

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-rHDLs) 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 nanodisks 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

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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 plasma³ 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 radionucleotides 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 therapeutics. 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.⁹⁻¹¹ 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 (eg. 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. Reconstructed 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).¹⁷ These are reconstituted with phospholipids and apolipoproteins and used as a vehicle for systemic delivery of drugs, therapies and as imaging agents.¹⁷ These are highly useful for targeted and efficacious systemic delivery of siRNAs.¹⁸ Besides, rHDL, discoidal high-density lipoproteins are also generated by the apolipoprotein-mediated solubilization of membrane lipids in vivo.¹⁹ These discoidal SMAaf-based lipid nanoparticles carry drugs deep into tissues mainly to metastatic sites (Table 1).²⁰

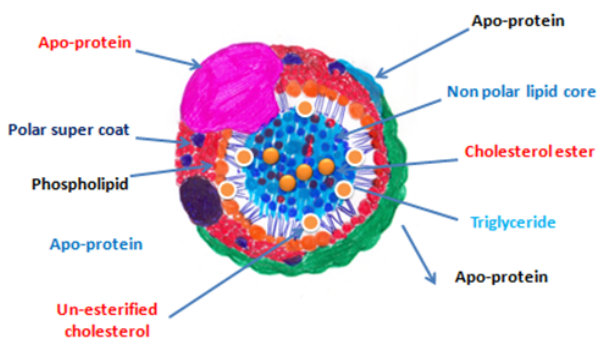


Figure 1 Lipoprotein serves as a carrier for transporting lipids.

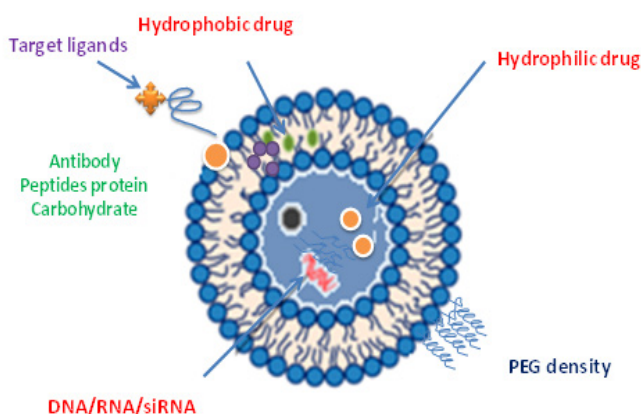


Figure 2 Lipoprotein as a targeted drug carrier.

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.²¹ 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 form 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.

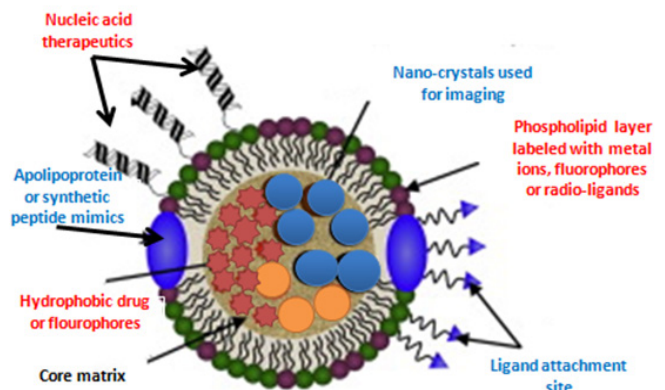


Figure 3 Lipoproteins and lipoprotein mimetics for imaging and drug delivery.

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	0.17-0.36
source	Gut	Liver	VLDL/ILDL	Gut, Liver
Size	75-1200nm	30-80nm	25-35nm	8-12nm
Half life	5-13min	2-5 min	15 hr	11-12hr
	B48	B100	B100	
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

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.²² Chylomicrons are the largest lipoproteins produced in the intestinal tract. Their main function is transport of dietary triglycerides and cholesterol. Very Low Density Lipoproteins

(VLDL) is 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.²

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.⁶ 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 phase 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 metalloproteinase is used for release of liposomal contents that is formed by incorporating sequence-specific collagen-mimetic peptides MMP-9. More specially, encapsulating carboxyfluorescein (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

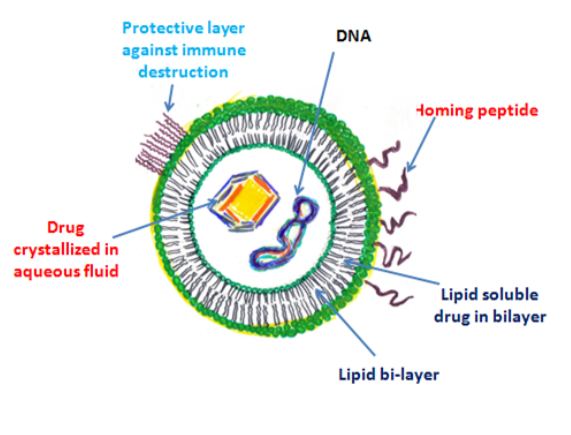


Figure 4 A typical liposome for drug delivery.

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.⁹ 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.³⁶ 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.³⁸ More specifically, drug targeting occurs through by endogenous transport vehicles.³⁹ Drug-low density lipoprotein complexes are used in treatment of intracellular infections.⁴⁰ 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-trifluoroacetyladiamycin-14-valerate-LDL complex or LDL particle upload 100 drug molecules and send to vital organs.⁴¹ Apolipoprotein B is cell-penetrating

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.⁴² Plasma lipoproteins are also used as drug carriers (Table 2).²¹

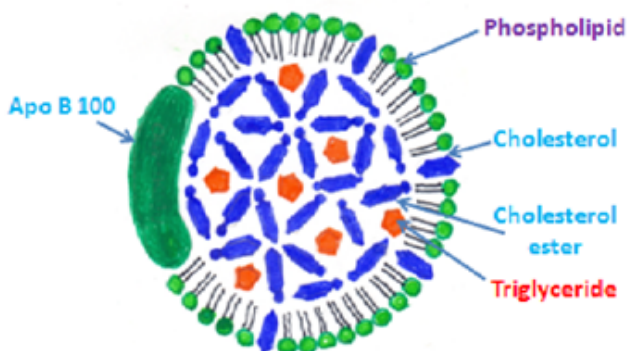


Figure 5 Structural components of a lipoprotein molecule.

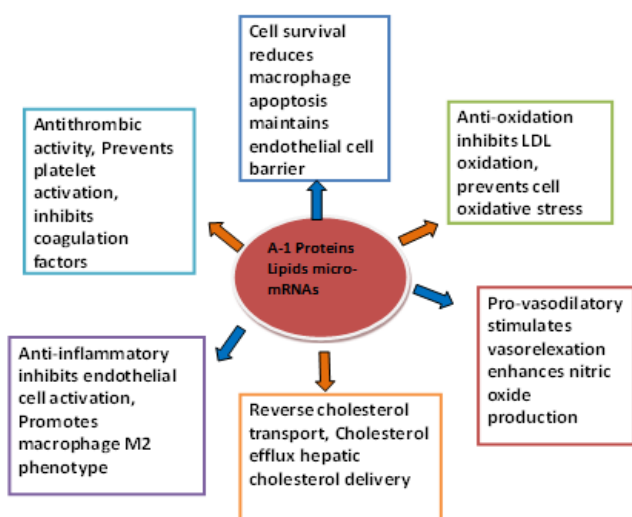


Figure 6 Use of lipoproteins for various therapeutic purposes.

HDL carrier vehicles

Biomimetic HDL nanoparticles

Biomimetic HDL-like nanoparticles (NP) can carry diverse groups of therapeutic agents such as chemotherapies, nucleic acids, proteins and carbohydrate colplexes.¹⁴ These smaller sized nanoparticles can freely navigate through interstitial space mainly for targeting tumors.⁴³ 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 amphipathic apolipoproteins, lipid-loading and hydrophobic agent-incorporating

characteristics. These manage protein-protein interactions and show heterogeneity¹⁵ and are showed great clinical application.⁴⁴ 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.⁴⁵

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*.¹⁹ 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.⁴⁶ These are prepared by thin-film dispersion/detergent dialysis.⁴⁶ Similarly, recombinant high density lipoproteins are reconstituted with apolipoprotein AI cysteine mutants. It is used as delivery vehicles for 10-hydroxycamptothecin and showed targeted receptor-mediated uptake (Table 3).⁴⁷

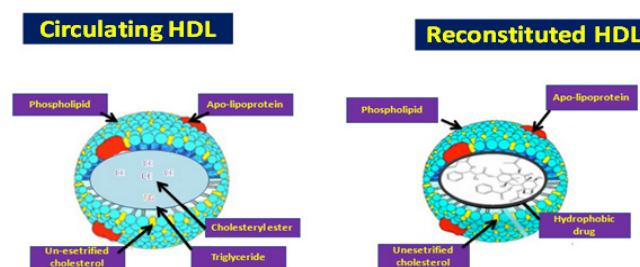


Figure 7 Diagrammatic diagrams of HDL and reconstituted HDL used for various therapeutic purposes.

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.⁴⁸ rHDL complexes can carry drug molecules deep into the tissues.⁴⁹ These are also used as imaging agents⁵⁰ and are better tolerated than the corresponding dosages of either Taxol or Abraxane. HDLs have diverse functions that provide significant opportunities for cancer therapy.⁵¹ 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).¹⁷ These vehicles are used to target tumor by delivering diverse drug payloads.¹³ 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.⁴³

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	+	+	+	+	Antianginal and antiarrhythmic medication, synthetic lipid A antagonist that blocks lipopolysaccharide (LPS) from binding at the cell surface MD2-TLR4 receptor
Paxlitexal	–	–	+	+	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, pharmaceuticals,	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
Polyacetates	Submicron drug carrier	Deoxystreptamnel.	Potent tumor promoter
Polyalkylcyano 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.⁵² Naturally HDL transports cholesterol throughout 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.⁵³ For making them biocompatible these are coated with polyethylene glycol (PEG). Without PEG coating, particles are quickly trapped in the reticuloendothelial system when these are intravenously administered.⁵² HDL particles bind to their endogenous receptors, which also found on cancer cells. These lipoprotein nanocarriers mimic enzymes and can stay in circulation for much larger period, while largely evading the reticuloendothelial cells in the body's defenses. Thus lipoprotein and lipoprotein-based nanoparticles also serve much better than those other drug delivery vehicles. Phospholipid nanodiscs are also engineered for development of drug delivery systems.⁵² The incorporation of DLF into the rHDL nanoparticles protects against hydrolysis in the systemic circulation. DLF is used as a probe to track the movement and metabolism of HDL core constituents, including cancer chemotherapeutic agents.⁵⁴

Systemic delivery of siRNA therapeutics

Short interfering RNAs (siRNAs) molecules are also used for therapeutics of many human diseases that follows gene silencing mechanisms.⁴⁵ 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.⁵⁵

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.⁵⁶ It assists in transport of endogenous macromolecules and therapeutic agents to specific cells or tissues in the body. More specifically, lipopeptide particles coupled in vivo are proved more useful as drug delivery vehicles.⁵⁷ Liposome-based formulations are also prepared by using acetylated-LDL (Ac-LDL) as delivery vehicles for BPD (Table 4).⁵⁸

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.⁵⁹ Probuocol bound to chylomicron enhance lymphatic delivery by increasing the amount of the drug solubilized in propylene glycol or Transcutol HP.⁶⁰ Lipophilic drugs are carried by chylomicrons that are secreted by the small intestine and transported in lymph (Table 5).⁶¹

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

Delivery vehicle	Therapeutic agents	Ligand	Matching receptors
Polyethylamine	Doxorubicin/shAkt1	Glycyrrhetic acid	Glycyrrhetic receptor
Dextran	Curcumin		
Polyethylamine	Plasmid PCMVluc27	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-I
Bovine serum albumin	5-flourouracil	Heat labile enterotoxin subunit B	Ganglioside GM1
Ruthenium nanoparticles	[Ru(bpy) ₂ (4-B)](ClO ₄) ₂ .H ₂ O	Epigallocatechin gallate	67kDa laminin receptor
Liposome	Plasmid DNA	5-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

Table Continued

Delivery vehicle	Therapeutic agents	Ligand	Matching receptors
LDL nanoparticles	Folate	Folates produce and maintain new cells. It transport folate-conjugates; thus, the folate-drug conjugation can improve tumor-targeted drug delivery.	Participate in nucleotide synthesis, folate receptors are highly over expressed in cancer cells.
Liposomes	Polyunsaturated fatty acids (α -linolenic acid; linoleic acid, arachidonic acid; eicosapentaenoic acid; and docosahexaenoic acid	They can be attached to the tumor cell membrane more easily, which results in disruption fluidity of the cell membranes.	Tumor progression is reduced by modulating p53, p16, and p27 expression and cell cycle regulation, as well as by inducing cell death by apoptosis and necrosis.
Liposomes	Cholesterol	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	Polysaccharides, polyacrylamide polyvinyl alcohol; polyvinylpyrrolidone; PEG-containing copolymers (polyoxamers; poloxamines; polysorbates; and PEG copolymers)	Prevent opsonin binding to nanoparticles. Recognition of phagocytosis of nanoparticles by the mononuclear phagocytic system,	Enhance the blood circulation time
Liposomes	Cationic surfactants	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 (CO)	R4F peptide	Paclitaxel oleate DiR-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 stearyl-triphenyl phosphonium	Human adipose-derived MSCs Mouse monocyte/macrophage RAW 264.7 cells
rHDL	Egg yolk PC, cholesterol, CO	ApoA-I	siRNA/oligolysine mixture Paclitaxel All-trans-retinoic acid Fenretinide Valrubicin	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	5nm 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

Name	Lipid Type	Lipoprotein Component	Loaded drug	Target
rHDL/Chol-siRNA	Soybean PC Cholesterol Cholesteryl ester	ApoA-I	Cholesterol conjugated siRNA	Liver cancer cell line Human liver subcutaneous tumor Xenograft
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-NT	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 nanodiscs	DMPC Glycerophospholipid DMTAP (cationic)	ApoA-I	siRNA	Hepatoma cells
rHDL nanodiscs	Pyrophephorbide-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 CO	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/oligolysine 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	poA-I	5nm 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

Drug delivery using nanotherapeutic molecules

Nanovectors

Lipoprotein nanostructures such as nanovectors are also used in nanotherapeutics.⁶² These show high compatibility and better performance and are also used in photodynamic therapy (PDT).⁶² 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.⁶³ Drug-loaded human low density lipoproteins carry adriamycin derivative AD 32 or the N-mustard derivative WB 4291.⁶⁴ Cremophore EL is an important vehicle for the administration of hydrophobic drugs.³⁸ It effects distribution of taxol (anticancer) to serum lipoproteins (LDL).⁶⁵ Changes on lipoprotein composition can be attributed mainly to cremophore vehicle, by using ethanol contents.⁶⁶ Oily nano vehicles

are also used to deliver drugs in lymphatic system.⁶⁷ Lipophilic drugs incorporated in lactosylated HDL are taken up rapidly and selectively by parenchymal liver cells.⁶⁸ rHDL is used for incorporation and transport of hydrophobic and amphiphathic 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.⁶⁹ 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.⁷⁰ Nascent high density lipoprotein (HDL) particle is reconstituted (rHDL) naturally by self arrangements of phospholipids in a disk-shaped

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.⁷¹ 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 chimera is 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.⁷¹ Apolipoprotein A-I is used in ND formation and antigen recognition.

Nanodisk vehicle is prepared for delivery of curcumin, a polyphenol having anti-cancer properties. Incorporation of curcumin into ND generates a water soluble formulation suitable for intravenous delivery.⁷² Similarly, two distinct water insoluble drugs AMB-ND (amphotericin B) display potent anti-fungal and anti-protozoal activity, ATRA-ND (all trans retinoic acid) are also transferred by using nanodisks for treatment of cancer.⁷³ Cationic lipid is included in the ND formulation that generates intact nanometer sized positively charged ND. Cationic lipid ND stably bound 23-mer double stranded oligonucleotides. Cationic lipid ND-bound siRNA efficiently knocked down a target gene in hepatocarcinoma cells. Drug delivery via lipoprotein-based carriers is best model to transport therapeutic agents to the site of invasion and metastasis.^{74,75}

Table 6 Examples of synthetic LDL nano-particles

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

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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Conflict of interest

The author declares that there is no conflict of interest.

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