# Plasma Lipoproteins as Crucial Components of Host Defence Against Infections

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http://dx.doi.org/10.5772/67601

### Abstract

Interactions between lipoproteins and infectious microorganisms are diverse and often multifaceted. There is a growing body of evidence which suggests that circulating plasma lipoproteins play an important role in warding off various infections. They are increasingly recognized as vital components of the host immune system. The purpose of this chapter is to provide the reader with an overview of this emerging domain. We review the anti-infective role of different lipoprotein particles and their components and further highlight the known molecular mechanisms involved therein. Instances where lipoproteins facilitate infections instead of protecting against them are also summarized. Finally, broad implications for the future in this active line of research are discussed.

**Keywords:** lipoproteins, apolipoproteins, lipids, infection, immune system

## 1. Introduction

Circulating lipoproteins are macromolecular complexes of lipids and specific proteins (known as apolipoproteins). They facilitate the transport and distribution of various lipids (such as cholesterol, cholesteryl esters, triglycerides, and phospholipids) via blood throughout the body. Owing to their hydrophobicity, they are otherwise sparingly soluble in the predominantly aqueous plasma [1]. Scientific work on plasma lipoproteins has historically focused on their role in atherosclerotic changes and cardiovascular health. Much of the impetus in this line of enquiry was provided by the Framingham Heart Study (FHS) that was started in 1948 by the National Heart Institute (NHI). The FHS and a number of large clinico-epidemiological studies thereafter have been instrumental in advancing our knowledge about the link between circulating lipoproteins and cardiovascular health [1–5]. There is a growing body

of evidence suggesting that plasma lipoproteins are crucial players in a host of other conditions as well, viz. neurodegeneration [6], psychiatric ailments [7], and various cancers [8, 9], to name a few.

Although the earliest reports about the relationship of lipids and lipoproteins with various infections date back to 1940s and 1950s [10–12], yet the interest on lipoproteins for a long time was mostly revolved around noncommunicable disorders. However, in a marked departure from this conventional outlook, the importance of circulating lipoproteins in relation to infectious diseases is now widely recognized. Perhaps the best example in this regard is the study of the role of high-density lipoproteins (HDL) particles in conferring immunity against *Trypanosoma brucei brucei* in humans [13]. This change in the outlook is probably due to the fact that derangements (quantitative as well as qualitative) in plasma lipoproteins that were earlier documented in a variety of infections, viz. bacterial, viral, and parasitic [14–16] have now been corroborated by experimental evidence as well [17–19], such that there is an improved understanding of the underlying mechanisms at a molecular level.

Lipoproteins represent structurally and functionally a very diverse species of complex particles with dynamic interactions that travel throughout the body through circulation. Thus, they are increasingly appreciated as components of the innate immune system [15, 17, 20]. Recent evidence suggests that lipoproteins are also involved in adaptive immune responses [21]. On the basis of difference in hydrated densities (as determined by their rate in sedimentation on ultracentrifugation in salt solutions), human plasma proteins have been traditionally divided into four major groups—chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) [1, 4, 5]. Apart from these four major groups, sometimes, other lipoprotein classes are also described, such as intermediate-density lipoproteins (IDL)—produced by catabolism of VLDL, and lipoprotein(a) [Lp(a)]—which is structurally similar to LDL and has a density range that overlaps that of HDL [1, 4, 5]. Many of these lipoprotein particles or their components (e.g., lipids or apolipoproteins) have been found to exert anti-infective role.

This chapter aims to review this emerging domain where plasma lipoproteins are now widely recognized as important players of the host immune system. We have summarized the different types of lipoprotein derangements during various infections, the anti-infective role of lipoproteins in conferring protection against pathogens, and the known molecular mechanisms involved therein.

## 2. Lipoproteins in relation to various infections

Lipoprotein derangements and infections appear to have a bidirectional relationship. This means that alterations in circulatory lipoproteins can modulate or predispose to infections, and conversely, alterations in circulating lipoproteins can be an outcome of the infections themselves. In other words, lipoprotein derangements can both be a contributory cause and a resultant effect of infections. The focus of this chapter is predominantly on the former relationship which underscores the role of lipoproteins in modulating susceptibility to infections.

The latter relationship is linked to the active phase of the infection and has been recorded in relation to several kinds of infectious agents [10–12, 22–24]. Such lipoprotein derangements are a part of the acute-phase responses (APR) mounted by the body and are beyond the scope of this chapter. Similarly, lipoprotein derangements can occur as a result of drug therapy against infections (e.g., dyslipidemia in HIV-AIDS patients due to anti-retroviral therapy) [25–28] and are outside the purview of this chapter too.

Generally speaking, most of the experimental and clinical evidences suggest that high levels of lipoproteins and lipids are protective against respiratory and gastrointestinal infections [29–31]. Case studies in homogenous populations residing in high-infection environments affirm this view. For instance, the Tsimane people of Bolivian Amazon have very high burden of infection, and this is often attributed to the low levels of lipids and lipoproteins [32]. Likewise, in the Shipibo people, another indigenous group in the Amazon, the density of parasitic infection correlates inversely to the HDL levels [33]. Further, reduced levels of apolipoproteins in hospital-based studies have been reported to be associated with increased susceptibility to nosocomial infections following severe trauma [34]. However, generalizations are difficult and exceptions to these trends have also been reported [28], and the mechanism involved is not clear.

In the account that follows, we give an overview of different infections where lipoproteins provide protection.

## 2.1. Viral infections

Lipoproteins, particularly HDL particles, have been found to account for part of the broad nonspecific antiviral activity of human serum [35, 36]. Such antiviral activity of lipoproteins has been detected across a wide spectrum of enveloped as well as nonenveloped DNA and RNA viruses. Examples include Rabies virus, Rubella virus, Japanese encephalitis virus (JEV), Poliovirus, Epstein-Barr virus (EBV), Herpes simplex virus (HSV), Vaccinia virus, New Castle disease virus, and Vesicular stomatitis virus (VSV), to name a few [35, 37–41]. This is in tune with the protection conferred by other components of the innate immune system, which are often nonspecific and broad-based. However, some lipoproteins (e.g., LDL and VLDL) have been found to be particularly active against certain viruses (e.g., JEV, Rubella, Rabies, and VSV) [35, 38, 40].

## 2.2. Bacterial infections

Lipoproteins are protective against several toxins produced by pathogenic bacteria. Lipoproteins can neutralize lipopolysaccharides (LPS) from Gram-negative bacteria [30, 36, 42]. LPS are implicated in complications of Gram-negative bacteraemia such as endotoxic shock and disseminated intravascular coagulation. Several classes of lipoproteins, such as LDL, VLDL, HDL, Lp(a), and chylomicrons, can potentially help in neutralizing LPS [30, 36, 43–45]. In fact, infusion of reconstituted HDL particles (rHDL) has been shown to protect against Gram-negative bacteraemia and endotoxic shock and to further blunt the LPS-induced unregulated activation of the coagulation cascade [46–48].

Lipoproteins are protective against Gram-positive organisms too. Lipoproteins have been shown to inactivate lipotechoic acid (LTA) and alpha-toxin from Gram-positive bacteria such as *Staphylococcus aureus* [30, 36, 49].

In addition to these toxin-neutralizing effects, lipoproteins can directly interact with cell surface virulence factors in bacteria and help in limiting their pathogenicity. Such interactions have been noted in infections by *Yersinia pestis* [50] and many Group A *Streptococcus* (GAS) strains [30, 51]. Besides, experiments in knockout animals have revealed that apoE-/- mice are susceptible to infection by *Listeria monocytogenes* and *Mycobacterium tuberculosis* [52, 53].

### 2.3. Parasitic infections

Humans are immune to infection by the parasite *Trypanosoma brucei brucei*. This protection is attributed to a subset of HDL particles called trypanosome lytic factors (TLFs), present in human serum [13]. TLFs have also been shown to ameliorate infection by *Leishmania* sp. [15]. However, this protection does not extend against other trypanosomes such as *Trypanosoma cruzi*, *Trypanosoma brucei rhodesiense*, and *Trypanosoma brucei gambiense* [13]. Lipoproteins are suggested to modulate the infectivity of malaria parasite and *Schistosoma* as well [36, 54–56].

## 3. Anti-infective mechanisms of lipoproteins

The biological mechanisms for the anti-infective role of lipoproteins are diverse. While, in some instances, the complete ensemble of a lipoprotein particle has been found to contribute to the immunological defenses, in some other occasions the individual constituents (such as apoproteins or lipid moieties such as phospholipids and cholesterol) are credited to be involved [36, 41, 57]. A broad scheme of the anti-infective mechanisms with respect to circulating lipoproteins is provided below. Experimental evidences from in vivo and in vitro studies suggest that these schemes are actually recurring themes. These strategies are common to a variety of antimicrobial defenses mobilized by circulating lipoproteins against a plethora of infectious agents.

### 3.1. Inhibiting the entry of intracellular pathogens into host cells

Lipoproteins can inhibit the attachment and subsequent entry of pathogens into their target cells. This defensive mechanism of lipoproteins has been particularly well described in relation to viruses. The presence of HDL is capable of retaining viruses on the cell surface, lending credibility to this idea. Apoproteins (such as apoA-I) in host circulatory lipoproteins contain stretches of amphipathic residues that have been proposed to interact with amphipathic counterparts in alpha-helices of viral envelope glycoproteins. These interactions interfere with membrane fusion and entry of viruses into host cells. Synthetic amphipathic peptide analogues of apoA-I can also exert similar effects [36, 58, 59]. In fact, such analogues have been found to inhibit HIV-induced syncytium formation [60]. Inhibition of viral penetration inside host cells is also supported by VLDL. Recent in vivo studies have revealed that VLDL in serum effectively blocks hepatitis C virus (HCV) cell attachment, thereby acting as a restriction factor

against HCV infection [18]. Clinical studies have earlier revealed that serum level of apoC-III (an integral apolipoprotein in VLDL) was a significant predictor of chronic hepatitis C infection and associated hepatic fibrosis [16].

Alternatively, viral infection stimulates production of interferons, which in turn induce secretion of some soluble forms of lipoprotein receptors. These soluble receptors can modulate viral pathogenesis. For instance, a soluble LDL receptor shed during hepatitis and rhinovirus infections is used by the viruses for gaining entry into their respective host target cells [36]. However, endogenous LDL competes with these viruses or such similar viruses for cellular uptake, protecting the host against infection. Such receptors are also implicated in virus assembly and budding [61, 62]. Likewise, a VLDL receptor fragment that binds rhinoviruses has also been described in cell culture studies [63].

In addition to viruses, circulating lipoproteins have been found to prevent the entry of nonviral intracellular pathogens. For example, lipoproteins can interfere with the adhesion of *Salmonella typhimurium* to host cells and subsequent organ invasion [64].

### 3.2. Inactivating the effect of microbial toxins

Lipoproteins effectively neutralize bacterial toxins such as LPS (from Gram-negative bacteria) and LTA (from Gram-positive bacteria) and enhance their clearance. The mechanisms involved in inactivating LPS are particularly well established [30, 36, 42–45, 65, 66]. The lipid components of lipoproteins are vital in this regard. Ultrastructural studies have shown that LPS binding with LDL causes fatty acyl chain of crucial lipid moieties in LPS to be incorporated into the phospholipid surface of lipoproteins. This masks the active sites of LPS and attenuates their toxic action [36, 67].

Binding with lipoproteins also enhances the clearance of LPS. During Gram-negative bacteremia, LPS released in the circulation is primarily taken up by macrophages in liver (Kupffer cells). The macrophages thus activated cause a splurge of pro-inflammatory cytokines, which are responsible for the LPS-induced septic shock. However, binding of LPS with lipoproteins prevents this and causes two-pronged benefits. Firstly, on binding with lipoproteins, the uptake of LPS by hepatic macrophages decreases, which prevents their activation and cytokine release [36, 68–70]. Lipoproteins can prevent the LPS-mediated activation and release of cytokines from peripheral monocytes/macrophages too. Lipoproteins have been found to promote the release of LPS from the cell surface of monocytes to which they were bound, further dampening the cellular response [36, 71]. Secondly, the lipoprotein bound LPS are instead taken up by hepatocytes that lead to their rapid secretion into bile [36, 68–70]. Triglyceride-rich lipoproteins such as chylomicrons and VLDL are especially active in accelerating the clearance of LPS in this fashion [36, 68].

In a somewhat analogous manner, lipoproteins are believed to neutralize the toxic effects of LTA [72]. Further, potent peptide toxins such as phenol-soluble modulins (PSM) secreted by bacteria such as *Staphylococcus aureus* can also be inactivated by lipoproteins such as HDL, LDL, and VLDL. Highest binding and neutralizing potentials of *Staphylococcal* PSMs are displayed by HDL [17].

### 3.3. Lysis of pathogens

Certain pathogens are directly lysed by plasma lipoproteins or their components. A good example of this is the lysis of the parasite *Trypanosoma brucei brucei* [13, 36]. This lipoprotein-mediated lysis is attributed to two distinct trypanosome lytic factors (TLFs), namely TLF1 and TLF2. TLF1 is actually a lipid-rich subset of HDL that contains mostly apoA-I and haptoglobulin-related protein (HRP) with some amount of other proteins such as apoA-II, apoL-I, and paraoxonase. On the other hand, TLF2 is lipid-poor lipoprotein complex that contains apoA-I, HRP, and immunoglobulin M [73–75]. It is believed that apoL-I and HRP in TLFs target the parasites within the acidic parasitophorous vacuoles of macrophages and damage them directly without taking recourse to macrophage activation [15]. It is noteworthy that *Trypanosoma cruzi*, a trypanosome to which humans are susceptible, cleaves apoA-I, the chief protein constituent of HDL using cruzipain, a cysteine protease present in the cell membrane as well as internal lysosomal structure of the parasite [76]. Such targeted breakdown of vital lipoprotein constituents may aid the *Trypanosoma cruzi* parasite in evading the anti-parasitic action of TLFs.

### 3.4. Promoting opsonization

Experiments involving in vitro and ex vivo systems have suggested that some lipoproteins such as LDL may act as opsonins and enhance phagocytosis of several types of Group A *Streptococcus* (GAS) bacteria by monocytes. Interaction of LDL with CD36 scavenger receptor expressed in monocytes and streptococcal collagen such as protein 1 (Scl1) present on the cell surface of GAS is believed to underlie this phagocytosis promoting activity [19].

### 3.5. Activation of complement system

Lipid-free and HDL-associated apoA-I can activate the host complement pathways which is effective in killing the gastrointestinal pathogen, *Yersinia enterocolitica*. The C-terminal domain of apoA-I is the primary effector site responsible for this bactericidal property [77].

### 3.6. Inhibition of plasminogen recruitment

Many pathogens recruit human plasminogen (which is an integral part of the fibrinolytic system) in the course of their pathogenesis. This helps them in penetrating tissue barriers and facilitate invasion. Some pathogens even secrete plasminogen activators to amplify the effect. For example, streptokinase produced by GAS is a highly specific activator for plasminogen. Thus, it is believed that many infections can be inhibited and prevented considerably if recruitment and activation of host plasminogen by pathogens can be blocked. Lp(a) is believed to be a vital component of the host defense system in this context. Apo(a) present in Lp(a) shares a high degree of homology with plasminogen. Thus, it competes for the binding of plasminogen to pathogens. It reduces the amount of plasminogen immobilized on the pathogen surface and further inhibits the activation of plasminogen by activators such as streptokinase. In vitro studies have demonstrated the inhibition of streptokinase to catalyze the activation of plasminogen. Thus Lp(a) can help in preventing infections and promoting wound healing and repair of tissue injuries [29, 51, 78–81].

### 3.7. Chemical modification of lipoproteins

Infections and the associated inflammatory responses lead to oxidative stress and generation of reaction oxygen species (ROS). ROS induces chemical modifications in several lipoprotein species, most notable of which is oxidative changes in LDL [82]. Oxidized LDL (oxLDL) contributes to immune responses against invading pathogens in several ways. OxLDL upregulates scavenger receptor expression in macrophages, which facilitates their ingestion of Gram-positive and Gram-negative bacteria by phagocytosis. One of the oxidized components in oxLDL, namely oxidized 1-palmitoyl-2-arachidonyl-*sn*-glycero-3-phosphorylcholine (oxPAPC), modulates LPS-mediated signaling pathways in favor of the host. It inhibits LPS-induced adhesion of neutrophils to endothelial cells (thereby limiting LPS-induced tissue damage) and checks unregulated pro-inflammatory pathways [30, 82–86]. Besides, oxLDL has been shown to block cellular entry by several HCV strains [87] and malarial sporozoites [88].

Further, oxLDL elicits the production of natural antibodies against the membrane phospholipid, phosphorylcholine (PC). These anti-PC antibodies may target PC epitopes present in a broad spectrum of pathogens and provide protection against them. These include Gram-positive bacteria, Gram-negative bacteria, trematodes, nematodes, and even fungi [30, 89–93].

### 3.8. Acting in concert with acute-phase responses

The acute-phase response (APR), characterized by acute specific changes in concentration of plasma proteins, in response to noxious stimuli (such as infection) serves to protect the host from further injury. It helps in neutralizing the invading microbes, limits the extent of tissue damage, and promotes tissue repair and regeneration. In many instances, lipoproteins work with players of the APR in tandem and help in projecting antimicrobial defenses of the body.

For example, lipoprotein-binding protein (LBP) is an acute-phase protein carried on lipoproteins [36, 94]. It is associated with HDL, LDL, VLDL, and chylomicrons. LBP catalyzes the detoxification of bacterial toxins such as LPS and LTA by lipoproteins. LBP can modulate the effects of LPS by binding to the lipid A moiety of the latter. During infections, very high concentrations of LBP are attained, which helps in transferring LPS (and LTA) to lipoproteins for inactivation. LBP is also produced in the intestine and in the lungs where it is believed to play important roles in mobilizing local immune responses against bacterial LPS [36, 72, 94–96].

C-reactive protein (CRP) is another acute-phase protein that is associated with LDL and VLDL. Infection by the parasite *Schistosoma* leads to increase in serum CRP. CRP can activate platelets, which have cytotoxic effects against schistosomes. Such cytotoxic effects are exerted by activated monocytes as well. However, LDL binds to the surface of schistosomes, which masks them from activated monocytes. This is circumvented by oxidative changes in the parasite-bound LDL brought about by ROS from activated monocytes. OxLDL is endocytosed by the monocytes through scavenger receptors, which exposes the parasite to attack by monocytes and other immune cells [54, 55].

### 3.9. Redistribution of lipids to immune cells

During infection, there are quantitative and qualitative changes in plasma lipoproteins due to redistribution of lipids to the immune cells and areas of cellular injury. These changes are believed to potentiate the immune system and enhance healing in the host that helps to tide over the infective crisis [36]. For instance, there is an increase in triglyceride-rich VLDL particles, which provide lipid substrates to macrophages of the activated immune system. Similarly, there is a decrease in HDL levels. Since HDL is the central component of reverse cholesterol transport (RCT) pathway, such decrements in its level help in conserving cholesterol in peripheral sites. It has been found that during the acute phase of infection, there is an increase in apolipoprotein serum amyloid A (apoSAA) and concurrent decrease in apoA-I. ApoSAA redirects cholesterol away from catabolism in hepatocytes and delivers cholesterol to other cells. Cholesterol is required for new membrane synthesis in areas of cellular injury that accompany infections. Cholesterol may also be used for activation and proliferation of lymphocytes [97–101].

## 4. Lipoproteins as double-edged sword of the immune system

The immune system is a double-edged sword. Autoimmune diseases and hypersensitivity reactions are classic examples in this regard. The lipoproteins (as components of the immune system) have no exception. Lipoproteins may facilitate invasion and spread of infection by certain pathogens to the detriment of the host. Besides, lipoproteins are important risk factors for some other disorders. The following are certain examples:

- The obligate intracellular parasite, *Toxoplasma gondii*, is dependent on host cholesterol from extracellular LDL for growth and replication. The parasite resides in a special parasitophorous vacuole to which cholesterol is delivered by uptake of LDL through receptor-mediated endocytosis [102].

- There are tremendous requirements of various lipids for successful replication of the malaria parasite in the host. These requirements are met by the parasite by scavenging and modifying lipids from the host itself. Lipids such as phospholipids and free fatty acids (FFA) can be obtained from circulating lipoproteins or directly from the serum and used without further modification. Or else, the scavenged lipids are modified by elongation and desaturation reactions and subsequently incorporated as diacylglycerols and triacylglycerols [103–108].

- Similarly, a large number of viruses can hijack the host lipid and lipoprotein machinery to their benefit [109, 110]. It is increasingly appreciated that viruses can modulate lipid metabolism, composition, and signaling in the host to facilitate their entry [111–113], replication [109, 114, 115], and assembly [116–119].

- Fungal pathogens require ergosterol to grow and thrive in the host tissues. The supply of ergosterol is maintained by the endogenous sterol synthesis pathway present in the fungus. The azole group of antifungal drugs inhibits this fungal sterol synthesizing pathway.

However, the opportunistic fungal pathogen *Candida glabrata* can circumvent such ergos-terol-deprived killing by utilizing host sterols instead. It can take up cholesterol from host circulating lipoproteins and use it for its survival in the presence of azole antifungals [120].

- Infusion of lipoproteins in volunteers has been documented to enhance growth of *Candida albicans* as well [14].

- Lipoproteins can undergo changes in their structure and composition during infections, which may be harmful to the host. As described earlier, oxLDL can help in protecting the host from the adverse effects of bacteria, viruses, and parasites. Though initially these effects are beneficial and hence desirable, yet prolonged presence of oxLDL may contribute to atherosclerosis. OxLDL plays a pivotal role in formation of lipid laden foam cells that trigger atherogenic changes [36, 82, 121, 122].

- Besides, PC, which is expressed in a number of pathogens and is targeted by natural antibodies elicited by oxLDL (described earlier), can paradoxically contribute to persistence and invasiveness of certain pathogens, such as *Haemophilus influenzae* [123, 124].

- The cholesterol-rich Lp(a) is notorious for its atherogenic and thrombotic effects. Although recent studies have described anti-infective processes in relation to Lp(a), it is nonetheless an established risk factor for cardiovascular disorders [1, 4, 5].

## 5. Conclusion and future directions

As our knowledge about the role of lipoproteins as crucial components of the immune system continues to advance, two types of implications for the future have emerged. First, there is the possibility of characterizing the lipoprotein-pathogen interactions in greater detail. This will lead to an improved understanding of the pathophysiological significance of these interactions and may help in elucidating novel anti-infective mechanisms. For instance, a very recent study has described serum lipoproteins as critical components for pulmonary innate defense against quorum-sensing-based pathogenesis by *Staphylococcus aureus* [125]. Second is the potential use of drug therapies to modulate lipoprotein-pathogen interactions with the aim of controlling infections. As discussed earlier, reconstituted HDL and apoA-I mimetic peptides have shown promise in this regard [46–48, 60]. Further, drugs targeting lipid metabolism have also been suggested. For example, plant extracts modulating lipoprotein metabolism have shown promising antimalarial properties [126]. Similarly, there is potential for developing therapeutics targeting fatty acid synthesis (which is required by many viruses) as broad-spectrum antiviral agents [110, 118].

To conclude, lipoproteins are increasingly recognized as important players of the host immune system. They offer a multitude of strategies to ward off infections and limit their detrimental effects in the body of the host. At times, many of these strategies act together in a complementary manner, rather than being mutually exclusive. On the other hand, an anti-infective mechanism resulting from a particular lipoprotein-pathogen interaction that may be beneficial for one specific infection may not be applicable sometimes in another

infection [127]. Instead, such an interaction may promote infection and lead to untoward effects (as the previous examples show). As seen from the examples in the text, the interactions between host lipoproteins and invading pathogens are complex and multifaceted. This warrants further studies and very detailed knowledge of the different lipoprotein-pathogen interactions to design effective therapeutic options.

## Conflict of interest

None.

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