HHS Public Access

Author manuscript

Wiley Interdiscip Rev Nanomed Nanobiotechnol. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2015 May ; 7(3): 298–314. doi:10.1002/wnan.1308.

Learning from Biology: Synthetic Lipoproteins for Drug Delivery

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Abstract

Synthetic lipoproteins represent a relevant tool for targeted delivery of biological/chemical agents (chemotherapeutics, siRNAs, photosensitizers and imaging contrast agents) into various cell types. These nanoparticles offer a number of advantages on drugs delivery over their native counterparts while retaining their natural characteristics and biological functions. Their ultra-small size (<30nm), high biocompatibility, favorable circulation half-life and natural ability to bind specific lipoprotein receptors *i.e.* low-density lipoprotein receptor (LDLR) and Scavenger receptor class B member 1 (SRB1) that are found in a number of pathological conditions (*e.g.* cancer, atherosclerosis), make them superior delivery strategies when compared to other nanoparticle systems. We review the various approaches that have been developed for the generation of synthetic lipoproteins and their respective applications *in vitro* and *in vivo*. More specifically, we summarize the way to address the limitation on use of reconstituted lipoproteins by means of natural or recombinant apolipoproteins, as well as apolipoprotein mimetic molecules. Finally, we provide an overview of the advantages and disadvantages of these approaches and discuss future perspectives for clinical translation of these nanoparticles.

Keywords

lipoprotein; nanoparticle; drug delivery; receptor-mediated; apolipoprotein; mimetic peptide; HDL; LDL

1. Introduction

Part of the great promise of nanomedicine has been its potential to enhance delivery and activity of bioactive/imaging agents into relevant cell types *in vivo* in a manner that minimizes toxicity to patients by enhancing specificity of activity in target cells [1]. Certainly, the use of liposomal nanoparticles as delivery vehicles represents a seminal technique in nanomedicine. Indeed ongoing efforts to further develop these and other nanoparticles as delivery platforms remain the mainstay in the field [2]. Despite FDA approval and their application in the clinic, liposomal particles suffer from a number of

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shortcomings including low encapsulation efficiency, fast burst release of drugs, poor storage stability and lack of tunable triggers for drug release and extracellular release of payload [3–5]. Significant efforts have been devoted to modify liposomal particles so as to address these shortcomings and to find additional delivery tools for pharmaceutical agents [4]. In this regard, the use of lipoprotein based nanoparticles is currently being investigated as a viable alternative for enhancing drug delivery.

Lipoproteins are assemblies of proteins and lipids, and constitute the endogenous carriers that naturally exist in the body and are responsible for the transportation of cholesterol in the circulation to maintain the homeostatic balance [6]. The typical structure of lipoproteins is composed of a neutral lipid core, an outer shell of phospholipids and amphipathic apolipoproteins that confer water solubility and precise size control [7]. The structure of lipoproteins such as LDL had been assumed to be spherical. However, using high performance gel filtration chromatography (HPGC), Teerlink et al (2004) suggested that LDL may be in fact discoidal. In this analysis, researchers examined 160 LDL preparations and showed that diameters calculated from volume correlate poorly with diameters determined by HPGC [8]. Overall, lipoproteins are typically divided into four groups (based on factors such as size, density, buoyancy and the type of major apolipoproteins (Table 1). The subclasses of lipoproteins include Chylomicron, VLDL (very low density liprotein), LDL (small low density lipoprotein) and HDL [9].

Amphipathic apolipoproteins functions as structural components of lipoprotein particles. Apo B represents the structural apolipoprotein found in chylomicrons (Apo B-48), the atherogenic VLDL (ApoB-100) and LDL (ApoB-100). Apo B-48 (synthesized in gut) and Apo B-100 (synthesized in liver) are two isoforms of ApoB existed in the plasma. Either isoforms is responsible for the transport of lipids from the liver and/or gut to peripheral tissues. As each lipoprotein contains one ApoB molecule, it is possible to ascertain the total load of circulating atherogenic particles in the system [10]. Apo B-100 functions as a recognition signal for the cellular binding and internalization of LDL particles by the ApoB/E receptor [11]. The major apoliproprotein associated with anti-atherogenic HDL is primarily ApoA-I. Nevertheless other proteins (ApoA-II, ApoA-IV, ApoC (C-I, C-II, and C-III) and Apo E are also found associated with HDL [11] [12]. Further, HDL can be further subdivided into larger, less dense HDL2 or smaller, denser HDL3 according to particles' density, but most HDL in the body is found in the form of HDL3 [13]. ApoA-I is responsible for the reverse cholesterol transport from peripheral tissues back to the liver for catabolism [14]. Thus HDLs play relevant roles with respect to anti-inflammatory, antioxidant, and profibrinolytic activities, as well as cardiovascular disease, cancer, Alzheimer's and dementia [12, 15].

2. Rationale for the use of lipoproteins as delivery vehicles

2.1 Biocompatibility and favorable structure

Lipoproteins offer a number of advantages over other nanoparticles. First of all, lipoprotein nanoparticles are biocompatible and are thus both largely avoid detection by mononuclear phagocytic cells in the body's defense system and can be readily broken down and recycled by cells [1]. The natural structure of lipoproteins (lipophilic surface and hydrophobic

compartment) mediates their ability in functional delivery of hydrophobic triacylglycerols and cholesteryl esters[16], indicating their amiable potential for delivery of hydrophobic bioactive compounds (Figure). Their long blood circulation characteristics allow a favorable systemic drug delivery without the need of PEGylation [17]. The role of lipoproteins in drug delivery is further enhanced by their small size which allows superior penetration through interfibrillar openings in tumors.[5, 18, 19]. The size of these nanoparticles, however, is large enough to avoid rapid elimination by kidneys [20].

2.2 Receptor-mediated targeted delivery

The intracellular uptake of lipoproteins (either in the form of LDL and HDL) is governed by receptor-mediated interactions. The specificity of this uptake represents an additional advantage of lipoprotein based delivery vehicles by allowing targeted and discriminatory delivery of payloads to specific cell types of interest based on their expression of lipoprotein receptors. Indeed the presence of receptors for both LDL and HDL have been noted in a variety of cancer types [21–25], as well as in non-neoplastic diseases [26, 27]. For instance, Guo et al. (2011) has recently shown that the number of cells positive for LDLR expression in glioblastoma (GBM) tissue is significantly higher than that found in normal tissue (85% versus 29% for GBM and normal adjacent tissue respectively, $P<0.0001$). [28]. Similarly, using semi-quantitative RT-PCR, Chen and Hughes-Fulford (2001) showed that, unlike the case of normal fibroblasts, the levels of LDLR are not feedback regulated by addition of exogenous LDL in prostate cancer cells PC3 [25]. Similar use of this semi-quantitative RT-PCR approach has shown increased expression of LDLR in 7 out 11 tumor samples from colon cancer patients compared with paired normal colonic mucosa [29]. In the case of SR-BI, Leon et al. (2010) showed that increased expression in SR-BI (2 fold increase) in the progression in the progression to castration-resistance in the LNCaP xenograft model [30]. However, it should be noted that a number of normal tissues do show expression of lipoprotein receptors. This expression represents an important consideration as the use of LDL or HDL based nanoparticles may result in off-site toxicity.

The lipoprotein receptors can be functionally divided into two groups. Group 1 represents endocytic receptors such as LDL receptor (LDLR) and LDLR related proteins and scavenger receptor type A (SRAs) that bind lipid carrying lipoproteins and serve to facilitate lysosomal delivery. The second group is composed of receptors such as scavenger receptor type B member 1 (SR-BI; encoded by SCARB1 gene), scavenger receptor type B member 2 (SR-BII, encoded by SCARB2) and CD36 that mediate lipid exchange at the plasma membrane without cellular uptake of the protein component of the particle [31].

As the first lipoprotein receptor to be isolated and cloned [32], LDL receptor (LDLR) has served as the model to examine the role of intracellular trafficking, endocytosis and vesicle recycling [31]. In terms of structure, LDLR is closely related to the other members of the LDL receptor-related (LRP) family of proteins. These additional members include LRP1, LRP1b, megalin/LRP2, very low-density lipoprotein receptor, MEGF7/LRP4, and LRP8/ apolipoprotein E receptor 2 [33]. The function of LDLR has been primarily ascribed to mediate the regulation of cholesterol homeostasis by endocytosis of lipoproteins by means of the clathrin-dependent pathway [34]. Indeed, in terms of its activity, the LDL receptor

accounts for approximately two thirds of LDL clearance in the body [35]. A new perspective is slowly emerging that suggests that these receptors are further involved in a number of other physiological functions acting as signal transducers [33, 36]. Recent work by dos Santos et al (2014) suggested that LDL may also play a relevant role in breast cancer [37]. Their work showed that LDL-cholesterol but not HDL-cholesterol induces changes in gene expression and enhanced proliferation, migration and loss of adhesion in a number of breast cancer cell lines.

Acton et al. [38] were the first to provide evidence for SR-BI as a receptor for HDL. These studies identified the ability of this receptor to bind HDL and to selectively mediate cholesterol oleate uptake [38]. The SR-BI and HDL binding interaction is influenced by the relative content of ApoA-I versus ApoA-II in alpha HDL. In this regard, SR-BI shows greater affinity to ApoA-II-enriched particles but has reduced lipid uptake activity [39]. Beyond its binding to HDL, SR-BI can tightly bind phosphatidylserine (PS) and phosphatidylinositol (PI)-containing liposomes, but not phosphatidylcholine, phosphatidylethanolamine, or sphingomyelin liposomes [40]. Evidence provided by De La Llera-Moya et al. suggests that interaction between HDL and SR-BI serves to facilitate the bidirectional flux between HDL and plasma membrane by reorganization of lipids within cholesterol- and caveolae-rich domains within the plasma membrane [41]. Unlike SRAs, or LDLR which are located in clathrin-coated pits and that target internalized lipoproteins to lysosomes; SR-BI is found primarily in calveolae. This difference allows SR-BI to target internalized lipids into non-endosomal and non-lysosomal compartments [42–44] and thus mediate a more specific uptake than that mediated by LDLR [5]. The lipid transfer activity ascribed to SR-BI is suggested to occur via the formation of a hydrophobic channel through which cholesterol diffuses from the HDL particle into the plasma membrane [45].

SR-BI is expressed in a number of normal tissues including liver, adrenal and ocular and steroidogenic tissue, where its expression can be affected by a number of factors [46, 47]. In the liver parenchymal cells, for example, SR-BI expression is down-regulated by cholesterol and estradiol and up-regulated by polyunsaturated fatty acids [14]. Equally, the expression of SR-BI has been shown to be regulated by various transcription factors including HIF2 [48] and MITF [49]. Disease conditions have been also implicated in alterations of SR-BI expression. Qiu *et al*. have recently noted the up-regulation of SR-BI as well as caveolin in non-alcoholic fatty disease liver [26]. In addition, growing evidence links the expression of SR-BI with various cancer types. For instance, recent evidence suggests that SR-BI is a potential biomarker for nasopharyngeal carcinoma [50]. The high levels of SR-BI expression have also been noted in prostate, breast, colorectal and ovarian cancers [21–23]. In all these conditions the increased levels of SR-BI may serve to address the putative heightened cholesterol requirements by these cancer cells [22], thus being a potential target for cancer theranostics.

3. Development of lipoproteins delivery vehicles

The use of chylomicrons-like particles as delivery vehicles has been noted previously (see Rensen et al. for review [51]). Despite the fact that these preparations have been used to deliver a variety of agents to hepatocytes (e.g. antiviral analogues DNA fragments and pro-

drugs)[52–54], their applications in other conditions such as cancer remain limited [55]. The aforementioned expression of LDL and HDL receptors in various tumor types has driven more significant efforts to develop these lipoproteins as delivery vehicles for bioactive agents into cancer cells as well as other disease conditions.

As early as 1979, Krieger et al [56] successfully replaced the native core of LDL with cholesteryl linoleate suggesting that a similar approach could be used to incorporate hydrophobic compounds into LDL. Since then, a number of applications have made use of this lipoprotein both *in vivo* and *in vitro* (tables 2 and 3). While some studies have examined the use of LDL in atherosclerosis treatment (delivery of dexamethasone into macrophages to prevent transformation into foam cells [57]), the preponderance of efforts for LDL nanoparticles have been made with the aim of delivering agents into cancer cells (i.e. anticancer drugs; see table 2). However, a significant challenge in this regard is that the number of cancers that overexpress LDL receptors is limited.

The suitability of HDL particles as delivery vehicles was investigated by Kader et al. [58]. These early efforts showed that 5-fluorouracil (5-FU), 5-iododeoxyuridine (IUdR), doxorubicin (Dox) and vindesine could be successfully incorporated into both LDL and HDL resulting in lower IC50 and that uptake could be modulated by regulating the levels of lipoprotein receptors. A number of studies have now shown the applicability of HDL-like nanoparticles to deliver anticancer drugs (table 3). The application of these particles could extend potentially to other diseases conditions including cardiovascular diseases, Alzheimer's disease, Type II diabetes, stroke, as well as for antifungal and antiviral treatment [5]. In addition, the specific nature of cytosolic delivery mediated by the HDL receptor, SR-BI, may benefit the efficient delivery of siRNAs to enhance RNAi by circumventing the lysosomal pathway [59, 60]. The application of LDL nanoparticles for this purpose is more limited in that it requires the incorporation of endosomal disruption techniques in order to prevent siRNA degradation [61].

3.1 Native Lipoprotein

The use of native lipoproteins as part of nanoparticle delivery systems offers a number of significant advantages. Principally endogenous lipoproteins do not induce an immune response and are not recognized by the reticuloendothelial system (RES) [51]. Indeed, a number of reports show efficacy of drug loaded LDL particles *in vivo* and *in vitro*[62]. Others have shown loading of native LDL with, amongst others, photosenzitizers [63], nucleosides [64] and fluorescent imaging agents [65]. Despite these advantages, the use of native lipoproteins as components of delivery nanoparticles is hindered by a number of factors. In the case of LDL, for instance, it has been noted that its storage leads to natural aggregation of these molecules [66]. In addition, the use of native LDL or HDL is limited by difficulties in isolating procedures [66], loading of therapeutic agents [67] and concerns with respect to safety [68]. Similar concerns have been raised for the use of chylomicrons that are isolated from human lymph [69]. These challenges have limited the use of native chylomicrons, LDL and HDL lipoproteins as part of delivery nanoparticles [16, 58]. As a result, the focus of lipoprotein nanoparticles development has shifted towards the use of synthetic lipoproteins [70].

3.2 Synthetic reconstituted lipoproteins - an extension of biological approaches

Reconstituted lipoproteins are the most widely studied class of synthetic lipoproteins. Contrary to their native counterparts, which are directly isolated from human donors and applied as is, reconstituted lipoproteins are formed using isolated apolipoproteins (recombinant or naturally derived) combined with various lipids, natural or synthetic [5]. In general, a reconstituted lipoprotein contains one single type of apolipoprotein and one or a few defined lipid components. This offers several advantages over the native lipoprotein. First of all, since all components of the lipoprotein nanoparticle are known, they can be characterized individually to better understand the overall formulation. In addition, adjusting these individual components, such as lipid/protein stoichiometry, lipid type, and apolipoprotein choice, can control the nanoparticles to exhibit uniform physiochemical properties such as uniform size, zeta potential, core and surface loading, etc. Finally, these reconstituted lipoproteins possess and take advantage of the known functions ascribed to native lipoproteins, which includes natural targeting, enzyme/pathway activation, cellular uptake and lipid transfer.

However, the development of reconstituted lipoprotein-based formulations has been hindered by limited availability of apoliproteins (Apo B-100, ApoA-I and Apo E). This imposes significant challenges to the scalability of the manufacture of these particles [71]. The development of recombinant apolipoproteins has been one approach that has been pursued to address this limitation. This approach has been undertaken based on the close similarity between recombinant molecules and their native counterparts [51]. Law et al. successfully cloned human ApoB-100 into an expression vector thus resulting in the 560 amino acid sequence for this protein [72]. These and other efforts have utilized recombinant ApoB-100 to examine defining elements of its biology. For instance, Boren et al. [73] used recombinant wild-type and mutant ApoB-100 molecules to identify specific sequences that are relevant for its interaction with the LDL receptor. However, the use of recombinant ApoB-100 for the generation of LDL is limited owing to the large size of this molecule (over 4500 amino acids), as well as the poor water solubility of this molecule [70].

The use of recombinant Apo-AI, which is produced by means of bacterial, plant and yeast systems, has provided a partial solution to the limitations imposed by isolation of native Apo-AI. This advancement has enhanced the viability of HDL-type delivery vehicles [71, 74–76].

3.2.1 Reconstituted LDL—Early work by Walsh *et al*. [77] described a method for the reconstitution of LDL using ApoB solubilized from human plasma and its recombination with phospholipid using sodium deoxy-cholate. Subsequently, Ginsburg et al [78] reported a process for solubilizing ApoB of LDL with phospholipid/cholesterol ester microemulsions to generate reassembled LDL particles which exhibited many of the structural properties of native LDL (e.g. competition with human ^{125}I-LDL for binding to LDL receptor). Similar approaches have been described by Lundberg [79] which combined phosphatidylcholine, a hydrophobic drug (mustard carbamate) and Apo B-100 to successfully generate a 23-nm reconstituted LDL particle that was taken up by the LDL receptor of cultured fibroblasts. By the same token, Hirata et al. showed that the combination of LDL-like emulsions and

detergent solubilized ApoB-100 displayed a fractional CO clearance rate similar to that of LDL derived cholesteryl ester [80]. Early work showed that reconstituted LDL could be effectively loaded with a variety of agents including fluorescent probes [56], chemotherapeutic agents/cytotoxic drugs [67, 81, 82] and siRNA [83]. More recent work has highlighted the viability of reconstituted LDL as a vehicle for delivery of photodynamic and imaging agents. For instance, reconstituted LDL which has been loaded with bacteriochlorin e6 bisoleate (Bchl-BOA) or napthalocyanine has shown efficacy as a photodynamic therapy agent delivery system [84, 85]. In the case of Marrotta et al. [84] Bchl-BOA-LDL was able to mediate a delay in tumor regrowth in xenografts of human hepatoblastoma G2 (HepG2) tumors. Further work by Corbin et al. [86] showed successful incorporation of amphiphilic gadolinium (Gd)-diethylenetriaminepentaacetic acid chelates into LDL thus generating a novel magnetic resonance imaging contrast agent that retained similar diameter/surface charge and selective uptake as the native LDL particle. Similarly, Allijn *et al* [87] showed that incorporation of fluorescently labeled gold nanocrystals into LDLs created a CT and optical contrast agent that maintained the biological functions of native LDL both *in vitro* and *in vivo*.

As the LDL receptor also recognizes ApoE, an alternative approach has been the use of ApoE for the generation of LDL [51]. Vogel et al. [88] showed that recombinant and natural plasma ApoE bind equally well to LDL receptor and that both were cleared at similar rates from circulation. The incorporation of recombinant Apo-E into nanoparticles may facilitate a more specific uptake than that mediated by LDL [51]. Recombinant ApoE has been used in the generation of ApoE enriched liposomes to mimic LDL targeting of tumors cells and delivery of biological agents [69].

In addition to these applications, Zheng et al. [89] have demonstrated that LDL nanoparticles can be modified so as to target different receptors and cell types. In this work, the conjugation of folate to ApoB-100 was able to reroute folate-LDL particle towards cells expressing folate receptor (KB cells) and away from those expressing LDL receptor (HepG2), thus expanding the horizon of lipoproteins for targeting delivery.

3.2.2 Reconstituted HDL—Reconstituted HDL (rHDL) is manufactured in the form of nanodiscs or spherical nanoparticles through the self-assembly of isolated or recombinant ApoA-I or ApoE with a phospholipid/cholesteryl ester emulsion [90]. Cargos of the nanoparticle, whether encapsulated in the core or conjugated on the surface, can be either added directly into the emulsion or after particle formation. The resultant nanoparticle retains both the physiochemical properties as well as the biological functions of the native HDL. As a versatile drug delivery vehicle, cargos carried by the rHDL nanoparticle include a diverse range of chemotherapeutics, siRNAs, photosensitizers and imaging agents (Table 3). Its small size (~10 nm), natural targeting ability (SR-BI receptor), unique delivery pathway, simple surface chemistry, and ability to solubilize hydrophobic molecules make rHDL a favorable alternative delivery strategy compared with some of the current nanoparticles.

A good example of a versatile rHDL is the formulation developed by McConathy et al in 2008 [71]. This rHDL formulation, made from egg yolk PC, cholesterol, cholesteryl oleate

(CO) and recombinant ApoA-I, encapsulated paclitaxel (PTX) in its core. The resulting nanoparticle had flotation properties and size (11.4 nm) very similar to that of the native HDL. Studies demonstrated that rHDL delivery increased the effectiveness of PTX against ovarian, prostate and breast cancer cell lines *in vitro* and reduced the *in vivo* toxicity of PTX in C57/BL6 mice, where the weight loss of the animals did not reach 15% even with 100 mg/kg PTX dosage, compared to 15% weight loss reached with 30 mg/kg Taxol or 70 mg/kg Abraxane. In a follow up study in 2010 [91], Mooberry et al studied the biological mechanisms in which the rHDL delivered PTX is taken up into cancer cells. Through radiolabeling of the core contents (PTX and CO) of rHDL, *in vitro* cell uptake study showed that the CO and PTX had significantly higher cell uptake by SR-BI positive cells compared to SR-BI negative cells. In addition, competition studies demonstrated that 10-fold excess of rHDL or native HDL3 significantly inhibited the PTX uptake. These results validated that the rHDL delivery were indeed specifically mediated by the SR-BI protein. The authors also conjugated folic acid onto the rHDL surface and demonstrated the ability of the modified rHDL to target folic acid receptor. This shows that rerouting the rHDL nanoparticles to actively target a receptor other than SR-BI is entirely achievable. These rHDL were further explored in its potential to carry and deliver siRNAs for *in vivo* RNAi applications [92]. In this case, the siRNA was coupled to oligolysine peptides to achieve a neutralizing effect and was encapsulated in the core of the rHDL to achieve a robust loading of 4 mg siRNA/mL (>90% loading efficiency). More recently, this rHDL formulation has been extended to encapsulate retinoids for the treatment of neuroblastoma [93] and valrubicin to enhance its functionality in prostate and ovarian cancer cell lines [94].

Thaxton *et al* [95] developed an rHDL formulation that encapsulated 5 nm gold nanoparticles. The gold nanoparticles were first incubated with ApoA-I, after which disulfide and amine functionalized lipids (PDP PE and DPPC) were added to form the Au-rHDL. These nanoparticles mimicked the general size and structure of HDL, and were able to bind to cholesterol (Kd = 4 nM). A later study [96] showed that these Au-rHDLs were able to mimic the biological function of native HDLs, and delivered gold nanoparticles specifically through the SR-BI pathway, in which the cellular uptake of gold from Au-rHDL is three fold higher in SR-BI positive lymphoma cells (SUDHL-4) compared with SR-BI negative cells (Jurkat). These Au-rHDLs were also shown to be able to manipulate the cellular cholesterol flux in lymphoma cells. In addition, thesenanoparticles were found to adsorb antisense cholesterylated DNA and deliver them to human cells to regulate target gene expression [97].

rHDL nanodiscs, which are usually formed in the same manner as the spherical rHDLs but without cholesteryl ester, has also been studied for drug delivery. In 2011, Ghosh et al [98] developed an ApoA-I driven rHDL nanodisc formulation that incorporated and delivered curcumin, a bioactive molecule with poor absorption and low bioavailability when taken orally. The nanodiscs helped solubilize curcumin and enhanced its therapeutic effect through delivery [98, 99]. Specifically, in mantle cell lymphoma (MCL) cells, curcumin nanodiscs induced ~70% cell apoptosis, much higher compared to free curcumin (<20%) and empty nanodiscs (<10%). In addition, by using ApoE instead of ApoA-I on these nanodiscs, the delivery of curcumin to glioblastoma multiforme cells was significantly enhanced, as

evidenced by an over two fold increased curcumin internalization of these cells compared with ApoA-I nanodiscs and free curcumin [100]. Modification of the lipid component of the rHDL nanodisc can lead to some unique properties. Ng et al [101] has used porphyrin-lipid as the sole lipid component along with ApoA-I, ApoE3 or membrane scaffold protein 1E3D1 to develop an rHDL nanodisc formulation (10–30 nm in size). The resultant porphyrin nanodiscs have porphyrin's photoactivities highly quenched in the intact particles, but could efficiently restore the fluorescence and singlet oxygen generation when the nanostructure is disrupted. Therefore, porphyrin nanodiscs can be used not only as an activatable fluorescent imaging probe, but also as a smart photosensitizer in phototherapeutic applications. Recent work by Ghosh et al [102] demonstrated that by incorporating a synthetic cationic lipid (DMTAP) into the rHDL lipid component, researchers enabled the rHDL nanodisc (20–50 nm in size) to incorporate oligonucleotides (dsOligo) and siRNAs. . It was found that at 1:1 dsOligo:DMTAP charge ratio the dsOligo was completely loaded onto the nanopdiscs as determined by electrophoresis and ultracentrifugation. *In vitro* experiments showed that the nanodiscs carrying GAPDH specific siRNAs were able to reduce the GAPDH enzyme activity by 60% in HepG2 cells. Recently, Duivenvoorden *et al* [103] developed a rHDL disc formulation that incorporated simvastatin and delivered them to atherosclerotic plaques, one of the natural accumulation sites of HDL. MRI and optical imaging were used to determine the pharmacokinetics and biodistribution of the rHDL, achieved through co-loading of gadolinium and fluorescent dye labeled statin. Flow cytometry of the spleen cells demonstrated that the labeled rHDLs were mostly taken up by macrophages and Ly-6c^{hi} (Gr-1^{hi}) monocytes, and no toxic effects were observed in liver, kidney or myocytes for the rHDLs at a dose of 60 mg/kg statin. *In vivo* study demonstrated that a 3-month low dose statin-rHDL (15 mg/kg statin, bi-weekly infusion) treatment inhibited plague inflammation progression (27% decrease in total plaque area and 37% decrease in plaque macrophage content compared to daily oral statin treatment at 15 mg/kg statin), while a 1-week higher dose regimen (60 mg/kg statin, four infusions over one week) improved the efficacy further (36% decrease in total plaque area and 77% decrease in macrophage positive area compared to the low dose treatment).

In addition to above examples, rHDL has been used to deliver therapeutic agents for various other diseases. These include the delivery of fungicides [104], antimicrobial agents [105], viruses [106] and antivirals [107] in various cell and animal models. One potentially useful application of rHDL delivery is in the treatment of Alzheimer's disease (AD). It has been shown that low levels of HDL and impaired ApoE relates to increased risks of AD [108, 109]. To treat this problem, Song et al in 2014 [109] developed rHDL nanodiscs, formulated by phospholipid DMPC and ApoE3, that demonstrated high binding affinity to Amyloid-β (Aβ) (KD 5.88×10^{-9} M for binding to Aβ1-40 monomer, higher than ApoE3 alone, which was 3.06×10^{-9} M) as well as the ability to cross the blood-brain barrier (BBB) (0.4 %ID/g in the brain), thus resulting in the reduced memory loss in mice with AD. The authors concluded that the ability of the rHDL to cross the BBB is due to its small size (28 nm), which further validates the advantage of HDL delivery compared to larger size nanoparticles.

4. Lipoprotein-like nanoparticles using mimetic peptides

Although synthetic reconstituted lipoproteins extended the feasibility of lipoprotein delivery vehicles, the use of recombinant ApoB-100 or Apo-AI is still limited by the significant effort and time required for manufacturing relevant amounts of apolipoproteins, including the removal of the tag from the recombinant protein and performance of additional steps for the purification of the secreted protein (e.g. proApoA-I [76]). The other type of synthetic lipoproteins has been developed by employing peptides which mimic the functional properties of apolipoproteins to build lipoprotein-like nanoparticles. The major advantage of such synthetic lipoproteins is that they overcome several challenges faced by using apolipoproteins, such as their purity, quantity, length of process time, as well as their safety [5, 75]. As a result, the synthetic lipoproteins may significantly simplify the scaled-up manufacturing, as well as accelerate the clinical translation of the lipoprotein-based drug delivery. .

4.1 Synthetic-peptide-mimetic LDL-like nanoparticles

As discussed earlier, the use of ApoB-100 protein in synthetic LDL has encountered several difficulties owing to the size and complexity of the ApoB-100 protein [110]. Therefore, an alternative strategy for synthetic LDL is the use of ApoB-100 mimetic peptides. In 2002, Baillie et al [111] developed synthetic LDL (sLDL) formulations using lipid emulsions and four amphipathic peptides containing the ApoB receptor domain. *In vitro* cell proliferation assays using a lymphoma cell line demonstrated that the sLDLs behaved in a way that mimics the native LDL. It was observed that by utilizing different peptides, variable proliferation was achieved, which implied that the interaction with the LDLR can be controlled by varying peptide configurations.

The use of such synthetic LDLs as drug delivery vehicles was studied in 2007 by Nikanjam et al [112]. They developed a synthetic LDL formulation, termed nano-LDL, from microemulsions of phosphatidyl choline, triolein and cholesteryl oleate, as well as a 29-amino acid bifunctional peptide, which contained a lipid binding motif and the LDLRbinding domain of ApoB-100. This peptide is water soluble and readily binds to lipid emulsions in the manufacturing process. The nano-LDLs were sonicated and extruded to have a size of 10.5 nm. Through fluorescent labeling of the lipid and peptide moieties on the nano-LDL, it was shown through fluorescence microscopy that the nano-LDLs bound to the surface of glioblastoma multiforme (GBM) cells in a similar pattern as the plasma-derived LDLs. This binding was inhibited after the introduction of a LDL inhibitor, suramin, further confirming that the nano-LDLs bound specifically to LDLR. In addition, the peptide and the lipid components of these nano-LDLs were co-localized within the lysosome following particle internalization, which further validated the specific receptor mediated uptake of the nanoparticles. In a later study [81], paclitaxel oleate was incorporated into the core of these nano-LDLs (nLDL-PO). The optimal PO loading was found to be 6 % wt. of nano-LDL. *In vitro* GBM cell survival assay demonstrated high cell killing by nLDL-PO (90% cell death after 72 hours compared to less than 10% in PO alone at 10 uM PO dose), and was time, concentration, and cell line dependent. Again, the use of LDLR inhibitor, suramin, significantly decreased the cell killing by nLDL-PO, confirming that the naparticles

specifically utilized the LDL pathway. Overall, although such synthetic LDL as delivery vehicles hold great promise, more in-depth studies regarding the physiochemical properties of the nanoparticles are still necessary. The key-limiting issue of LDL aggregation with long term storage is likely to extend to synthetic LDLs. In recent years, the research interest in synthetic LDLs has really diminished. Table 2 presents some of the examples of synthetic LDL that have been studied as drug delivery vehicles over the past 15 years.

4.2 Synthetic Peptide mimetic HDL-like nanoparticles

As noted above, although recombinant ApoA-I has been made using bacterial expression systems, a number of challenges arise relating to their purity and quantity [75]. As risks of pathogen contamination in human-derived samples also limit the safe application of ApoA-I. As a result, complex steps must be employed to ensure the isolated ApoA-I is pathogen free [113]. To overcome these challenges, synthetic peptide analogs are utilized in the formulation process. These peptides are largely based on the amphipathic helical repeating structure of ApoA-I. Although they do not directly reflect the specific amino acid sequence of ApoA-I, their physiochemical properties resemble ApoA-I and the family of exchangeable apolipoproteins. These peptides, such as the widely investigated 18 amino acid 4F peptide, have been shown to have anti-inflammatory, anti-oxidant, anti-atherogenic and anti-tumour effects, and have been reviewed elsewhere [114–116].

The Zheng lab has developed a synthetic HDL-like nanoparticle using a synthetic ApoA-I mimetic peptide [117]. This nanoparticle, termed synthetic HDL-mimicking peptide phopholipid scaffold (HPPS), was formulated through self-assembling interactions between the ApoA-I mimetic peptide, phospholipid, and cholesteryl ester. Same as HDL, with no addition of cholesteryl esters or other hydrophobic cargo, the HPPS took form of nanodiscs, while after cargo incorporation the HPPS were spherical nanoparticles of 10–15 nm in size. Through incorporation of a hydrophobic dye (DiR-BOA) in its core and fluorescently labeling the phospholipid or peptide, confocal microscopy demonstrated that the DiR-BOA fluorescence intensity was 55 fold higher in SR-BI positive cells versus SR-BI negative cells, and 98% of the intensity was inhibited by the introduction of native HDL. Furthermore, in SR-BI positive cells, the phospholipid and peptide were found to be retained on the cell surface while the DiR-BOA was mostly found in the cell cytosol and not in lysosomes, as evidenced by non-co-localization of DiR-BOA signal with that of LysoTracker, as well as a subcellular fractionation study. This demonstrated that the HPPS exhibits properties and a delivery mechanism that is SR-BI dependent, mimicking that of the native HDL. Additional *in vivo* study using mice bearing subcutaneous SR-BI positive (KB) and negative (HT1080) tumors demonstrated that the HPPS preferentially accumulated in the SR-BI positive tumors (3.8 fold higher fluorescence intensity in KB versus HT1080), and this accumulation was evident at 72 hours post injection. The delivery mechanism of HPPS were further investigated in depth in a recent study [59], which validated the HDL mimicking ability of the HPPS, and enhanced the understanding of HDL delivery pathway. In this study, through fluorescent labeling of the components of the HPPS, it was found that HPPS specifically recognized and bound to SR-BI receptor. Through interactions with SR-BI after binding, the fluorescent cargo carried inside the HPPS were transported directly into the cell cytosol without entire HPPS internalization. Such cytosolic transport pathway was

also found to be independent of temperature and energy, and was significantly inhibited by disruption of lipid rafts using filipin or methyl-β-cyclodextrin. The authors concluded that this cytosolic delivery predominately mediated through a lipid rafts/caveolae-like pathway.

Based on their HDL-mimicking abilities and good stability, HPPS has been studied as an efficient delivery vehicle carrying chemotherapeutics, siRNAs, and imaging contrast agents to tumour sites and into tumour cells [17, 18, 59, 60, 117–119]. In an in vivo study [118], HPPS carrying paclitaxel-oleate were shown to be able to significantly reduce the toxicity of paclitaxel to non-malignant cells, thus resulting in selective cytotoxicity towards cancer cells. HPPS delivery of siRNA has also shown good efficacy in delivery siRNA into tumor cells to knock down the target oncogene in vivo [17, 60, 119]. In this case, the sense strand of the siRNA was conjugated with cholesterol, which was inserted into the phospholipid monolayer and served as an anchor to hold the siRNA on the HPPS surface. The cytosolic delivery of siRNA through HDL-mimicking provided a crucial alternative to conventional endocytosis, and prevented the endosomal degradation of the siRNAs [120]. Loading of siRNAs onto HPPS also improved its *in vivo* circulation half-life from 0.95 hour to 3.9 hours, and enhanced its distribution in tumours [119]. However, it should be noted that the half-life of the HPPS core load has been reported to be 15 hours [117], suggesting that the siRNAs likely dissociated from the HPPS in circulation. *In vivo* efficacy studies [17, 119] have demonstrated that HPPS delivered bcl2 specific siRNA achieved over 40% knock down of the bcl2 gene in a KB subcutaneous tumour model as well as an orthotopic PC3 prostate tumour model, which in turn resulted in significantly slower tumour growth (42% KB tumour volume increase versus 200–300% in controls) and higher cell apoptosis (40% in KB tumour versus 5–16% in controls).

Marrache et al [121] have also developed a synthetic HDL formulation to detect the vulnerable plaques by targeting the collapse of mitochondrial membrane potential that occurs during apoptosis. The synthetic HDL encapsulated diagnostically active quantum dots (QD) for optical imaging. These nanoparticles are much larger than native HDLs, with hydrodynamic diameters of 100–200 nm, in which the authors determined to be the optimum formulation for mitochondria targeting. The encapsulation efficiency of the QD was 70–80%. These nanoparticles exhibited a half-life of 72 hours *in vivo*, and showed good stability (stable in serum for 7 days), nontoxic (less than 10% cell killing *in vitro*), and nonimmunogenic (no secretion of IL-6 and TNF-α after incubation with macrophages) properties. Confocal microscopy and flow cytometry both demonstrated that the targeted nanoparticles were able to detect apoptotic macrophages (increase in nanoparticle fluorescent intensity inside apoptotic macrophages).

In addition to oncology, synthetic HDLs using mimetic peptides also have the potential to play a vital part in the treatment of Alzheimer’s disease. One study demonstrated that orally administered ApoA-I mimetic peptide D4F can bind amyloid-β (Aβ) in the brain and form aggregates to reduce the amyloid burden and improve cognitive function [122]. Therefore, using D4F synthetic HDLs, one could improve the bioavailability of the peptide for the CNS disease treatment.

Overall, synthetic HDLs present an attractive strategy in drug delivery vehicles. Some recent synthetic HDL drug delivery vehicles have been summarized in Table 3.

5. Future Perspective

The application of synthetic lipoproteins as delivery vehicles for various molecules and agents has been diverse, ranging from delivering chemotherapeutics, antiviral and antifungal agents, to siRNAs and imaging agents. These applications offer great potential in the translation of the synthetic lipoproteins into the clinical setting. Currently, the most widely used area for synthetic lipoproteins has been in oncology, where the development of these nanoparticles has taken advantage of the overexpression of receptors for these lipoproteins in cancer cells (e.g. LDLR and SR-BI). In a number of instances, the early stages of elucidating the efficacy of these particles has been performed with the aid of cancer cell lines that either show natural or genetically-induced overexpression of these receptors. A significant question that remains to be addressed, and which could influence the applicability of lipoproteins in cancer treatment, is whether these cell lines faithfully represent the levels of expression in the clinic. Efforts are now underway to pursue such studies using large clinical tissue microarrays from various tumour types. In this regard, the aim is to determine the extent of receptor overexpression, whether this is homogenous throughout the tumor, and whether levels of these receptors vary between different stages of cancer (e.g. primary tumor versus metastatic disease). This strategy provides a screening tool for the types of tumor that can be preferentially treated by lipoprotein-like nanoparticles. Cancer patients with these types of tumor can be further screened individually to determine the pretreatment expression level of these receptors, enabling the potential to maximize the treatment efficacy in high SR-BI expressing cancer patients.

Currently there is little research examining exchanges between artificial and endogenous lipoproteins. As the development of lipoprotein nanoparticles becomes more prevalent, it will be important to determine the extent to this potential exchange could affect biodistribution and efficacy of these particles.

An additional challenge is that LDLR and SR-BI are also highly expressed in normal tissues (e.g. SR-BI in liver and adrenal glands) such that delivery of cytotoxic agents by these nanoparticles may result in damage to these tissues. This undesired effect could be circumvented by the use of agents that specifically target relevant molecules in tumor cells. This could be achieved, for instance, by the delivery of siRNAs for mutant genes that play a significant role in tumor cell growth/survival (e.g. BRAF V600E in melanoma). Alternatively, additional targeting moieties can be added to the synthetic lipoproteins (21), rerouting them to preferentially reach specific tumor cells or diseased sites, and thereby personalizing the treatment. Lastly, in order to increase the relevance of LDL and HDL nanoparticles as a tool for treatment of cancer in the clinic, it is also essential to conduct extensive preclinical examination of their efficacy against advanced metastatic disease, which is the typical presentation of patients in clinical trials.

It is important to note that lipoproteins represent only one class of lipid-based nanoparticles in development. Liposomes, for instance, have shown significant advances both as delivery

and diagnostic tools [123, 124] and indeed represent the nano-vehicles further along in clinical application [125, 126]. Additional advances have been achieved in the use of porphysomes (nanoparticles formed by self-assembly of porphyrin and lipid conjugates) as tools for novel therapeutic approaches [127, 128]. All experience gained from these nanoparticles development can be employed for developing advanced lipoprotein delivery system.

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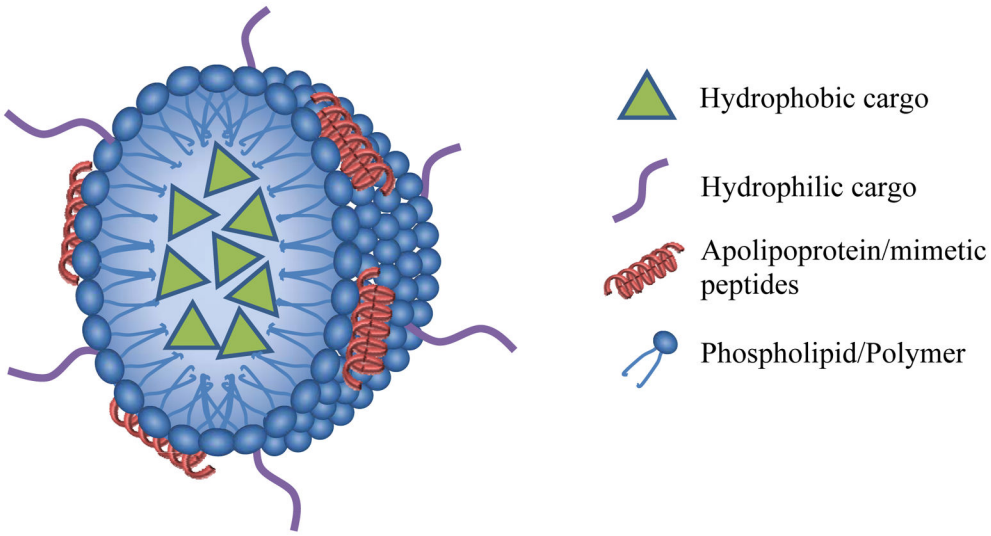

Figure.

The schematic (not drawn to scale) of a lipoprotein drug delivery vehicle. As depicted, it has the ability to carry both hydrophobic molecules through encapsulation in the core, and hydrophilic molecules through conjugation/insertion on its surface.

Table 1

Characteristics that define lipoproteins. Adapted from [129, 130]

	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 (X 10^6 Da)	400	10–80	2.3	0.17–0.36
size	75–1200 nm	30–80 nm	25–35 nm	8–12 nm
source	Gut	liver	VLDL via ILDL	Gut, liver
Half-life§	5–13 min	2–5 min	15 hr	11–12 hr
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
	B48	B100	B100	
	C-I, C-II, C-II	C-I, C-II, C-II		C-I, C-II, C-II
	E	E		E

*Diameter of nanoparticle based on spherical shape

§half-life of lipoproteins in rats [131, 132] [120, 133]

Table 2

Examples of synthetic LDL nanoparticles

Name	Lipid component	Lipoprotein component	Cargo	Target	Ref
Nano-LDL	PC Triolein	ApoB mimetic peptide	Paclitaxel oleate	Glioblastoma multiforme cells	[81]
sLDL	Egg yolk PC Triolein Cholesteryl Oleate	ApoB mimetic peptides		Lymphoma cell line	[111]
rLDL	Extracted LDL Trolein	ApoB	Bacteriochlorin e6 bisoleate	PDT in human liver subcutaneous tumor xenografts	[84]
(rITG) LDL	Extracted LDL Trolein	ApoB	Poly-iodinated triglyceride	Liver cancer cells	[134]
LDL/dextran	Extracted LDL Dextran	ApoB	Hypericin	Human glioma cell line	[135]
Au-LDL	LDL	ApoB	Au-MHPC	CT and optical imaging in subcutaneous tumor xenografts	[87]

Table 3

Recent studies that utilized synthetic HDL nanoparticles for the delivery of chemotherapeutic agents, siRNAs, nanoparticles, and imaging agents.

Name	Lipid component	Protein component	Cargo	Target/model	References
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	[17, 60, 118, 119]
sHDL	POPC	L37pA and D37pA ApoA-I mimetic peptides	CO	Human umbilical vein endothelial cells I/R injury rat heart model	[136]
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	[121]
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	[71, 91–94]
HDL-NP	PDP PE DPPC	ApoA-I	5nm gold nanoparticles Antisense cholesterylated DNA	Lymphoma cell lines Human cells	[95–97]
V156K- rHDL	POPC Cholesterol	ApoA-I	Rapamycin	Human monocyte cell line Human dermal fibroblasts Zebra fish model	[104]
rHDL/Chol-siRNA	Soybean PC Cholesterol Cholesteryl ester	ApoA-I	Cholesterol conjugated siRNA	Liver cancer cell line Human liver subcutaneous tumor Xenograft	[137]
TA-rHDL	Glycerol trioleate Cholesterol, CO	ApoA-I	Tanshinone IIA	Mouse macrophage cell line	[138, 139]
GBCA-HDL		ApoA-I Synthetic peptide	GBCA (MR contrast agent)	Macrophages ApoE-deficient mouse model of atherosclerosis	[140]
rHDL nanodiscs	DMPC	ApoE3-NT	Curcumin	Construct bearing LDLR ligand binding domains	[141]
rHDL nanodiscs	DMPC	ApoA-I	Curcumin	Human hepatocellular carcinoma cell line Mantle cell lymphoma cells	[98, 99]
rHDL nanodiscs	DMPC	ApoA-I ApoE	Curcumin	glioblastoma multiforme cells	[100]
Cationic rHDL nanodiscs	DMPC Glycerophospholipid DMTAP (cationic)	ApoA-I	siRNA	Hepatoma cells	[102]

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Name	Lipid component	Protein component	Cargo	Target/model	References
rHDL nanodiscs	Pyropheophorbide-conjugated lipid	ApoA-I ApoE3	Pyro	SR-BI over-expressing cell line (photosensitization)	[101]
[S]-rHDL	Lyso PC DMPC	ApoA-I	Simvastatin	atherosclerotic plaques in Apo-E knockout mice	[103]