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ORIGINAL RESEARCH ARTICLE

Lipoproteins within the lymphatic system: Insights into health, disease, and therapeutic implications

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ABSTRACT

This analysis of contemporary findings aims to enhance our understanding of lipoprotein biology within the lymphatic system and its relevance to human health and disease. It delves into the complex interrelationship between lipoproteins and the lymphatic system, encompassing their diverse classes and pivotal roles in the absorption and transport of drugs, vitamins, and xenobiotics. Lipoproteins consist of a hydrophobic core comprising non-polar lipids and a hydrophilic membrane composed of phospholipids, free cholesterol, and apolipoproteins. The lymphatic system collaborates with lipoproteins in the absorption and transport of dietary lipids. Simultaneously, it plays a vital role in the regulation of body fluid levels and acts as a formidable defense mechanism against infections. Lipoprotein classes encompass chylomicrons, chylomicron remnants, very low-density lipoproteins, intermediate density lipoproteins, low-density lipoproteins, high-density lipoproteins, and lipoprotein (a). Understanding the intricate relationship between lipoproteins and the lymphatic system holds immense implications for comprehending the underlying pathological processes of various diseases such as atherosclerosis, diabetes and obesity among others. By shedding light on the interplay between lipoproteins and the lymphatic system, this report underscores the significance of conducting research that contributes to the advancement of our knowledge in this field. Ultimately, such research paves the way for potential therapeutic interventions and novel strategies to address numerous disorders.

Keywords: lymphatic; lipoproteins; chylomicrons; drug delivery; pathophysiology

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1. Introduction

Lipoproteins are complex particles that consist of a hydrophobic core of non-polar lipids surrounded by a hydrophilic membrane made up of phospholipids, free cholesterol, and apolipoproteins[1]. These lipoproteins are responsible for various functions such as the absorption and transport of dietary lipids, the transport of lipids from the liver to peripheral tissues, and the reverse transport of lipids from peripheral tissues to the liver and intestine. They also play a role in removing toxic compounds such as bacterial endotoxin from areas of infection[1–5]. The lymphatic system works in conjunction with lipoproteins to absorb and transport dietary lipids. Additionally, it plays a vital role in regulating body fluid levels, maintaining the balance of fluids throughout the body. Furthermore, the lymphatic system contributes to the body's defense against infections[6]. The relationship between lipoproteins and the lymphatic system have significant implications for the pathophysiology of various diseases.

2. Lipoprotein classes

Plasma lipoproteins are classified into seven classes based on size, lipid composition, and apolipoproteins. These include chylomicrons, chylomicron remnants, very low-density lipoproteins (VLDL), VLDL remnants which are termed intermediate density lipoproteins (IDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL), and lipoprotein (a) (Lp (a))[4]. Some recognize only four to five main categories, including chylomicrons, LDL, VLDL, HDL, or chylomicrons, VLDL, IDL, LDL, and HDL, respectively, with the rest being grouped under these categories (chylomicron remnants with chylomicrons, and Lp (a) with LDL)[7–9] (**Figure 1** and **Table 1**). NMR continues to be commonly employed for structure elucidation and quantification of chemical mixtures. However, its exceptional sensitivity to the size and density of macromolecules made it highly valuable in the subclassification of major lipoproteins[10].

Table 1 summarizes the composition of the main lipoproteins categorized based on their buoyant densities.

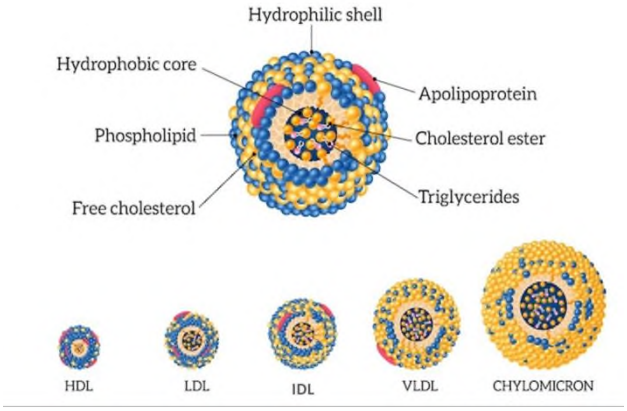

Figure 1. Structure of different lipoprotein classes.
* HDL: high-density lipoprotein; LDL: low-density lipoprotein; IDL: intermediate-density lipoprotein; and VLDL: very low-density lipoprotein.

Table 1. Properties (density and size) and major components of main lipoprotein classes.

Lipoprotein	Density (g/ml)	Size (nm)	Major lipids	Major apoproteins
Chylomicrons	<0.930	75–1200	Triglycerides	Apo B-48, Apo C, Apo E, Apo A-I, A-II, A-IV
VLDL	0.930–1.006	30–80	Triglycerides	Apo B-100, Apo E, Apo C
IDL	1.006–1.019	25–35	Triglycerides cholesterol	Apo B-100, Apo E, Apo C
LDL	1.019–1.063	18–25	Cholesterol	Apo B-100
HDL	1.063–1.210	5–12	Cholesterol phospholipids	Apo A-I, Apo A-II, Apo C, Apo E

3. Role of various lipoproteins in transporting drugs, vitamins, and xenobiotics

Lipoproteins, such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL), play a role in transporting various drugs, vitamins, and xenobiotics within the lymphatic system[11,12]. Cholesterol is a component of all lipoproteins and is transported within the lymphatic system to and from cells and tissues by LDL and HDL, respectively[13]. Fat-soluble vitamins, including A, D, E, and K, are transported within the lymphatic system in association with lipoproteins such as LDL and HDL[11]. Some xenobiotics, such as polychlorinated biphenyls (PCBs) and dioxins, are lipophilic and are transported within the lymphatic system in association with lipoproteins such as LDL and HDL[14]. However, not all drugs, vitamins, and xenobiotics are transported in the same way within the lymphatic system, and the extent to which they bind to and are

transported by lipoproteins can vary. The presence of these substances in the lymphatic system can also impact its functioning and overall health.

Chylomicrons, also known as cyclic lipoproteins, play a pivotal role in transporting dietary lipids, such as triglycerides and cholesterol, from the small intestine to various parts of the body. They also facilitate the absorption of fat-soluble vitamins, including A, D, E, and K[6]. Notably, chylomicrons are crucial for drug absorption since they have the ability to transport lipophilic drugs that would otherwise have poor absorption through the gastrointestinal tract. Lipophilic drugs, characterized by their ability to dissolve in lipids, can be absorbed through the same mechanisms as dietary lipids[15].

When lipophilic drugs are ingested, they become incorporated into chylomicron particles during their formation in the intestinal cells. Subsequently, these chylomicrons enter the lymphatic system and are transported to the bloodstream, facilitating the distribution of drugs to target tissues[15,16].

The absorption of drugs via chylomicrons can be influenced by various factors, including the size of the chylomicron particles, the drug dosage, and the dietary lipid intake[6,17]. The size of chylomicron particles can impact the rate and extent of drug absorption. Larger particles are typically cleared more slowly from the lymphatic system, leading to prolonged drug exposure and potentially higher bioavailability. Additionally, the dosage of the drug can affect its absorption through chylomicrons. Higher doses may saturate the transport capacity of chylomicrons, resulting in lower absorption rates and potentially increased variability in drug exposure. Furthermore, an individual's dietary lipid intake can influence drug absorption via chylomicrons. Consuming a high-fat meal can enhance chylomicron formation, thereby increasing drug absorption. Conversely, a low-fat meal may reduce chylomicron formation and subsequently decrease drug absorption[18]. Therefore, understanding the role of chylomicrons in drug absorption is crucial for optimizing drug delivery and improving therapeutic outcomes.

4. Role of chylomicrons in drug absorption

Chylomicrons are large lipoproteins that are rich in triglycerides and are formed in the intestinal cells or enterocytes from dietary lipids. The main structural protein in chylomicrons is apolipoprotein 48, although some enterocytes also form Apo B-100 chylomicrons. Other apolipoproteins that can associate with chylomicrons include A-I, A-II, A-IV, C-I, C-II, C-III, and E[4,15,16,19].

Triglycerides from food are hydrolyzed into free fatty acids (FFA), diglycerides (DG), and 2-monoglycerides (2-MG) as they pass through the gastrointestinal tract and reach the small intestine. In enterocytes, these hydrolysis products are re-esterified and packaged into chylomicrons[17,18]. The formation of chylomicrons begins in the endoplasmic reticulum (ER), where Apo B-48 is transported across the ER membrane by the microsomal triacylglycerol transport protein (MTP). In the ER lumen, Apo B-48 associates with phospholipids, mainly phosphatidylcholine (PC), and some TAG to form pre-chylomicrons, which are then transported to the Golgi apparatus for glycosylation and association with other apolipoproteins. The transport vesicles then bud off from the Golgi apparatus and fuse with the basolateral membrane of enterocytes to release the chylomicrons into the lamina propria[9,19–21]. The intestinal lymphatic capillaries take up chylomicrons and deliver them to the venous circulation via the thoracic duct[18].

Chylomicrons play a crucial role in delivering nutrients to muscles and adipose tissues, facilitated by their interaction with lipoprotein lipase (LPL). This enzyme, found in muscle and adipocytes is anchored to the capillary endothelium near these tissues. The activation of LPL relies on Apo C-II, which is present on the surface of chylomicrons. When activated, LPL hydrolyzes the triglycerides in chylomicrons, breaking them down into free fatty acids that can be taken up by adjacent muscle cells and adipocytes for energy or storage[22,23]. Additionally, some of the free fatty acids released from chylomicrons bind to albumin and are transported to other tissues[23].

As the triglycerides in chylomicrons are hydrolyzed by LPL, the chylomicrons reduce in size and transform into chylomicron remnants. During this process, these remnants acquire Apo E and transfer their apolipoproteins, including Apo A and Apo C, to other lipoproteins, mainly HDL. The transfer of Apo C-II from chylomicrons to HDL decreases the ability of LPL to further break down triglycerides. However, it's essential to note that another apolipoprotein, Apo C-III, plays a significant role in regulating lipid metabolism by inhibiting LPL's action. Apo C-III acts as a potent inhibitor of LPL activity, resulting in reduced hydrolysis of triglycerides in chylomicrons and other lipoprotein particles. Consequently, this inhibition leads to impaired lipolysis and delays the clearance of chylomicron remnants from the circulation[23–25].

Moreover, Apo C-III's interference goes beyond LPL inhibition. It also affects another critical process in lipoprotein clearance, which involves Apo E. Apo E is essential for the uptake of chylomicron remnants by the liver, achieved through interactions with specific receptors on hepatocytes. However, Apo C-III can compete with Apo E for binding to lipoprotein particles, reducing the availability of Apo E and subsequently interfering with efficient lipoprotein clearance[24]. The chylomicron remnants, with Apo E still present, bind to various hepatic receptors, including the LDL receptor, LRP, and syndecan-4, and are taken up by hepatocytes. The cholesterol in these particles is then used by hepatocytes to produce VLDL, bile acids, or secreted into the intestine with bile[4,25–27]. As we have explored the essential role of lipoproteins, especially chylomicrons, in facilitating the delivery of drugs from the small intestine through the lymphatic system to the bloodstream, it becomes imperative to further investigate the relationship between lymphatic conduits and lipoproteins in the context of how these conduits influence lipoprotein dynamics and their potential applications in therapeutics. By shedding light on these mechanisms, we can uncover valuable insights that enable us to optimize lipoprotein-based drug delivery systems and identify new therapeutic targets.

5. The impact of lymphatic conduits on lipoprotein dynamics and therapeutic potential

The role of lymphatic conduits in maintaining fluid balance is crucial as they drain excess interstitial fluid from the body back into the bloodstream. These conduits also serve as the entry point for different macromolecules, including lipoproteins, on their journey to the bloodstream. Recent studies have highlighted the significance of the lymphatic journey of lipoproteins, which has a direct impact on various physiological processes[18,28]. For example, acute exposure to low-density lipoprotein (LDL) has been linked to an increase in the frequency of contraction of collecting lymphatic vessels and subsequent lymphatic flow[29]. This finding suggests that LDL may modulate lymphatic function, which could have implications for fluid homeostasis and the transport of other macromolecules via lymph. Moreover, the removal of cellular cholesterol through peripheral lymph high-density lipoprotein (HDL) is believed to play a critical role in completing the journey of peripheral tissue cholesterol to the liver[30]. This function is particularly important near the heart, as lymph-mediated HDL trafficking from artery walls has been shown to decrease the size of atherosclerotic plaques[31]. In the context of atherosclerosis, the accumulation of low-density lipoprotein (LDL) within the arterial wall leads to the formation of plaques. These plaques consist of lipids, immune cells, smooth muscle cells, and connective tissue[32]. Further studies are needed to elucidate the underlying mechanisms and explore the therapeutic implications of lymph-mediated HDL trafficking in the context of atherosclerosis and cardiovascular health.

Deficiencies in lymphatic function can have direct effects on lipoprotein profiles and related physiological processes. For example, decreased levels of plasma HDL and its related protein and lipid have been documented upon lymphatic diversion[33]. Similarly, increased levels of plasma very low-density lipoprotein (VLDL) and LDL have been linked to lymphatic vessel dysfunction in mouse models of atherosclerosis[30]. Elevated plasma LDL and decreased HDL levels are major risk factors for the metabolic syndrome, which is associated with atherosclerosis, obesity, increased blood pressure, and glucose intolerance[34].

The intestinal lymphatic system is a promising route for delivering drugs with poor solubility and bioavailability. Examples of drugs and formulations delivered via the intestinal lymphatic system include lipophilic drugs such as cyclosporine, which is used to prevent organ rejection in transplant patients. Oral administration of cyclosporine in a self-emulsifying drug delivery system (SEDDS) improved its bioavailability by promoting lymphatic uptake[35]. Another example is the anti-cancer drug paclitaxel, which has low solubility in water and poor oral bioavailability. Oral administration of paclitaxel in a lipid-based formulation improved its absorption and lymphatic uptake, leading to increased efficacy against cancer[36]. Additionally, lipid-based formulations have been used to deliver peptides and proteins via the lymphatic system. For example, insulin has been incorporated into lipid-based formulations and shown to enhance its lymphatic transport and reduce its degradation[37]. Overall, the intestinal lymphatic system has shown promise as a delivery route for a range of drugs and formulations.

6. Conclusions

While significant progress has been made in unraveling the intricacies of lipoprotein trafficking and remodeling within the lymphatics, there remains a considerable amount of unknowns regarding the detailed mechanisms and factors that regulate these processes. The gaps in our understanding present an opportunity for further exploration and research. By delving deeper into these processes, we have the potential to advance our knowledge, identify novel therapeutic interventions, and pave the way for innovative approaches to tackle a wide range of diseases associated with lipoprotein dysfunction and lymphatic related diseases.

Author contributions

Conceptualization, MY, NMD, NBC and RL; writing—original draft preparation, MY and NMD; writing—review and editing, NMD, NBC and RL; supervision, NBC, NMD and RL.

Conflict of interest

The authors declare no conflict of interest.

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