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A high-density lipoprotein-mediated drug delivery system☆

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ABSTRACT

High-density lipoprotein (HDL) is a comparatively dense and small lipoprotein that can carry lipids as a multifunctional aggregate in plasma. Several studies have shown that increasing the levels or improving the functionality of HDL is a promising target for treating a wide variety of diseases. Among lipoproteins, HDL particles possess unique physicochemical properties, including naturally synthesized physiological components, amphipathic apolipoproteins, lipid-loading and hydrophobic agent-incorporating characteristics, specific protein–protein interactions, heterogeneity, nanoparticles, and smaller size. Recently, the feasibility and superiority of using HDL particles as drug delivery vehicles have been of great interest. In this review, we summarize the structure, constituents, biogenesis, remodeling, and reconstitution of HDL drug delivery systems, focusing on their delivery capability, characteristics, applications, manufacturing, and drug-loading and drug-targeting characteristics. Finally, the future prospects are presented regarding the clinical application and challenges of using HDL as a pharmacodelivery carrier.

Contents

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1. Introduction

Lipoproteins are macromolecular compounds composed of diverse proteins and lipids, and they are found in mammals. Impaired lipoprotein metabolism leads to many disorders, including familial hypercholesterolemia, atherosclerosis (AS), diabetes, obesity, cancer, and infectious diseases. In humans, lipoprotein metabolism comprises two interconnected pathways. In the first pathway, apolipoprotein B (apoB)-containing lipoproteins deliver lipids, mainly triglycerides (TGs) and cholesterol, from the intestine and liver to other tissues. Excess levels of apoB-containing lipoproteins can lead to the deposition of cholesterol on vessel walls or in peripheral tissues and the development of a number of diseases. A classic example is AS, which is one of the most common cardiovascular diseases (CVDs) and the major pathology contributing to CVDs. By contrast, another pathway within lipoprotein metabolism uses high-density lipoprotein (HDL), which removes excessive cholesterol from peripheral tissues and transports it to the liver for secretion through a process known as reverse cholesterol transport (RCT) [1]. Moreover, HDL can also exert other protective effects, such as antioxidative, anti-inflammatory, antiapoptotic, and anti-infective activities. It also suppresses the production of reactive oxygen species (ROS) and intracellular oxidative stress [2,3].

Many epidemiological studies have shown an inverse and independent correlation between the level of HDL and the risk of CVD [4–6]. Low levels of HDL have been widely recognized as improving predictions related to the development of CVD events [7,8]. In addition, obesity is the clearest determinant of decreased HDL levels. The increased storage of body fat has an adverse impact on the concentration of HDL-cholesterol (HDL-C), suggesting that the HDL levels are closely associated with the degree of obesity and the distribution of adipose tissue [9–11]. Small and dense HDL particles are more prevalent in metabolic syndromes, such as type 2 diabetes (T2D), indicating that aberrant changes in HDL size are associated with these conditions [12,13]. In addition to its role in CVD, HDL-C may be a significant biomarker for many other diseases, such as psoriasis [14], rheumatoid arthritis [15], and liver fibrosis [16]. Emerging evidence has revealed that HDL also plays a role in cancer development. A low level of HDL-C is a risk factor for diverse categories of cancer, including breast cancer [17,18] and gastric cancer [19].

Hence, HDL is known as the "good" cholesterol, and strategies that increase HDL levels or improve its functions are potential treatment methods for a diverse range of diseases. Therefore, because of the various functions of HDL, techniques involving the use of HDL-targeted therapies to treat people with CVDs, inflammatory diseases, and some other diseases have been extensively studied. For example, reconstituted HDL (rHDL) is a promising new potential therapy for acute coronary syndrome (ACS) [20,21] with significant antidiabetic effects in addition to reducing platelet aggregation and thrombus formation [22,23]. Synthetic HDL-mimicking nanoparticles (HDL-NPs) are characterized by a controlled conjugate size and specific spherical shape. The chemical components on the surface of biomimetic HDL-NPs are assembled to resemble natural HDLs, thus serving as promising therapeutic targets for cancer, CVD, and immune diseases [20,24–26]. In this respect, many HDL mimetics have also been investigated in animal models of AS and in early-stage clinical trials [27,28].

HDL plays an essential role in RCT and plasma lipid transport. HDL metabolism begins with apolipoprotein A-I (apoA-I), which is synthesized de novo in the liver and small intestine. The initial cholesterol uptake, during which nascent HDL acquires peripheral tissue cholesterol, involves an interaction with apoA-I and adenosine triphosphate (ATP)-binding cassette transport protein A1 (ABCA1) in macrophages. The transfer of cholesterol results in the formation of nascent discoidal HDL particles. The free cholesterol (FC) is then esterified by lecithin–cholesterol acyltransferase (LCAT), which is synthesized in the liver. The cholesterol esters (CEs) that are formed by LCAT are internalized into the hydrophobic core of HDL particles, where they form larger spherical HDL particles as the uptake of FC progressively increases. When cholesterol-rich HDL particles are transported to the liver, they bind to the scavenger receptor class B type I (SR-BI), and the CE in HDL particles is absorbed by hepatic cells through caveolins. The cholesterol is then eliminated as bile acids via secretion into the bile in the liver.

Because of their unique properties, HDL particles have been explored for their use as a vehicle for drug delivery. It has been widely demonstrated that HDL can combine with hydrophobic drugs, which it incorporates into its phospholipid core to promote effective delivery [29–31]. Damiano et al. suggested that templated HDL-NPs are effective as potential therapies and molecular drug delivery systems [32]. Moreover, HDL can selectively deliver anticancer agents when used in cancer therapies [33]. Thus, because of the wide range of applications of HDLs as drug delivery systems and therapeutic vehicles, we discuss the current knowledge of HDLs, focusing on their structures, constituents, biogenesis and remodeling, and their drug delivery and drug-targeting capabilities.

2. Structure, constituents, biogenesis, and remodeling of HDL

The predominant function of lipoproteins is to transport lipids throughout the body. Lipoproteins are rich in various types of proteins, lipids, and apolipoproteins. Furthermore, they are composed of polar and nonpolar lipids that can be solubilized by apolipoproteins.

2.1. Structure of HDL

Compared with other lipoproteins, HDL is a comparatively dense and small lipoprotein, and its structure is mainly dependent on the availability of its apolipoprotein [34]. The main component of HDL is apoA-I, which represents nearly 70% of the protein content of HDL [20,35]. Based on differences in the compositions of HDL particles, this group of lipoproteins can be generally classified as follows: lipid-rich spherical HDLs, lipid-poor discoid HDLs, and lipid-free apoA-I.

ApoA-I is a 28-kDa protein synthesized in the intestines and liver, from which it is released in a lipid-free state. The structure of apoA-I includes some amphipathic alpha-helices (Fig. 1A). apoA-I combines with lipids, the composition of which determines the final size and shape of HDL. Because the protein contains segments with polar and nonpolar surfaces, lipid-free apoA-I possesses both positive and negative charges and is highly solvent exposed [36,37]. The crystal structure of human apoA-I, at a resolution of 2.4 Å, shows that apoA-I contains an N-terminal four-helix bundle [37]. In addition, two alpha-helices are present in the C-terminus of lipid-free apoA-I, and these structures form a hairpin-like domain that allows apoA-I to interact with other molecules [37].

Discoid lipid-poor HDLs comprise two ring-shaped apoA-I molecules (Fig. 1B). The main components of discoid HDLs are apolipoproteins, which can efficiently solubilize phospholipids [36]. In discoid HDLs, the hydrophobic surfaces of apoA-I can interact with the aliphatic regions of lipids. Currently, it is widely accepted that apoA-I possesses double belts [38–41] (Fig. 1C), which are two ring-shaped molecules in apoA-I. One of these structures is at the top, and the other at the bottom, which wraps around a patch of phospholipid bilayer. In the double-belt model, two apoA-I molecules are located, each on its own leaflet, in an antiparallel orientation. The double-belt model proposes that the amphipathic helices of apoA-I in their central region arrange themselves into an antiparallel "double belt" with a helix 5 to 5 registry [36,38].

Spherical HDL particles are the dominant HDL form in human plasma. In spherical HDLs, the amphipathic helices of apoA-I are situated on the surface of the molecule. The hydrophilic faces of apoA-I can therefore interact with the aqueous phase, whereas the hydrophobic faces combine with lipids [36]. In spherical particles, apoA-I also serves as an organizing scaffold responsible for maintaining a stable lipid structure (Fig. 1D).