

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Plasma Lipoproteins as Crucial Components of Host Defence Against Infections

Kaustubh Bora and Probodh Borah

Additional information is available at the end of the chapter

<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 anti-microbial 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 non-viral 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 haptoglobin-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 ergosterol-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.

Author details

Kaustubh Bora^{1*} and Probodh Borah²

*Address all correspondence to: kaustubhbora1@gmail.com

1 Regional Medical Research Centre, N.E. Region (ICMR), Dibrugarh, Assam, India

2 Department of Animal Biotechnology, Bioinformatics Infrastructure Facility (BIF) and State Biotech Hub (SBT-Hub), College of Veterinary Sciences, Guwahati, Assam, India

References

- [1] Voet D, Voet JG. Lipid and membranes. In: Biochemistry. 4th ed. Asia: John Wiley & Sons (Asia) Pvt Ltd; 2011. pp. 386–466.
- [2] Sullivan LM, Vasan RS, Benjamin EJ, D'Agostino RB Sr. The burden of increasing worldwide cardiovascular disease. In: Fuster V, o'Rourke RA, Poole-Wilson P, Walsh RA, et al. editors. Hurst's the heart. 12th ed. New York: Tata McGraw Hill Medical; 2007.
- [3] Truswell AS. Experimental pathology in St. Petersburg. In: Cholesterol and beyond the research on diet and coronary heart disease 1900–2000. 1st ed. Dordrecht, The Netherlands: Springer; 2010. pp. 5–8.
- [4] Glew RH. Lipid metabolism II: pathways of metabolism of special lipids. In: Devlin TM, editor. Textbook of biochemistry with clinical correlation. 7th ed. The United States of America: John Wiley & Sons, Inc; 2011. pp. 707–749.
- [5] Remaley AT, Rifai N, Warnick GR. Lipids, lipoproteins, apolipoproteins and cardiovascular risk factors. In: Burtis CA, Ashwood ER, Bruns DE, editors. Tietz textbook of clinical chemistry and molecular diagnostics. 5th ed. 1st Indian Reprint. India: Elsevier (Reed Elsevier India Private Limited); 2012. pp. 731–805.

- [6] Wei Q, Wang H, Tian Y, Xu F, Chen X, Wang K. Reduced serum levels of triglyceride, very low density lipoprotein cholesterol and apolipoprotein B in Parkinson's disease patients. *PloS One*. 2013;**8**:e75743. doi:10.1371/journal.pone.0075743
- [7] van Reedt-Dortland AKB, Giltay EJ, van Veen T, van Pelt J, Zitman FG, Penninx BWJH. Associations between serum lipids and major depressive disorder: results from the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry*. 2010;**71**:729–736.
- [8] Marrer E, Wagner A, Montaye M, Luc G, Amouyel P, Dallongeville J, Ducimetiere P, Bingham A, Arveiler D, Velten M. Lipoprotein(a) plasma levels and the risk of cancer: the PRIME study. *Eur J Cancer Prev*. 2013;**22**:286–293.
- [9] dos Santos CR, Domingues G, Matias I, Matos J, Fonseca I, de Almeida JM, Dias S. LDL-cholesterol signalling induces breast cancer proliferation and invasion. *Lipids Health Dis*. 2014;**13**:16. doi:10.1186/1476-511X-13-16
- [10] Nishishita S. Studies on the fluctuation of the lipid content of the blood in the fever period. *Jpn J Exp Med*. 1941;**19**:97–107.
- [11] Man EB, Kartin BL, Durlacher SH, et al. The lipids of serum and liver in patients with hepatic diseases. *J Clin Invest*. 1945;**24**:623–643.
- [12] Banerjee S, Bhaduri JN. Serum protein bound carbohydrates and lipids in cholera. *Proc Soc Exp Biol Med*. 1959;**101**:340–341.
- [13] Hajduk SL, Hager KM, Esko JD. Human high density lipoprotein killing of African trypanosomes. *Annu Rev Microbiol*. 1994;**48**:139–162.
- [14] Netea MG, Curfs JH, Demacker PN, Meis JF, Van Der Meer JW, Kullberg BJ. Infusion of lipoproteins into volunteers enhances the growth of *Candida albicans*. *Clin Infect Dis*. 1999;**28**:1148–1151.
- [15] Samanovic M, Molina-Portela MP, Chessler ADC, Burleigh BA, Raper J. Trypanosome lytic factor, an antimicrobial high-density lipoprotein, ameliorates Leishmania infection. *Plos Pathog*. 2009;**5**:e1000276. doi:10.1371/journal.ppat.1000276
- [16] Rowell J, Thompson AJ, Guyton JR, Lao XQ, McHutchison JG, McCarthy JJ, Patel K. Serum apolipoprotein C-III is independently associated with chronic hepatitis C infection and advanced fibrosis. *Hepatol Int*. 2012;**6**:475–481.
- [17] Surewaard BGJ, Nijland R, Spaan AN, Kruijtz JAW, de Haas CJC, van Strijp JAG. Inactivation of staphylococcal phenol soluble modulins by serum lipoprotein particles. *PloS Pathog*. 2012;**8**:e1002606. doi:10.1371/journal.ppat.1002606
- [18] Tao J, Kang KD, Hall SD, Laube AH, Liu J, Renfrow MB, Novak J, Luo G. The serum very-low density lipoprotein serves as a restriction factor against hepatitis C virus infection. *J Virol*. 2015;**89**:6782–6791.

- [19] Zhou L, Liu L, Yang J, Li Y, Bai W, Liu N, Li W, Gao Y, Xu L, Liu Z, Han R. LDL acts as an opsonin enhancing the phagocytosis of group A streptococcus by monocyte and whole human blood. *Mol Microbiol Immunol*. 2016;**205**:155–162.
- [20] Sprong T, Netea MG, van Der Ley P, Verver-Jansen TJG, Jacobs LEH, Stalenhoef A, van der Meer JWM, van Deuren M. Human lipoproteins have divergent neutralizing effects on *E. coli* LPS, *N. Meningitidis* LPS, and complete Gram-negative bacteria. *J Lipid Res*. 2004;**45**:742–749.
- [21] Wang SH, Yuan SG, Peng DQ, Zhao SP. HDL and apoA-I inhibit antigen-presentation mediated T cell activation by disrupting lipid rafts in antigen presenting cells. *Atherosclerosis*. 2012;**225**:105–114.
- [22] Gallin JI, Kaye D, O'Leary WM. Serum lipids in infection. *N Engl J Med*. 1969;**281**:1081–1086.
- [23] Alvarez C, Ramos A. Lipids, lipoproteins and apoproteins in serum during infection. *Clin Chem*. 1986;**32**:142–145.
- [24] Visser BJ, Wieten RW, Nagel IM, Grobusch MP. Serum lipids and lipoproteins in malaria. *Malaria J*. 2013;**12**:442.
- [25] Friis-Moller N, Sabin CA, Weber R, et al. Combination anti-retro viral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003;**349**:1993–2003.
- [26] Bernal E, Masia M, Padilla S, Ramos JM, Martin-Hidalgo A, Gutierrez F. Insulin resistance in HIV-infected patients receiving long term therapy with efavirenz, lopinavir/ritonavir and atazanavir. *Med Clin (Barc)*. 2007;**129**:252–254.
- [27] Bernal E, Masia M, Padilla S, Gutierrez F. High-density lipoprotein cholesterol in HIV-infected patients: evidence for an association with HIV-1 viral load, anti-retroviral therapy status, and regimen composition. *AIDS Patient Care STDS*. 2008;**22**: 569–575.
- [28] Anastos K, Lu D, Shi Q, Tien PC, Kaplan RC, Hessol NA, Cole S, Vigen C, Cohen M, Young M, Justman J. Association of serum lipid levels with HIV serostatus, specific anti-retroviral agents, and treatment regimens. *J Acquir Immune Defic Syndr*; 2007;**45**:34–42.
- [29] Han R. Plasma lipoproteins are important components of the host defense system? *J Immunol*. 2009;**182**:134–174.
- [30] Han R. Plasma lipoproteins are important components of the immune system. *Microbiol Immunol*. 2010;**54**:246–253.
- [31] Ravnskov U. High cholesterol may protect against infections and atherosclerosis. *QJM*. 2003;**96**:927–934.
- [32] Vasunilashorn S, Crimmins EM, Kim JK, Winking J, Gurven M, Kaplan H, Finch CE. Blood lipids, infection, and inflammatory markers in the Tsimane of Bolivia. *Am J Hum Biol*. 2010;**22**:731–740.

- [33] Wiedermann U, Stemberger H, Unfried E, Widhalm K, Kundi M, Altenriederer M, Savedra M, Wiedermann G. Intestinal worm burden and serum cholesterol or lipid concentration in a Shipibo population (Peru). *Zentralbl Bakteriol.* 1991;**275**:279–286.
- [34] Femling JK, West SD, Hauswald EK, Gresham HD, Hall PR. Nosocomial infections after severe trauma are associated with lower apolipoproteins B and AII. *J Trauma Acute Care Surg.* 2013;**74**:1067–1073.
- [35] Singh IP, Chopra AK, Coppenhaver DH, Ananatharamaiah GM, Baron S. Lipoproteins account for part of the broad non-specific antiviral activity of human serum. *Antiviral Res.* 1999;**42**:211–218.
- [36] Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res.* 2004;**45**:1169–1196.
- [37] Shortridge KF, Ho WK, Oya A, Kobayashi M. Studies on the inhibitory activities of human serum lipoproteins for Japanese encephalitis virus. *Southeast Asian J Trop Med Public Health.* 1975;**6**:461–466.
- [38] Shortridge KF, Ho WK. Comparison of the activities in inhibition of haemagglutination by different togaviruses for human serum lipoproteins and their constituents. *J Gen Virol.* 1976;**33**:523–527.
- [39] Chisari FV, Curtiss LK, Jensen FC. Physiologic concentrations of normal human plasma lipoproteins inhibit the immortalization of peripheral B lymphocytes by the Epstein-Barr virus. *J Clin Invest.* 1981;**68**:329–336.
- [40] Seganti L, Grassi M, Mastromarino P, Pana A, Superti F, Orsi N. Activity of human serum lipoproteins on the infectivity of rhabdoviruses. *Microbiologica.* 1983;**6**:91–99.
- [41] Huemer HP, Menzel HJ, Potratz D, Brake B, Falke D, Utermann G, Dierich MP. *Herpes simplex* virus binds to human serum lipoprotein. *Intervirology.* 1988; **29**:68–76.
- [42] Emancipator K, Csako G, Elin RJ. *In-vitro* inactivation of bacterial endotoxin by human lipoproteins and apolipoproteins. *Infect Immun.* 1992;**60**:596–601.
- [43] Ulevitch RJ, Johnston AR, Weinstein DB. New function for high density lipoproteins. Their participation in intravascular reactions of bacterial lipopolysaccharides. *J Clin Invest.* 1979; **64**:1516–1524.
- [44] Eichbaum EB, Harris HW, Kane JP, Rapp JH. Chylomicrons can inhibit endotoxin activity *in-vitro*. *J Surg Res.* 1991;**51**:413–416.
- [45] Harris HW, Eichbaum EB, Kane JP, Rapp JH. Detection of endotoxin in triglyceride-rich lipoproteins *in-vitro*. *J Lab Clin Med.* 1991;**118**:186–193.
- [46] Hubsch AP, Casas AT, Doran JE. Protective effects of reconstituted high-density lipoprotein in rabbit Gram-negative bacteremia models. *J Lab Clin Med.* 1995;**126**:548–558.

- [47] Parker TS, Levine DM, Chang JC, Laxer J, Coffin CC, Rubin AL. Reconstituted high-density lipoprotein neutralizes gram-negative bacterial lipopolysaccharides in human whole blood. *Infect Immun*. 1995;**63**:253–258.
- [48] Casas AT, Hubsch AP, Doran JE. Effects of reconstituted high-density lipoprotein in persistent gram-negative bacteremia. *Am Surg*. 1996;**62**:350–355.
- [49] Bhakdi S, Trantum-Jensen J, Utermann G, Fussle R. Binding and partial inactivation of *Staphylococcus aureus* alpha toxin by human plasma low density lipoprotein. *J Biol Chem*. 1983;**258**:5899–5904.
- [50] Makoveichuk E, Cherepanov P, Lundberg S, Forsberg A, Olivecrona G. pH6 antigen of *Yersinia pestis* interacts with plasma lipoproteins and cell membranes. *J Lipid Res*. 2003;**44**:320–330.
- [51] Han R, Caswell CC, Lukomska E, Keene DR, Pawlowski M, Bujnicki JM, Kim JK, Lukomski S. Binding of the low-density lipoprotein by streptococcal collagen-like protein Scl1 of *Streptococcus pyogenes*. *Mol Microbiol*. 2006;**61**:351–367.
- [52] Roselaar SE, Daugherty A. Apolipoprotein E-deficient mice have impaired innate immune responses to *Listeria monocytogenes in-vivo*. *J Lipid Res*. 1998;**39**:1740–1743.
- [53] Martens GW, Arikan MC, Lee J, Ren F, Vallerskog T, Kornfeld H. Hypercholesterolemia impairs immunity to tuberculosis. *Infect Immun*. 2008;**76**:3464–3472.
- [54] Bout D, Joseph M, Pontet M, Vorng H, Deslee D, Capron A. Rat resistance to schistosomiasis: platelet-mediated cytotoxicity induced by C-reactive protein. *Science*. 1986;**231**:153–156.
- [55] Xu X, Remold HG, Caulfield JP. Potential role for scavenger receptors of human monocytes in the killing of *Schistosoma mansoni*. *Am J Pathol*. 1993;**142**:685–689.
- [56] Sinnis P, Willnow TE, Briones MR, Herz J, Nussenzweig V. Remnant lipoproteins inhibit malaria sporozoite invasion of hepatocytes. *J Exp Med*. 1996;**184**:945–954.
- [57] Mastromarino P, Seganti L, Orsi N. Relationship between enzymatic modifications of serum low density lipoproteins and their haemagglutination inhibiting activity towards Sindbis virus. *Arch Virol*. 1980;**65**:37–44.
- [58] Martin I, Dubois MC, Saermark T, Ruyschaert JM. Apolipoprotein A-1 interacts with the N-terminal fusogenic domains of SIV (simian immunodeficiency virus) GP32 and HIV (human immunodeficiency virus) GP41: implications in viral entry. *Biochem Biophys Res Commun*. 1992;**186**:95–101.
- [59] Srinivas RV, Birkedal B, Owens RJ, Anantharamaiah GM, Segrest JP, Compans RW. Antiviral effects of apolipoprotein A-I and its synthetic amphipathic peptide analogs. *Virology*. 1990;**176**:48–57.

- [60] Owens BJ, Anantharamaiah GM, Kahlon JB, Srinivas RV, Compans RW, Segrest JP. Apolipoprotein A-I and its amphipathic helix peptide analogues inhibit human immunodeficiency virus-induced syncytium formation. *J Clin Invest.* 1990;**86**:1142–1150.
- [61] Fischer DG, Tal N, Novick D, Barak S, Rubinstein M. An antiviral soluble form of the LDL receptor induced by interferon. *Science.* 1993;**262**:250–253.
- [62] Hofer F, Gruenberger M, Kowalski H, Machat H, Huettinger M, Kuechler E, Blass D. Members of the low density lipoprotein receptor family mediate cell entry of a minor group common cold virus. *Proc Natl Acad Sci USA.* 1994;**91**:1839–1842.
- [63] Marlovits TC, Abrahamsberg C, Blaas D. Very-low density lipoprotein receptor fragment shed from HeLa cells inhibits human rhinovirus infection. *J Virol.* 1998;**72**:10246–10250.
- [64] Netea MG, Joosten LAB, Keuter M, Wagener F, Stalenhoef AFH, van der Meer JWM, Kullberg BJ. Circulating lipoproteins are a crucial component of host defense against invasive *Salmonella typhimurium* infection. *PLoS One.* 2009;**4**:e4237. doi:10.1371/journal.pone.0004237
- [65] Netea MG, de Bont N, Demacker PN, Kullberg BJ, Jacobs LE, Verver-Jansen TJ, Stalenhoef AF, Van der Meer JW. Lipoprotein(a) inhibits lipopolysaccharide-induced tumor necrosis factor alpha production by human mononuclear cells. *Infect Immun.* 1998;**66**:2365–2367.
- [66] Harris HW, Grunfeld C, Feingold KR, Rapp JH. Human very low density lipoproteins and chylomicrons can protect against endotoxin-induced death in mice. *J Clin Invest.* 1990;**86**:696–702.
- [67] Victorov AV, Medvedeva NV, Gladkaya EM, Morozkin AD, Podrez EA, Kosykh VA, Yurkiv VA. Composition and structure of lipopolysaccharide-human plasma low density lipoprotein complex. Analytical ultracentrifugation, ³¹P-NMR, ESR and fluorescence spectroscopy studies. *Biochim Biophys Acta.* 1989;**984**:119–127.
- [68] Harris HW, Grunfeld C, Feingold KR, Read TE, Kane JP, Jones AL, Eichbaum EB, Bland GF, Rapp JH. Chylomicrons alter the fate of endotoxin, decreasing tumor necrosis factor release and preventing death. *J Clin Invest.* 1993;**91**:1028–1034.
- [69] Read TE, Harris HW, Grunfeld C, Feingold KR, Calhoun MC, Kane JP, Rapp JH. Chylomicrons enhance endotoxin excretion in bile. *Infect Immun.* 1993;**61**:3496–3502.
- [70] Read TE, Grunfeld C, Kumwenda Z, Calhoun MC, Kane JP, Feingold KR, Rapp JH. Triglyceride-rich lipoproteins improve survival when given after endotoxin in rats. *Surgery.* 1995;**117**:62–67.
- [71] Kitchens RL, Wolfbauer G, Albers JJ, Munford RS. Plasma lipoproteins promote the release of bacterial lipopolysaccharides from the monocyte cell surface. *J Biol Chem.* 1999;**274**:34116–34122.

- [72] Grunfeld C, Marshall M, Shigenaga JK, Moser AH, Tobias P, Feingold KR. Lipoproteins inhibit macrophage activation by lipoteichoic acid. *J Lipid Res.* 1999;**40**:245–252.
- [73] Raper J, Fung R, Ghiso J, Nussenzweig V, Tomlinson S. Characterization of a novel trypanosome lytic factor from human serum. *Infect Immun.* 1999;**67**:1910–1916.
- [74] Raper J, Portela MP, Lugli E, Frevert U, Tomlinson S. Trypanosome lytic factors: novel mediators of human innate immunity. *Curr Opin Microbiol.* 2001;**4**:402–408.
- [75] Vanhamme L, Paturiaux-Hanocq F, Poelvoorde P, Nolan DP, Lins L, Van Den Abbeele J, Pays A, Tebabi P, Van Xong H, Jacquet A, Moguilevsky N, Dieu M, Kane JP, De Baetselier P, Brasseur R, Pays E. Apolipoprotein L-I is the trypanosome lytic factor of human serum. *Nature.* 2003;**422**:83–87.
- [76] Miao Q, Santamaria C, Bailey D, Genest J, Ward BJ, Ndao M. Apolipoprotein A-I truncations in Chagas disease are caused by cruzipain, the major cysteine protease of *Trypanosoma cruzi*. *Am J Pathol.* 2014;**184**:876–984.
- [77] Biedzka-Sarek M, Metso J, Kateifides A, et al. Apolipoprotein A-I exerts bactericidal activity against *Yersinia enterocolitica* serotype O:3. *J Biol Chem.* 2011;**286**:38211–38219.
- [78] Lahteenmaki K, Edelman S, Korhonen TK. Bacterial metastasis: the host plasminogen system in bacterial invasion. *Trends Microbiol.* 2005;**13**:79–85.
- [79] Edelberg JM, Gonzalez-Gronow M, Pizzo SV. 1989. Lipoprotein a inhibits streptokinase-mediated activation of human plasminogen. *Biochemistry.* 1989;**28**:2370–2374.
- [80] Sun H, Ringdahl U, Homeister JW, Fay WP, Engleberg NC, Yang AY, Rozek LS, Wang X, Sjobring U, Ginsburg D. Plasminogen is a critical host pathogenicity factor for group A streptococcal infection. *Science*; 2004;**305**:1283–1286.
- [81] Sun H. The interaction between pathogens and the host coagulation system. *Physiology (Bethesda).* 2006;**21**:281–288.
- [82] Memon RA, Staprans I, Noor M, Holleran WM, Uchida Y, Moser AH, Feingold KR, Grunfeld C. 2000. Infection and inflammation induce LDL oxidation *in-vivo*. *Arterioscler Thromb Vasc Biol.* 2000;**20**:1536–1542.
- [83] Miller YI, Viriyakosol S, Binder CJ, Feramisco JR, Kirkland TN, Witztum JL. Minimally modified LDL binds to CD14, induces macrophage spreading via TLR4/MD-2, and inhibits phagocytosis of apoptotic cells. *J Biol Chem.* 2003;**278**:1561–1568.
- [84] Bochkov VN, Kadl A, Huber J, Gruber F, Binder BR, Leitinger N. Protective role of phospholipid oxidation products in endotoxin-induced tissue damage. *Nature.* 2002;**419**:77–81.
- [85] Bengtsson T, Karlsson H, Gunnarsson P, Skoglund C, Elison C, Leanderson P, Lindahl M. The periodontal pathogen *Porphyromonas gingivalis* cleaves apoB-100 and increases the expression of apoM in LDL in whole blood leading to cell proliferation. *J Intern Med.* 2008;**263**:558–571.

- [86] Walton KA, Cole AL, Yeh M, Subbanagounder G, Krutzik SR, Modlin RL, Lucas RM, Nakai J, Smart EJ, Vora DK, Berliner JA. Specific phospholipid oxidation products inhibit ligand activation of Toll-like receptors 4 and 2. *Arterioscler Thromb Vasc Biol.* 2003;**23**:1197–1203.
- [87] Von Hahn T, Lindenbach BD, Boullier A, Quehenberger O, Paulson M, Rice CM, Mckeating JA. Oxidized low-density lipoprotein inhibits hepatitis C virus cell entry in human hepatoma cells. *Hepatology.* 2006;**43**:932–942.
- [88] Rodrigues CD, Hannus M, Prudencio M, Martin C, Goncalves LA, Portugal S, Epiphanyo S, Akinc A, Hadwiger P, Jahn-Hofmann K, Rohl I, Van Gemert GJ, Franetich JF, Luty AJ, Sauerwein R, Mazier D, Koteliansky V, Vornlocher HP, Echeverri CJ, Mota MM. Host scavenger receptor SR-BI plays a dual role in the establishment of malaria parasite liver infection. *Cell Host Microbe.* 2008;**4**:271–282.
- [89] Gillespie SH, Mcwhinney PH, Patel S, Raynes JG, Mcadam KP, Whiley RA, Hardie JM. Species of alpha-hemolytic streptococci possessing a C-polysaccharide phosphorylcholine-containing antigen. *Infect Immun.* 1993;**61**:3076–3077.
- [90] Weiser JN, Goldberg JB, Pan N, Wilson L, Virji M. The phosphorylcholine epitope undergoes phase variation on a 43-kilodalton protein in *Pseudomonas aeruginosa* and on pili of *Neisseria meningitidis* and *Neisseria gonorrhoeae*. *Infect Immun.* 1998;**66**:4263–4267.
- [91] Chou MY, Hartvigsen K, Hansen LF, Fogelstrand L, Shaw PX, Boullier A, Binder CJ, Witztum JL. Oxidation-specific epitopes are important targets of innate immunity. *J Intern Med.* 2008;**263**:479–488.
- [92] Kolberg J, Hoiby EA, Jantzen E. Detection of the phosphorylcholine epitope in streptococci, Haemophilus and pathogenic Neisseriae by immunoblotting. *Microb Pathog.* 1997;**22**:321–329.
- [93] Serino L, Virji M. Genetic and functional analysis of the phosphorylcholine moiety of commensal *Neisseria* lipopolysaccharide. *Mol Microbiol.* 2002;**43**:437–448.
- [94] Park CT, Wright SD. Plasma lipopolysaccharides binding protein is found associated with a particle containing apolipoprotein A-I, phospholipid, and factor H-related proteins. *J Biol Chem.* 1996;**271**:18054–18060.
- [95] Vreugdenhil AC, Snoek AM, van't Veer C, Greve JW, Buurman WA. LPS-binding protein circulates in association with apoB-containing lipoproteins and enhances endotoxin-LDL/VLDL interaction. *J Clin Invest.* 2001;**107**:225–234.
- [96] Vreugdenhil AC, Rousseau CH, Hartung T, Greve JW, van't Veer C, Buurman WA. Lipopolysaccharide (LPS)-binding protein mediates LPS detoxification by chylomicrons. *J Immunol.* 2003;**170**:1399–1405.
- [97] Cuthbert JA, Lipsky PE. Regulation of lymphocyte proliferation by cholesterol: the role of endogenous sterol metabolism and low density lipoprotein receptors. *Int J Tissue React.* 1987;**9**:447–457.

- [98] Kisilevsky R, Subrahmanyam L. Serum amyloid A changes high density lipoprotein's cellular affinity. A clue to serum amyloid A's principal function. *Lab Invest.* 1992;**66**:778–785.
- [99] Oiknine J, Aviram M. Increased susceptibility to activation and increased uptake of low density lipoprotein by cholesterol-loaded macrophages. *Arterioscler Thromb;* 1992;**12**:745–753.
- [100] Hauton D, Evans RD. Utilisation of fatty acid and triacylglycerol by rat macrophages: the effect of endotoxin. *Cell Physiol Biochem.* 2002;**12**:293–304.
- [101] Funk JL, Feingold KR, Moser AH, Grunfeld C. Lipopolysaccharide stimulation of RAW 264.7 macrophages induces lipid accumulation and foam cell formation. *Atherosclerosis.* 1993;**98**:67–82.
- [102] Coppens I, Sinai AP, Joiner KA. *Toxoplasma gondii* exploits host low density lipoprotein receptor-mediated endocytosis for cholesterol acquisition. *J Cell Biol.* 2000;**149**:167–180.
- [103] Palapac NMQ, Hiramane Y, Mi-Ichi F, et al. Developmental-stage-specific triacylglycerol biosynthesis, degradation and trafficking as lipid bodies in *Plasmodium falciparum*-infected erythrocytes. *J Cell Science.* 2004;**117**:1469–1480.
- [104] Mi-Ichi F, Kita K, Mitamura T. Intraerythrocytic *Plasmodium falciparum* utilize a broad range of serum-derived fatty acids with limited modifications for their growth. *Parasitology.* 2006;**133**:399–410.
- [105] Moll GN, Vial HJ, Ancelin L, et al. Phospholipid uptake by *Plasmodium knowlesi* infected erythrocytes. *FEBS Lett.* 1988;**232**:341–346.
- [106] Krishnegowda G, Gowda DC. Intraerythrocytic *Plasmodium falciparum* incorporates extraneous fatty acids to its lipids without any structural modification. *Mol Biochem Parasitol.* 2003;**132**:55–58.
- [107] Grellier P, Rigomier D, Clavey V, Fruchart JC, Schrevel J. Lipid traffic between high density lipoproteins and *Plasmodium falciparum*-infected red blood cells. *J Cell Biol.* 1991;**112**:267–277.
- [108] Vial HJ, Thuet MJ, Broussal JL, Philippot JR. Phospholipid biosynthesis by *Plasmodium knowlesi*-infected erythrocytes: the incorporation of phospholipid precursors and the identification of previously undetected metabolic pathways. *J Parasitol.* 1982;**68**:379–391.
- [109] Heaton NS, Perera R, Berger KL, Khadka S, Lacount DJ, Kuhn RJ, Randall G. Dengue virus non-structural protein 3 redistributes fatty acid synthase to sites of viral replication and increases cellular fatty acid synthesis. *Proc Natl Acad Sci USA.* 2010;**107**:17345–17350.
- [110] Heaton NS, Randall G. Dengue virus and autophagy. *Viruses.* 2011;**3**:1332–1341.
- [111] Agnello V, Abel G, Elfahal M, Knight GB, Zhang QX. Hepatitis C virus and other flaviviridae viruses enter cells via low density lipoprotein receptor. *Proc Natl Acad Sci USA.* 1999;**96**:12766–12771.

- [112] Von Hahn T, Rice CM. Hepatitis C virus entry. *J Biol Chem*. 2008;**283**:3689–3693.
- [113] Sabahi A. Hepatitis C virus entry: the early steps in the viral replication cycle. *Viol J*. 2009;**6**:117. doi:10.1186/1743-422X-6-117
- [114] Mackenzie JM, Khromykh AA, Parton RG. Cholesterol manipulation by West Nile virus perturbs the cellular immune response. *Cell Host Microb*. 2007;**2**:229–239.
- [115] Rothwell C, Lebreton A, Young Ng C, Lim JY, Liu W, Vasudevan S, Labow M, Gu F, Gaither LA. Cholesterol biosynthesis regulation modulates dengue viral replication. *Virology*. 2009;**389**:8–19.
- [116] Nguyen DH, Hildreth JE. Evidence for budding of human immunodeficiency virus type 1 selectively from glycolipid-enriched membrane lipid rafts. *J Virol*. 2000;**74**:3264–3272.
- [117] Zheng YH, Plemenitas A, Fielding CJ, Peterlin BM. Nef increases the synthesis of and transports cholesterol to lipid rafts and HIV-1 progeny viruses. *Proc Natl Acad Sci USA*. 2003;**100**:8460–8465.
- [118] Munger J, Bennett BD, Parikh A, Feng XJ, McArdle J, Rabitz HA, Rabinowitz JD. Systems level metabolic flux profiling identifies the fatty acid synthesis as a target for anti-viral therapy. *Nat Biotechnol*. 2006;**26**:1179–1186.
- [119] Samsa MM, Mondotte JA, Iglesias NG, Assuncao-Miranda I, Barbosa-Lima G, Da Poian AT, Bozza PT, Gamarnik AV. Dengue virus capsid protein usurps lipid droplets for viral particle formation. *PLOS Pathog*. 2009;**5**:e1000632. doi:10.1371/journal.ppat.1000632
- [120] Nagi M, Tanabe K, Nakayama H, Yamagoe S, Umeyama T, Oura T, Ohno H, Kajiwara S, Miyazaki Y. Serum cholesterol promotes the growth of *Candida glabrata*. *J Infect Chemother*. 2013;**19**:138–143.
- [121] Ishigaki Y, Katagiri H, Gao J, Yamada T, Imai J, Uno K, Hasegawa Y, Kaneko K, Ogihara T, Ishihara H, Sato Y, Takikawa K, Nishimichi N, Matsuda H, Sawamura T, Oka Y. Impact of plasma oxidized low-density lipoprotein removal on atherosclerosis. *Circulation*. 2008;**118**:75–83.
- [122] Shoenfeld Y, Wu R, Dearing LD, Matsuura E. Are anti-oxidized low-density lipoprotein antibodies pathogenic or protective? *Circulation*. 2004;**110**:2552–2558.
- [123] Weiser JN, Pan N, McGowan KL, Musher D, Martin A, Richards J. Phosphorylcholine on the lipopolysaccharide of *Haemophilus influenzae* contributes to persistence in the respiratory tract and sensitivity to serum killing mediated by C-reactive protein. *J Exp Med*. 1998;**187**:631–640.
- [124] Lysenko E, Richards JC, Cox AD, Stewart A, Martin A, Kapoor M, Weiser JN. The position of phosphorylcholine on the lipopolysaccharide of *Haemophilus influenzae* affects binding and sensitivity to C-reactive protein-mediated killing. *Mol Microbiol*. 2000;**35**:234–245.

- [125] Manifold-Wheeler BC, Elmore BO, Triplett KD, Castleman MJ, Otto M, Hall PR. Serum lipoproteins are critical for pulmonary innate defense against *Staphylococcus aureus* quorum sensing. J Immunol. 2016;**196**:328–335.
- [126] Oluba OM, Olusola AO, Eidanghe GO, Babatola LJ, Onyeneke EC. Modulation of lipoprotein cholesterol levels in *Plasmodium berghei* malarial infection by crude aqueous extract of *Ganoderma lucidum*. Cholesterol. 2012;**2012**:536396. doi:10.1155/2012/536396
- [127] Feingold KR, Grunfeld C. Lipids: a key player in the battle between the host and microorganisms. J Lipid Res. 2012;**53**:2487–2489.