyngeal carcinoma (NPC) cells *in vitro* without carrying any cargo [38]. The cargo-free HPPS particles further decreased tumor growth in nude mice bearing NPC subcutaneous tumors through a mechanism that involved neither tumor cell necrosis nor apoptosis [38]. While ApoA-I-mimetic peptides like the one on the HPPS NP have been shown to exhibit anti-tumor activities by reducing plasma levels of lysophosphatidic acid, a stimulator of cell migration, invasion and colony formation [77], the exact mechanism of action for HPPS particles is still unknown. In an alternative approach, our lab has successfully used HDL particles with a core made of gold [67,68], rather than CE, to selectively induce apoptosis in lymphoma cells [78]. Since the surface properties of our HDL-like NPs are similar to the ones of natural HDL, they compete for SR-B1 binding sites on cancer cells, and upon binding, selectively modulate cholesterol homeostasis. This ultimately leads to lymphoma cell apoptosis. Treatment of mice bearing B-cell lymphoma xenografts with HDL-like NP selectively inhibits B cell lymphoma growth. This suggests that our HDL-like NPs can not only be used for the delivery of nucleic acid cargoes [67], but are also intrinsically therapeutic agents due to an apparent cooperative effect that results from biomimicry and targeted alteration of cellular cholesterol homeostasis in B cell lymphoma [78].

Expert commentary

In conclusion, a significant body of data exists demonstrating that HDL-like NPs actively target cancer cells through receptor-mediated interactions and constitute a highly versatile, non-toxic delivery platform for a variety of different antineoplastic compounds, nucleic acids and photothermal agents. Additionally, certain HDL-like NPs may also serve as functional, single-entity therapies for cancer based upon the particles' ability to differentially modulate cellular cholesterol flux. Lastly, HDL-like NPs can be equipped with fluorescent dyes and imaging agents, allowing tracking of the particles in the human body and allowing further investigation of the structure-function relationships of HDLs and HDL-like particles. The mechanism by which HDL-delivered therapeutic agents may slow tumor progression is likely to be a combination of drug targeting and the intrinsic antineoplastic properties of both the drug cargo and the HDL-like NP carrier. Moreover, ApoA-I, a major component of many of the HDL-like constructs presented here, has been shown to reduce both tumor growth and metastasis and can even lead to tumor regression [79]. Finally, due to the close connection of cancer and inflammation, the anti-inflammatory properties of HDL could play a role in HDL-based cancer therapy as well [23,80]. In summary, further pre-

clinical and clinical development of these new approaches may offer tremendous new therapeutic opportunities for patients with cancer.

Five-year view

Due to the beneficial properties of HDL-like NPs as drug and nucleic acid delivery vehicles and as targeted single-entity therapies, drugs based on novel synthetic forms of HDL have the potential to be studied in early phase clinical trials. First-generation studies are likely to focus on the lymphoproliferative disorders where robust preclinical data have been generated. Since HDL-like NPs will eventually be targeted to the liver for excretion in the bile, the potential side effects of HDL-like NP-based therapies related to liver toxicity will certainly be examined in closer detail. However, several studies already suggest that HDL-like NPs do not display significant adverse effect in liver function and hepatocyte viability and have overall a very limited bio-toxicity [41,78,81]. Further, many HDL-like NPs are amenable to being scaled up for production as necessary for large clinical trials [43,78], ApoA-I has been scaled up and administered to humans in clinical trials [73–75], and alternatives to ApoA-I, like ApoA-I-mimetic peptides, have also been explored [31]. HDL-like NPs have great potential to display maximum clinical efficacy in the near future and provide paradigm shifting new approaches and therapies for cancer patients. Further insights into the modes of action of, and mechanisms of resistance to, HDL-like NP will refine the types of cancer, anti-cancer entities carried, and companion agents/approaches used in clinical studies.

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List of abbreviations

ABC	ATP-binding cassette transporter
ApoA-I	Apolipoprotein AI
ApoE	Apolipoprotein E
CE	Cholesteryl ester
chol-siRNA	Cholesterylated short interfering RNA
chol-ssDNA	Cholesterylated ssDNA
CHS	Moncholesterylsuccinate
FR	Folate receptor
HCC	Human hepatocellular carcinoma
HDL	High density lipoprotein
HPPS	HDL-mimicking peptide phospholipid scaffold

i.m.	Intramuscular
i.p.	Intraperitoneal
i.v.	Intravenous
LCAT	Lecithin-cholesterol-acyltransferase
LDL	Low density lipoprotein
miRNA	microRNA
NP	Nanoparticle
NPC	Nasopharyngeal carcinoma
s.c.	Subcutaneous
SR-B1	Scavenger receptor B1

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Papers of special note have been highlighted as:

* of interest

** of considerable interest

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Key issues

- High density lipoproteins (HDL) are natural nanoparticles that transport cholesterol to cancer cells and can, through receptor-mediated interactions, trigger downstream signaling cascades that promote cancer progression and migration.
- Synthetic forms of HDL (HDL-like NP) have been developed to target anticancer drugs, nucleic acids and phototherapeutic compounds to cancer cells.
- New forms of HDL-like NP have been shown to serve as intrinsically therapeutic agents that can differentially modulate cellular cholesterol homeostasis, therefore serving as potent cancer therapies for some types of cancer, including lymphoma.
- The production of recombinant forms of HDLs can be scaled to allow the conduct of human clinical trials.