Lipoproteins as drug delivery vehicles for cancer and tumor therapeutics

Abstract

Present article focuses on various lipoprotein based drug delivery vehicles used in cancer and tumor therapeutics. Starting from aqueous phase delivery through liposomes or unilamellar vesicles, biomimetic HDL nanoparticles, discoidal recombinant high-density lipoproteins (d-HDLs) are favorably used to deliver anticancer agents. LDL based carrier vehicles are reconstituted in many ways i.e. discoidal SMAaf-based lipid nanoparticles, nanovectors, LDL nanoparticles, SiRNA-HDL used for systemic delivery of short interfering RNA. This article also explains chemically and genetically engineered high-density lipoprotein (HDL)-like nanodiscs or “bicelles”, chylomicrons, and monoclonal antibodies and ligand-coupled lipoprotein as drug delivery vehicles. These are most promising delivery systems for anticancer drugs. Acetylated low-density lipoprotein is also used as a delivery vehicle for anti-infectious drugs. There is immense need of therapies, imaging agents, and drug delivery vehicles to combat rising number of cases of neoplasticity and tumors in population. For safe cancer therapeutics nano-sized site-specific drug delivery vehicles which might show bio-compatibility, bio-degradability, and receptor-mediated endocytosis are to be developed.

Keywords: LDL, HDL, liposomes , lipid nanoparticles , chylomicrons, nanodisks, drug carriers

Introduction

Lipoproteins are biological lipid carriers play important role in transport of fats within the body.1 These are natural nanoparticles which serve as drug-delivery vehicles due to their small size, long residence time in the circulation.2 Low-density lipoprotein (LDL) carries cholesterol in plasma and play important role in its metabolism in normal cells as well as in cancer cells.4 Lipoproteins carry high-drug payload and are used as delivery vehicles for transportation of chemotherapeutic agents. These bear unique targeting capabilities because of their easy transportation to cancer and tumor sites. LDL loaded with r11-DOX is used to treat cancer cells. LDL follows receptor pathway is used to deliver radionuclides for the treatment of neoplasms and tumors.5 Both liposomes and oil emulsions are also used to carry water-insoluble photosensitizers for treatment of tumors.6 Besides, low-density lipoproteins (LDLs) monoclonal antibodies are also most promising delivery vehicles for anticancer drugs. For delivery of therapeutic agents liposomes bind to some antibody and loaded drug are internalized by into macrophages via the receptor-mediated pathway for modified LDL.7 More specifically, loaded drug is assimilated through receptor-mediated pathway in cancer cells and its rate is much higher than that of normal cells. For transport of drugs to new targets, lipoproteins are bound to ligands. Lipoproteins structure is modified to tag nucleic acids, photosensitizers for its antitumor agents. These also act as biophysical devices like contrast agents and can be loaded with drugs, LPs and phospholipids. These natural drug nanocarriers escape any interaction with immune cells and reticuloendothelial systems.8 Hence, drugs loaded on LDLs safely transported to tumor cells without loss of their activity.9 After receptor-mediated uptake of drug-lipoprotein complex escape enzyme attack.2 Lipoproteins are safe, biocompatible, biodegradable, non-immunogenic and successfully carry diverse therapeutic molecules to the site of invasion.

Lipoproteins: transport vehicles of lipids

Lipoproteins are major transporters of cholesterol, triglycerides and other hydrophobic molecules in circulatory system (Figure 1). Lipoproteins are natural nanoparticles which also deliver certain lipophilic compounds such as fat-soluble vitamins and hormone and enzyme inhibitors.6,11 These also function as drug-delivery vehicles due to their smaller size, low affinity and high capacity binding, longer stay in the circulation. Moreover, both natural and reconstituted lipoprotein based systems are able to carry high high-drug payload12 and are used for delivery of therapeutic molecules (Figure 2).13 Based on their density, lipoproteins are categorized as chylomicron, very low density lipoprotein (VLDL), intermediate density lipoproteins (IDL), low density lipoprotein (LDL) and high density lipoprotein (HDL).

HDL (high-density lipoproteins) is smallest lipoprotein that also transports cholesterol from various tissues and back to the liver. These are composed of lipids, hydrocarbons, proteins, and nucleic acids (e.g. microRNA). HDL is denser and small lipoprotein that can carry lipids in form of aggregates in plasma. HDL possesses high protein / lipid ratio and non harmful as it load less cholesterol and play important role in cardiovascular diseases.14 Because of their smaller these show easy tissue penetration/retention and carry high amount of drugs in bound form to various tissues through circulation system.15 These also function as a lipid scavenger and removes harmful bad cholesterol. Hence, an elevated level of HDL lower downs risk of developing coronary heart diseases.16 HDL reuses and recycles LDL cholesterol by transporting it to the liver where cholesterol molecule is reprocessed. HDL scavenges extra cholesterol deposited on the inner walls of blood vessels. Besides natural HDL molecules, reconstituted high density lipoprotein (rHDL) is also prepared to deliver therapeutic agents. Reconstituted high density lipoproteins (HDL) are used to deliver a lipophilic anticancer drug. rHDL is biocompatible, safe, nano-vector that mimics the physical, chemical as well as physiological properties
of native high density lipoprotein (HDL). These are reconstituted with phospholipids and apolipoproteins and used as a vehicle for systemic delivery of drugs, therapies and as imaging agents. These are highly useful for targeted and efficacious systemic delivery of siRNAs. Besides, HDL, discoidal high-density lipoproteins are also generated by the apolipoprotein-mediated solubilization of membrane lipids in vivo. These discoidal SMααf-based lipid nanoparticles carry drugs deep into tissues mainly to metastatic sites (Table 1).

![Figure 1 Lipoprotein serves as a carrier for transporting lipids.](image1)

![Figure 2 Lipoprotein as a targeted drug carrier.](image2)

Low-density lipoprotein (LDL) carries cholesteryl esters to peripheral cells. It contains one major apolipoprotein (i.e. apo B-100), that allows LDL to bind to the LDL receptors on the peripheral cell surfaces. From where it is internalized by cells through a receptor mediated endocytosis. LDL is the endogenous carrier of cholesterol. The majority of cholesterol is obtained through the LDL receptor-mediated endocytosis mostly in the form of cholesterol ester. LDL particle is just like an oil droplet that is covered by a monolayer of phospholipid (Figure 3). LDL contains a lipid core that is made up of triglycerides (20%) and cholesteryl esters (80%). Low-density lipoprotein acts as a vehicle for targeting antitumor compounds to cancer cells. LDL is highly useful carrier molecule for hydrophobic drugs, but only lipophilic drugs partition into the core of the system. Since cholesterol is transported in ester from that is a native component of LDL. However, conjugation of an antitumor moiety with cholesterol facilitates the loading of drugs into LDL. Biocompatible, lipid-protein complexes are also ideal for loading and delivering cancer therapeutic and diagnostic agents. Natural lipoproteins and synthetic/reconstituted lipoproteins are widely used in clinical applications, particularly for cancer diagnostics/imaging and chemotherapy.

![Figure 3 Lipoproteins and lipoprotein mimetics for imaging and drug delivery.](image3)

### Table 1 Important properties of various lipoproteins

| Parameter | CM | VLDL | LDL | HDL |
|-----------|----|------|-----|-----|
| Diameter (nm) | 75-1200 | 30-80 | 19-25 | 5-12 |
| Density (g/ml) | <0.96 | 0.96-1.006 | 1.019-1.063 | 1.063-1.210 |
| Mw. | 400 | Oct-80 | 2.3 VLDL/IDL | 0.17-0.36 |
| Source | Gut | Liver | VLDL/IDL | Gut, Liver |
| Size | 75-1200nm | 30-80nm | 25-35nm | 8-12nm |
| Half life | 5-13min | 2-5min | 15hr | 11-12hr |
| Lipid composition | | | | |
| Triglyceride | 80-95 | 45-65 | 18-22 | 2-7 |
| Free cholesterol | 1-3 | 4-8 | 6-8 | 3-5 |
| Cholesterol ester | 2-4 | 6-22 | 45-50 | 5-20 |
| Phospholipid | 3-6 | 5-20 | 18-24 | 26-32 |
| Apolipoproteins | A-I, A-II, A-IV | A-I, A-II, A-IV | A-I, A-II, A-IV | A-I, A-II, A-IV |

Lipoprotein density and presence of cholesterol in it causes cardiovascular problems. Density also decides the presence of cholesterol in blood exhibit hypo- and/or hypercholesterolemia and triglyceridemia. Lipid transfer between lipoproteins is a part of reverse cholesterol transport. It takes place in the cell cytoplasm as well as sub-organelles. Lipoprotein free cholesterol ratio is a positive regulator of the pathways involved in sterol clearance. It modulates lipid transfer by altering the availability of CE and TG to LTP at the lipoprotein surface. Chylomicrons are the largest lipoproteins produced in the intestinal tract. Their main function is transport of dietary triglycerides and cholesterol. Very Low Density Lipoproteins

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Lipoproteins are synthesized in the liver that transport triglyceride to peripheral tissues. LDLR (LDL receptors) regulate the behavior of VLDL/LDL-associated drugs. These VLDL/LDL-bound drugs are cleared from the body by lipoprotein apheresis, a blood purification therapy that selectively removes VLDL/LDL particles from the bloodstream. This clearance also influences transport, metabolism, and the efficacy of drugs in humans. In present review article lipoprotein-based delivery are explained with their composition, target specificity and therapeutic efficacy and their use for delivery of poor water soluble drugs.7

Types of lipoprotein based drug delivery systems

Liposomes or unilamellar vesicles

Liposomes are carrier vehicles of therapeutic drugs mainly in fluid state. These display natural binding to LDL receptors and carry anticancer agents to deliver them in to the tissues (Figure 4). Further, drug delivery systems are also linked to ligands which could target these receptors. Liposomal anticancer drug delivery systems more efficiently distribute associated anticancer agents. Because slow and steady presence of liposomes in the blood lead to increase the therapeutic indices of the associated drugs. It results in an increase in the drug concentration in solid tumors and regions of infection and reducing the drug concentration. Furthermore, stability of liposomes in biological systems is very important in the targeting of anticancer agents. Because number of different factors influence liposomal integrity after introduction into the circulation such as: lipid-metabolism, exchange or transfer of liposomal lipid to plasma constituents or cellular membranes, interaction with plasma proteins, imperfect fusion of liposomes with cells involving partial release of entrapped material and release of lysosomal lipolytic enzymes during liposome induced endocytosis.23 Liposomes are safe as loaded drug has no chance to have resistance if used in cancer therapy.24 These are widely used to carry anticancer agents,25 polymer conjugates,26 bacterial27 and virus vectors.28 Liposomes are used as intravenous carriers of drugs and enzymes. Besides, drug delivery liposomes do mobilization of peripheral deposits of cholesterol. Liposomes are used to precede whole-particle uptake by receptors involved in lipoprotein metabolism. Liposomal contents also show direct interaction and disrupt membrane structure.29 Certain modifications in liposomes are possible by using varying quantity of lipid and drug type. It affects interactions liposome-lipoprotein interactions and sabotages the cancer cells at structure and show metabolic consequences as they are pH-sensitive.30

Lipid-based delivery vehicles, such as liposomes and oil emulsions are generally used for administration of water-insoluble photosensitizers. These are used in photodynamic therapy for treating tumours.4 Liposomes or oil vesicles are also prepared by using egg-yolk or rat-liver phosphatidylcholine. For this purpose both lipids and lipoproteins (HDL) in aqueous phage are tagged on Ultrogel AcA34.31 But for formation of anionic liposomes lactosylated low-density lipoproteins (LDL) are also used as adjuvants for delivery of antiseNSE oligonucleotides to Kupffer cells in liver. Liposomes are also formed from polymerizable diacetylenic phospholipids.32 Matrix metalloproteasein is used for release of liposomal contents that is formed by incorporating sequence-specific collagen-mimetic peptides MMP-9. More specially, encapsulating carboxylfluorescein (as a self-quenching fluorescent dye), is also used to form liposomes that also assists in detection and treatment of various human diseases.33 For delivery of Zn-phthalocyanine (ZnPc) and Sn-etiopurpurin (SnET2) incorporated in unilamellar liposomes or solubilized in a Cremophor-EL emulsion are intravenously provided to experimental animals.34

![Diagram of liposome](image)

**Figure 4** A typical liposome for drug delivery.

**LDL carrier vehicles**

Cholesterol is a major constituent molecule in low-density lipoproteins (LDLs). It plays important role in cellular homeostasis and production of steroids. Presence of higher levels of LDL in blood stream increases chances of a heart attack. High amount of LDL form bad plaque, and stuff that clog arteries and enhance the chances of heart attacks and strokes more likely. Low-density lipoproteins (LDLs) are internalized by the cell through receptor-mediated mechanisms (Figure 5). LDL is also taken up avidly by tumor cells to provide cholesterol for the synthesis of cell membranes. LDL is a good carrier of photosensitizer (berberine) in tumor cells.35 A synthetic nano-LDL (nLDL) particle containing paclitaxel oleate (nLDL-PO) was made by combining a synthetic peptide containing a lipid binding motif and the LDL receptor (LDLR) binding domain of apolipoprotein B-100 with a lipid emulsion consisting of phosphatidyl choline, triolein, and paclitaxel oleate. It is used as a drug delivery vehicle for glioblastoma multiforme.36 Similarly, a boronated analogue of LDL is synthesized that is used in boron neutron capture therapy.37 Both natural and reconstituted lipoproteins are used for various therapeutic purposes (Figure 6).

Low density lipoproteins (LDL) also act as a carrier for drug in emulsion.38 Acetylated low-density lipoprotein vehicle is developed that is chemically modified by the acetylation of lysine residues (Ac-LDL). This Ac-LDL carries anti-infectious drugs and its uptake is mediated through a specific scavenger receptor. Acetylated LDL-KOL is selectively accumulated through receptor-mediated assimilation within infected macrophages rather than in normal cells.39 More specifically, drug targeting occurs through by endogenous transport vehicles.40 Drug-low density lipoprotein complexes are used in treatment of intracellular infections.41 Reconstituted LDL is prepared by using lipophilic cytotoxic compound by two different methods. First method involves drug delivered to the cells via the LDL pathway that kill 100% of the cells. Another one is drug-delivery process via lipoprotein-type carriers, is the receptor-mediated uptake of the payload from the lipoprotein complex.2 N-trifluoroadracylendriamycin-14-valerate-LDL complex or LDL particle upload 100 drug molecules and send to vital organs.42 Apolipoprotein B is cell-penetrating

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peptides that efficiently deliver antigenic peptide. It binds to cell surface LDL receptor (LDLR) or cell surface-bound proteoglycans and is easily internalized into cells. Plasma lipoproteins are also used as drug carriers (Table 2).

**Figure 5** Structural components of a lipoprotein molecule.

**Figure 6** Use of lipoproteins for various therapeutic purposes.

**HDL carrier vehicles**

**Biomimetic HDL nanoparticles**

Biomimetic HDL-like nanoparticles (NP) can carry diverse groups of therapeutic agents such as chemotherapeutics, nucleic acids, proteins and carbohydrate colpexes. These smaller sized nanoparticles can freely navigate through interstitial space mainly for targeting tumors. These nanostructures possess high penetration/retention power and are used to deliver drugs in to intracellular space. These stream in circulation and for stay longer duration, can deliver clinically viable nanomedicines for cancer therapy. These particles are amphiphatic apolipoproteins, lipid-loading and hydrophobic agent-incorporating characteristics. These manage protein-protein interactions and show heterogeneity and are showed great clinical application. These show feasibility and superiority as drug delivery vehicles because of their use in photodynamic therapy. An example a biomimetic HDL nanoparticle is indocyanine green used in enhanced photodynamic therapy.

**Discoidal recombinant lipid nanoparticles**

Discoidal high-density lipoproteins d-rHDLs are generated by the apolipoprotein-mediated solubilization of membrane lipids in vivo (Figure 7). These are also reconstituted with phospholipids and apolipoproteins in vitro. These are used to deliver anticancer agents those who show poor water-solubility and selectivity. These are biocompatible, biodegradable, and enter into cell through receptor-mediated endocytosis. d-rHDLs fused with paclitaxel show higher cellular uptake and it is cytotoxic to human breast cancer cells. These are prepared by thin-film dispersion/detergent dialysis. Similarly, recombinant high density lipoproteins are reconstituted with apolipoprotein A1 cysteine mutants. It is used as delivery vehicles for 10-hydroxycamptothecin and showed targeted receptor-mediated uptake (Table 3).

**Figure 7** Diagrammatic diagrams of HDL and reconstituted HDL used for various therapeutic purposes.

**Recombinant high density lipoprotein**

Recombinant high density lipoprotein (rHDL) particles contain phosphatidylcholine, apolipoprotein A-1, cholesterol and cholesteryl esters in smaller concentration. These could bind three molecules of taxol per particle and form complexes. These are used as imaging agents and are better tolerated than the corresponding dosages of either Taxol or Abraxane. HDLs have diverse functions that provide significant opportunities for cancer therapy. Further, reconstituted high density lipoprotein (rHDL) is an excellent and highly biocompatible nanovector mimicking the physical, chemical as well as physiological properties of native high density lipoprotein (HDL). These vehicles are used to target tumor by delivering diverse drug payloads. Besides this, discoidal and spherical recombinant HDL particles loaded with cardiovascular drug tanshinone IIA (TA) are also reconstructed (TA-d-rHDL and TA-s-rHDL). Discoidal SMAaf-based lipid nanoparticles are also constructed and used as delivery vehicles. rHDL could be especially used as potential delivery vehicles of targeting atherosclerotic lesions.

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### Table 2: Plasma lipoproteins associate few drugs and carry them to target sites

| Compound | TRL | LDL | HDL | LDLp | Efficacy |
|----------|-----|-----|-----|------|----------|
| Propranolol and verapamil | _ | + | _ | + | Lipophilic compounds, Lactosylation of LDL and HDL induces rapid, galactose-specific uptake by Kupffer and parenchymal liver cells |
| Amphotericin B | _ | + | _ | + | Amphotericin B lipid complex, show renal toxicity |
| Abelcet | + | _ | + | _ | Decreased renal toxicity |
| Cyclosporine A | + | + | + | _ | Significant renal toxicity |
| Halofantrine | + | + | + | _ | Increased activity |
| Clozapine | _ | _ | + | + | Increased activity |
| Haldol | _ | _ | + | + | Increased activity |
| Eritoran | + | _ | + | _ | Investigational drug for the treatment of severe sepsis |
| Amiodarone | + | + | + | + | Anti-anginal and antiarrhythmic medication, synthetic lipid A antagonist that blocks lipopolysaccharide (LPS) from binding at the cell surface MD2-TLR4 receptor |
| Paxleitalexal | _ | _ | + | + | Anti-cancer, plant alkaloid |

### Table 3: Showing various lipoprotein-based drug delivery systems used for transport of anticancer drugs to the site of action

| Drug delivery systems | Drug carrier | Target | Safety |
|-----------------------|--------------|--------|--------|
| Polymers | Inert carrier to which a therapeutic is covalently linked, deliver drugs, macromolecules, cells and enzymes | Therapeutic proteins to their target site | Compatible, minimal or no toxic profile, polysaccharide-based polymers, |
| Microcapsules | Lipophilic drug, pharmaceutics, | Prolonged drug delivery of therapeutic biomolecules | Nano- and microcarriers depends on their colloidal stability |
| Micro-particles | Materials, including ceramics, glass, polymers, and metals | Membrane-anchored receptors and adhesion molecules, and transfer of microRNA | Safe, readily circulate in the vasculature, serve as shuttle modules and signaling transducers |
| Liposomes | Thin lipid films or lipid cakes are hydrated and stacks of liquid crystalline | Carriers for numerous molecules in cosmetic and pharmaceutical industries | Biocompatibility, biodegradability, low toxicity, and aptitude to trap both hydrophilic and lipophilic drugs |
| Micelles | A micelle or micella (plural micelles or micellae, respectively) is an aggregate (or supramolecular assembly) of surfactant molecules dispersed in a liquid colloid. | Act as emulsifiers that will allow a compound that is normally insoluble (in the solvent being used) to dissolve | Used for targeted drug delivery as gold nanoparticles, absorption of fat-soluble vitamins and complicated lipids |
| Polysorbate coated nanoparticles | Submicron drug carrier, temozolomide | Mimic LDL to cross the BBB, and enhance its brain-protective effects. | Safe |
| Polysaccharides and co-polymers | Submicron drug carrier | Drug delivery devices, controlled release of fungicides, used for selective water absorption from oil-water emulsions, purification of water | Non-toxic, biodegradable and available at low cost |
| Polyacettes | Submicron drug carrier | Deoxystreptaminel. | Potent tumor promoter |
| Polyacetylcyano acrylates(PCAS) | Submicron drug carrier | Nano particles cross BBB and carry neuroactive drugs | Safe biomaterial for drug delivery |
| Colloidal drug carriers | Emulsions, liposomes, nanoparticles | Polyoxypropylene, polyethylene glycol, ployoxyethylene | Liposomes and NPs, increasing drug efficacy and/or reducing their toxicity |
HDL-like nanoparticles

High-density lipoproteins (HDL)-like nanoparticles are used as drug carriers. Naturally HDL transports cholesterol throughout the body. Due to their small size (5-100 nm in diameter) of lipoproteins, these could carry therapeutic agents deep into tumors. HDL nanocomplexes are pH-responsive, undergo physicochemical changes and release enclosed drugs at acidic pH conditions. For making them biocompatible, these are coated with polyethylene glycol (PEG). Without PEG coating, particles are quickly trapped in the reticuloendothelial system when intravenously administered. HDL particles bind to their endogenous receptors, which are found on cancer cells. These lipoprotein nanocarriers mimic enzymes and can stay in circulation for much larger periods, while largely evading the reticuloendothelial cells in the body’s defenses. Thus lipoprotein and lipoprotein-based nanoparticles also serve much better than other drug delivery vehicles. Phospholipid nanodiscs are also engineered for development of drug delivery systems.

Systemic delivery of siRNA therapeutics

Short interfering RNAs (siRNAs) molecules are also used for therapeutics of many human diseases that follow gene silencing mechanisms. These are loaded on HDLs nanoparticles for systemic delivery. Synthesized biomimetic HDL is also being used as delivery vehicle for targeted and efficacious systemic delivery of siRNAs into the cytoplasm of the target cells. For intracellular delivery of siRNA, polymers with endosomolytic properties are used because they show endosomal escape. Apolipoprotein B is also used for efficient transfer of mRNA KD polyconjugates.

Ligand-coupled lipoprotein as drug delivery vehicles

Lipoproteins are natural nano-sized delivery vehicles which stream within the circulatory system of all mammals. Normally lipoproteins loaded with medicinal agents are transported widely in body organs and tissues. Lipoprotein bound to some ligand could redirect natural lipoprotein receptors to an alternate receptor of choice. It assists in transport of endogenous macromolecules and therapeutic agents to specific cells or tissues in the body. More specifically, lipoprotein particles coupled in vivo are proved more useful as drug delivery vehicles. Liposome-based formulations are also prepared by using acetylated-LDL (Ac-LDL) as delivery vehicles for BPD (Table 4).

Lipid-based formulations for lymphatic delivery

Chylomicrons based vehicles are prepared by administration of linoleic acid and arachis oil. These form high concentration of chylomicrons in the lymph but not generate VLDL or LDL. It depends on degree of unsaturation of the fatty acid; greater the unsaturation there will be more rapid onset of chylomicron. Probucol bound to chylomicron enhance lymphatic delivery by increasing the amount of the drug solubilized in propylene glycol or Transcutol HP. Lipophilic drugs are carried by chylomicrons that are secreted by the small intestine and transported in lymph (Table 5).

Table 4 Ligand based drug/gene delivery methods used for treatment of hepatocellular carcinoma

| Delivery vehicle | Therapeutic agents | Ligand | Matching receptors |
|------------------|--------------------|--------|--------------------|
| Polyethylamine   | Doxorubicin/shAktl | Glycyrrhetinic acid | Glycyrrhetinic receptor |
| Dextran          | Curcumin           |        |                    |
| Polyethylamine   | Plasmid PCMVIuc27  | Epidermal growth factor | Epidermal growth factor |
| N-succinyl chitosan LDL | Doxorubicin/siRNA Osthole Docasahexanoic acid | LDL | Low density lipoprotein receptor |
| Bovine serum albumin | Doxorubicin | Hematoporphyrin | Low density lipoprotein receptor |
| Lipoplexes       | Chol-siRNA         | Reconstituted high density lipoprotein | Scavenger receptor type B-1 |
| Bovine serum albumin | 5-flourouracil | Heat labile enterotoxin subunit B | Ganglioside GM1 |
| Ruthenium nanoparticles | [Ru(bpy)2(4-B)](CIO4)2.H2 | Epigallocatechin gallate | 67kDa laminin receptor |
| Liposome          | Plasmid DNA        | S-HT  | 5-HT receptor |
| Liposome          | Hydroxycamptothecine | Ocreotide | G-protein coupled receptors |
| Liposomes         | Hyaluronic acid    | Extracellular matrix compound | Specifically binds CD44 a biomarker of cancer cells. CD44 is a membrane protein that regulates various cellular responses |

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Folates produce and maintain new cells. It transport folate-conjugates; thus, the folate-drug conjugation can improve tumor-targeted drug delivery.

Therapeutic agents

Ligand

Matching receptors

LDL nanoparticles

Folate

They can be attached to the tumor cell membrane more easily, which results in disruption fluidity of the cell membranes.

Participate in nucleotide synthesis, folate receptors are highly over expressed in cancer cells.

Lipoproteins

Polyunsaturated fatty acids (α-linolenic acid; linoleic acid, arachidonic acid; eicosapentaenoic acid; and docosahexaenoic acid)

Cancer cells take up 100 fold more low density lipoprotein than normal cells due to up-regulated LDL receptors in cancer cells for membrane synthesis during cell division associated with malignant transformation process.

LDL is a good drug delivery vehicle for carrying anticancer agents.

Liposomes

Cholesterol

Prevent opsonin binding to nanoparticles. Recognition of phagocytosis of nanoparticles by the mononuclear phagocytic system,

Enhance the blood circulation time

Liposomes

Polysaccharides, polyacrylamide polyvinyl alcohol; polyvinylpyrrolidone; PEG-containing copolymers (polyoxamers; poloxamines; polysorbates; and PEG copolymers)

The positive charge of cationic surfactant interacts through electrostatics with the negatively charged phospholipids

These are successfully exposed on the cancer cell surface

Table 5 Synthetic HDL nanoparticles for the delivery of chemotherapeutic agents, siRNAs nanoparticles, and imaging agents

| Name          | Lipid Type | Lipoprotein Component | Loaded drug                                                                 | Target                                                                 |
|---------------|------------|-----------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|
| HPPS          | DMPC       | Cholesteryl oleate    | Paclitaxel oleate, Dye-BOA (optical imaging contrast agent) Cholesterol conjugated siRNA | Human KB subcutaneous tumor xenograft Orthotopic prostate tumor xenograft |
| sHDL          | POPC       | L37pA and D37pA ApoA-I mimetic peptides | CO                                                                            | Human umbilical vein endothelial cells I/R injury rat heart model       |
| HDL-mimicking NP | DSPE-PEG-COOH PLGA CO | 4F peptide | Quantum dot conjugated to PLGA-b-PEG Cationic strearyltriphenyl phosphonium | Human adipose-derived MSCs Mouse monocyte/macrophage RAW 264.7 cells     |
| rHDL          | Egg yolk PC, cholesterol, CO | ApoA-I | siRNA/oligolsyne mixture Paclitaxel All-trans-retinoic acid Fenretinide Valrubcin | Human orthotopic ovarian tumor xenografts, cancer cell lines (breast, prostate, ovarian), Neuroblastoma cell lines, Retinal pigment epithelial cells |
| HDL-NP        | PDP PE DPPC | ApoA-I | Smn gold nanoparticles Antisense cholesterylated DNA | Lymphoma cell lines Human cells                                        |
| V156K- rHDL   | POPC Cholesterol | ApoA-I | Rapamycin | Human monocyte cell line Human dermal fibroblasts Zebra fish model       |

Table Continued
Lipoproteins as drug delivery vehicles for cancer and tumor therapeutics

| Name             | Lipid Type                      | Lipoprotein Component | Loaded drug                        | Target                                      |
|------------------|---------------------------------|-----------------------|-------------------------------------|---------------------------------------------|
| rHDL/Chol-siRNA  | Soybean PC Cholesterol          | ApoA-I                | Cholesterol conjugated siRNA        | Liver cancer cell line Human liver subcutaneous tumor Xenograft |
|                  | Cholesteryl ester               |                       |                                     |                                             |
| TA-rHD           | Glycerol trioleate Cholesterol, CO | ApoA-I                | Tanshinone IIa                       | Mouse macrophage cell line                  |
| GBCA-HDL         | ApoA-I Synthetic peptide        |                       | GBCA (MR contrast agent)             | Macrophages ApoE-deficient mouse model of atherosclerosis |
| HDL              | POPC                            | L37pA and D37pA ApoA-I mimetic peptides | CO                                 | Human umbilical vein endothelial cells I/R injury rat heart model |
| GBCA-HDL         | ApoA-I Synthetic peptide        |                       | GBCA (MR contrast agent)             | Macrophages ApoE-deficient mouse model of atherosclerosis |
| rHDL nanodiscs   | DMPC                            | ApoE3-MT              | Curcumin                            | Construct bearing LDLR ligand binding domains |
| rHDL nanodiscs   | DMPC                            | ApoA-I                | Curcumin                            | Human hepatocellular carcinoma cell line    |
|                  |                                 |                       |                                    | Mantle cell lymphoma cells                 |
| rHDL nanodiscs   | DMPC                            | ApoA-I ApoE           | Curcumin                            | Glioblastoma multiforme cells              |
| Cationic rHDL    | DMPC                            | ApoA-I                | siRNA                               | Hepatoma cells                             |
| nanodiscs        | Glycero phospholipid DMTAP (cationic) | ApoA-I                |                                     |                                             |
| rHDL nanodiscs   | Pyrophosphoribid-conjugated lipid | ApoA-I ApoE3         | Pyro                                | SR-BI over-expressing cell line (photosensitization) |
| [S]-rHDL         | Lyso PC DMPC                    | ApoA-I                | Simvastatin                         | Atherosclerotic plaques in Apo-E knockout mice |
| HDL-mimicking NP | DSPE-PEG-COOH PLGA              | 4F peptide            | Quantum dot conjugated to PLGA-b-PEG Cationic stearyl-triphenyl phosphonium | Human adipose-derived MSCs Mouse monocyte/macrophage RAW 264.7 cells |
| rHDL             | Egg yolk PC, cholesterol, CO    | ApoA-I                | siRNA/oligolsyine mixture Paclitaxel All-trans-retinoic acid Fenretinide Valrubicin | Human orthotopic ovarian tumor xenografts Human cancer cell lines (breast, prostate, ovarian) Neuroblastoma cell lines, Retinal pigment epithelial cells Prostate and ovarian cancer cell lines |
| HDL-NP           | PDP PE DPPC                     | po-A                  | Smm gold nanoparticles Antisense cholisterlated DNA | Lymphoma cell lines Human cells |
| V156K- rHDL      | POPC Cholesterol                | ApoA-I                | Rapamycin                           | Human monocyte cell line Human dermal fibroblasts Zebra fish model |

Drug delivery using nanotherapeutic molecules

**Nanovectors**

Lipoprotein nanostructures such as nanovectors are also used in nanotherapeutics. These show high compatibility and better performance and are also used in photodynamic therapy (PDT). In PDT a photosensitizer is delivered with lipoproteins mainly by using lipid-based and Pluronic P123 formulations. These formulations are especially used for treatment of arthritis. Drug-loaded human low density lipoproteins carry adriamycin derivative AD 32 or the N mustard derivative WB 4291. Cremopore EL is an important vehicle for the administration of hydrophobic drugs. It effects distribution of taxol (anticancer) to serum lipoproteins (LDL). Changes on lipoprotein composition can be attributed mainly to cremophor vehicle, by using ethanol contents. Oily nano vehicles are also used to deliver drugs in lymphatic system. Lipophilic drugs incorporated in lactosylated HDL are taken up rapidly and selectively by parenchymal liver cells. rHDL is used for incorporation and transport of hydrophobic and amphipathic bio-molecules. Table 6

**Nanodisks**

Nanodisks (ND) are self assembled nanoparticles which are composed of phospholipid and apolipoprotein. Nanodisks are formulated with inclusion of significant amounts of bioactive agents. Besides this, nanodisks or “bicelles” are also constructed by using chemically and genetically engineered high-density lipoprotein (HDL). Its initial “nascent” form i.e. 10 nm disc of phospholipids fits in a bilayer, and can be easily synthesized in vitro by mixing recombinant apoA-I proteins with various phospholipids. Nascent high density lipoprotein (HDL) particle is reconstituted (rHDL) naturally by self arrangements of phospholipids in a disk-shaped

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bilayer with two or more apolipoprotein molecules circumscribing the edge of the disk. Nanodisks are biocompatible and their assembly is facile. These could be designed with high targeting specificity to finish tumors growth. Protein chimeras are used in targeting drug-enriched ND to specific tissues. These are used to load therapeutic molecules mainly antimicrobial agents. Members of the class of exchangeable apolipoproteins possess the unique capacity to transform phospholipid vesicle substrates into nanoscale disk-shaped bilayers. Apolipoprotein chimeras are also prepared by fusion of protein that recognize the antigen to which the alpha-vimentin scFv is (single chain variable antibody). Further, apolipoprotein scaffold, interchangeability transfer lipid and scaffold components, makes ND a versatile delivery platform. Apolipoprotein A-I is used in ND formation and antigen recognition.

Table 6 Examples of synthetic LDL nano-particles

| Name   | Lipid component | Lipoprotein component | Cargo              | Target                           |
|--------|-----------------|-----------------------|--------------------|----------------------------------|
| Nano-LDL | PC-Triolein        | ApoB mimetic peptide | Paclitaxel oleate   | Glioblastoma multiforme cells     |
| sLDL    | Egg yolk PC       | ApoB mimetic peptide | Bacteriochlorin e6  | PDT in human liver subcutaneous tumor xenografts |
| rLDL    | Extracted LDL Trolein | ApoB              | Poly-iodinated triglyceride | Liver cancer cells             |
| r(TG)LDL | Extracted LDL      | ApoB              | Hypericin           | Human gloma cell line            |
| LDL/dextran | Extracted LDL  | ApoB              | Au-MHPC             | CT and optical imaging in subcutaneous tumor xenografts |

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**Conflict of interest**

The author declares that there is no conflict of interest.

**Conclusion**

Lipoprotein-based drug delivery systems are efficient vehicles which carry anticancer drugs to the site of invasion. LP based strategies also assist in improving the therapeutic efficacy of drugs thus unsuitable or drugs with poor solubility and of limited application would have shown good action. Further, a step is needed to develop innovative drug delivery approaches to increase the target specificity of anticancer and antitumor drugs and lower down of their toxicity. For this purpose LPS and their sub-constituents can be used for making for drug delivery with sequestering of cholesterol from intracellular space. Three aspects LDL bound to drugs, LDL as nano carriers and boron capture therapy could assist more and more. In all approaches natural, bio-compatible, materials should be used. Therapeutic agents are transferred through receptor mediated endocytosis in cancer cells. There is a need to develop reconstituted lipoprotein drug delivery systems or nanodisks carriers, biophysical attachment of metals/drugs to lipid carrier particles and shuttling agents for increasing clinical applications of LDL systems particularly for cancer diagnostics/ imaging and chemotherapy. Targeting moieties are antibodies, charged molecules, proteins, lipoproteins, polysaccharides, low weight molecular weight ligands, hormones.

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