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REVIEW ARTICLE

Plasma lipoproteins are important components of the immune system

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ABSTRACT

Plasma lipoproteins (VLDL, LDL, Lp[a] and HDL) function primarily in lipid transport among tissues and organs. However, cumulative evidence suggests that lipoproteins may also prevent bacterial, viral and parasitic infections and are therefore a component of innate immunity. Lipoproteins can also detoxify lipopolysaccharide and lipoteichoic acid. Infections can induce oxidation of LDL, and oxLDL in turn plays important anti-infective roles and protects against endotoxin-induced tissue damage. There is also evidence that apo(a) is protective against pathogens. Taken together, the evidence suggests that it might be valuable to introduce the concept that plasma lipoproteins belong in the realm of host immune response.

Key words infection, innate immunity, lipoprotein(a), plasma lipoprotein.

A large body of evidence suggests that plasma lipoproteins may play an important role in host defense as a component of the innate immune system (1–3). Some of the viewpoints in these reviews are briefly summarized below. Infection and inflammation induce an APR with multiple alterations in lipid and lipoprotein metabolism. Briefly, in nonhuman primates and humans, VLDL concentrations are increased whereas LDL is either unchanged or decreased and HDL is decreased (For a review, see reference 3). Lipoproteins, including VLDL, LDL, lipoprotein(a) and HDL, can detoxify LPS from Gram-negative bacteria and LTA from Gram-positive bacteria, HDL being the most potent of these lipoproteins (2). The LPS- neutralizing role of HDL has been extensively studied both *in vitro* and *in vivo* (for reviews, see references 4, 5). Moreover, infusion of rHDL can blunt endotoxin-induced procoagulant activation in humans (6). Plasma HDL concentrations are significantly lower in patients with cirrhosis than in controls. Recently, an *ex vivo* study in which rHDL was incubated with either whole blood or monocytes from patients with severe cirrhosis showed that rHDL can significantly decrease LPS-induced overproduction of proinflammatory cytokines (tumor necrosis factor alpha and interleukin-10). This suggests that administration of rHDL might be protective against LPS-induced inflammation in cirrhosis patients (7).

S. aureus α-toxin is bound, and almost totally inactivated, *in vitro* by LDL (8). Hypocholesterolemic rats have been shown to have an increased endotoxin-induced mortality which can be ameliorated by injecting purified

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List of Abbreviations: *A. actinomycetemcomitans*, *Actinobacillus actinomycetemcomitans*; apo(a), apolipoprotein(a); apoA-I, apolipoprotein A-I; apoB100, apolipoprotein B100; apoE, apolipoprotein E; apoE−/−, apolipoproteinE-knockout; APR, acute phase response; *C. albicans*, *Candida albicans*; *E. coli*, *Escherichia coli*; GAS, group A *Streptococcus*; HCV, hepatitis C virus; HDL, high-density lipoprotein; *H. influenza*, *Haemophilus influenza*; *K. pneumoniae*, *Klebsiella pneumoniae*; LDL, low-density lipoprotein; LDLR, LDL receptor; LDLR−/−, LDL receptor-knockout; Lp(a), lipoprotein(a); LPS, lipopolysaccharide; LTA, lipoteichoic acid; oxLDL, oxidized LDL; oxPAPC, oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine; PAM, plasminogen binding group A streptococcal M-like protein; PC, phosphorylcholine; Plg, plasminogen; rHDL, reconstituted HDL; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; *T. cruzi*, *Trypanosoma cruzi*; TLF, trypanosome lytic factor; tPA, tissue plasminogen activator; uPA, urokinase-type plasminogen activator; VLDL, very low-density lipoprotein.

human LDL (9). In accordance, much epidemiological and clinical evidence suggests that high cholesterol may protect against respiratory and gastrointestinal infections (1).

Lipoproteins bind and neutralize a vast number of enveloped and non-enveloped DNA and RNA viruses. VLDL and LDL particularly protect against certain types of virus, such as togaviruses and rhabdoviruses, whereas HDL shows broader antiviral activity (3). Trypanosomes are unicellular parasites that cause sleeping sickness in animals. However, *Trypanosoma brucei* do not cause infection in humans because TLF, a subfraction of native human HDL containing haptoglobin-related protein, apolipoprotein L-I and apoA-I, protects against trypanosome infection (10).

Infection and inflammation cause oxidation of LDL (11). One of the oxidized components of oxLDL, oxPAPC, inhibits LPS-induced adhesion of neutrophils to endothelial cells and serves a protective role in endotoxin-induced tissue damage (12). In addition, both minimally oxidized LDL (13) and oxPAPC (14, 15) have been demonstrated to inhibit LPS signaling, consequently detoxifying LPS.

However, the anti-infective roles played by plasma lipoproteins have not been studied systematically. Here, we add some novel and/or relevant evidence and provide a theoretical analysis to support the role of plasma lipoproteins in the host defense system.

THE COMPLEX INTERPLAY BETWEEN HDL AND INFECTIONS

Leishmania can cause human leishmaniasis ranging from mild cutaneous and mucocutaneous lesions to fatal visceral infections. Recently, TLF was demonstrated to inhibit *Leishmania*-induced intracellular infection in TLF-transgenic mice by directly damaging *Leishmania* parasites which have proliferated in the phagolysosomes of macrophages, within which TLF accumulates and is activated under acidic conditions. However, TLF mice are not protected against infection by *T. cruzi*, which invades many cell types and transiently passes through phagolysosomes (16). The anti-infectious role of HDL may be attenuated by serum opacity factor, a virulence factor of class II M types of GAS, because it opacifies mammalian sera by binding and disrupting HDL (17).

HDL also has antiviral activity (18–20). A large number and variety of virus species can be inhibited from entering host cells by HDL. In the last decade studies have focused on the interplay between HDL and the influenza and hepatitis C viruses. D-4F, an apoA-I mimetic peptide, has been reported to have antiviral activity *in vivo,* whereas infection may cause HDL to lose its anti-inflammatory properties (21). In contrast, HDL may enhance HCV infection through the scavenger receptor class B type I (22–24). Another adverse effect is that infusion of reconstituted HDL can enhance the growth of *Candida albicans* (25). In addition, a recent report that apoA-I can neutralize LPS, whereas apoA-II may suppress this activity, further complicates the issue (26).

THE COMPLEX INTERPLAY BETWEEN LDL AND INFECTIONS

Netea and coworkers conducted a series of experiments to test whether LDLR−/− and apoE−/− mice are protected against lethal endotoxemia and severe Gram-negative infections (27–29). The results showed that the LDLR−/− mice have anti-*Klebsiella pneumoniae* capabilities due to an increase in endogenous LDL concentration (27), whereas apoE−/− mice, which have a great increase in VLDL and a lesser increase in LDL concentrations, are more susceptible to the infection than normal mice (28). These results indicate that the absence of apoE itself in the knock-out mice might abolish the *K. pneumoniae* LPS-neutralizing effect of lipoproteins, although high cholesterol concentrations are generated in these mice (28). However, a recent report shows that knockout of either apoE or the LDLR gene in mice results in a much higher resistance to infection by *Salmonella typhimurium* than is found in control mice (29). This may suggest a novel LDL-related anti-infective mechanism, other than detoxification of LPS, in which direct LDL-bacterial cell interaction might be involved (29).

Other instances of direct bacterial cell-LDL binding have also been reported. LDL can bind to pH6-Ag, a potential adhesive for the bacterial pathogen *Yersinia pestis* (30). We have also reported that, in M1, M12, M28 and M41 strains of GAS, apoB100-containing lipoproteins, mainly LDL, can bind to Scl1 (group A streptococcal collagen-like protein 1), which is a cell surface virulence factor of GAS (31). However, the pathophysiological significance of these LDL-pathogen interactions remains to be elucidated by more experiments including animal experiments. In addition, it may be valuable to test whether LDL is able to bind cells of other pathogenic bacteria.

Moreover, apoE−/− mice are more susceptible than control mice to *Listeria monocytogenes* (32) and *Mycobacterium tuberculosis* (33). Intraperitoneal pretreatment with LDL blocks *Vibrio vulnificus* LPS-induced lethality in mice (34). Therefore, the relationship between the anti-infective spectrum of lipoproteins (LDL and HDL) and LPS structure in different species of Gram-negative bacteria is highly complex. A recent study confirmed that LDL or HDL detoxify *E. coli* LPS more strongly than do whole *E. coli* or *Neisseria meningitides* (35). In contrast, in both apoE−/− and LDLR−/− mice, hypercholesterolemia

exacerbates virus-induced immunopathological liver disease (36) and decreases resistance to *C. albicans* (37, 38). These findings imply that neither apoE-containing lipoproteins nor LDL provide protective activity against the above two pathogens. However, the mechanism is unclear.

ANTI-INFECTIVE ACTIVITY OF OxLDL

OxLDL is able to up-regulate the expression of some scavenger receptors (Classes A and E) in macrophages; consequently it promotes phagocytosis of Gram-positive and Gram-negative bacteria and endotoxin clearance (39). In addition, the DNA of many pathogens which has been detected in atherosclerotic plaques (40, 41) may be due to bacterial ingestion by macrophages, on which some oxLDL-inducible scavenger receptors are highly expressed. Recently, it has been shown that infection causes an increase in oxidation of LDL and that oxLDL, in turn, promotes phagocytosis of the responsible pathogens (42).

Notably, the natural antibody against PC elicited by oxLDL (43, 44) might provide a broad protection against pathogens since PC has been detected on a number of prokaryotes including Gram-negative and Gram-positive bacteria (such as *S. pneumoniae*, *Bacillus* spp., *Clostridium* spp., *H. influenzae*, *N. meningitides*, *N. gonorrhoea*, *Pseudomonas aeruginosa*, *alpha-hemolytic streptococci*, *Actinobacillus actinomycetemcomitans*, and *T. cruzi)*, and parasites (such as the protozoan *Leishmania major*, trematodes, tapeworm, *Diphyllobothrium latum*, some gastrointestinal nematodes and all filarial nematodes), as well as many fungi (45–49). It has been repeatedly demonstrated that anti-PC antibody helps to prevent upper airway infections caused by *S. pneumoniae* and *H. influenzae* (50–53). The anti-PC antibody can also protect against *A. actinomycetemcomitans in vitro* (54). In contrast, disadvantages for the host in expression of PC by pathogens have also been reported, since PC mediates persistence and invasiveness (48). For example, surface PC appears to contribute to the persistence of *H. influenzae* in the respiratory tract (55, 56). The above contradictory findings might be explained by the difference in molecules to which PC is attached. On the one hand, PC is only a hapten, while on the other hand anti-PC antibodies usually recognize the PC epitope in oxidized phospholipids (57, 58). There have been no systematic studies on the anti-infective activities of anti-PC antibody so far. Thus, we suggest that it is necessary to extend the study of anti-infective properties of the anti-PC antibody to other pathogens. In addition, *in vitro* study has shown that oxLDL, but not native LDL, is a potent inhibitor of cell entry for a broad range of HCV strains (59) and for *Plasmodium sporozoite* (60).

Therefore, oxidation of LDL may be an important response of the host against infections. OxLDL induced by infection may initially protect the host from the harmful effects of bacteria, viruses, and parasites. However, the prolonged presence of oxLDL may contribute to atherosclerosis, since it is thought to play a central role in atherogenesis (61). Thus it obeys the rule that immunity is a double-edged sword (12). Furthermore, in addition to PC, other neoepitopes of oxLDL also induce production of anti-oxLDL antibodies, which may play an important role in the modulation of atherogenesis (62).

In contrast, an *in vitro* study has shown that mildly oxidized LDL inhibits production by human peripheral blood mononuclear cells of antibody against *C. albicans* (63). However, this has not been demonstrated *in vivo*. Thus, it would be valuable to further investigate the anti-infective spectrum of oxLDL.

POSSIBLE ANTI-INVASIVE ACTIVITY OF Lp(a)

Lp(a) has been studied extensively since it was first described 40 years ago (64–67). Lp(a) is present in humans, Old World nonhuman primates, and the European hedgehog. Lp(a) is a cholesterol-rich lipoprotein similar in structure to LDL, but containing an additional apo(a) moiety bound to apoB100 via a disulfide bridge. Apo(a) shares a high homology with Plg. It has been reported that Lp(a) is a risk factor for cardiovascular disease via both atherogenic and thrombotic mechanisms because Lp(a) contains LDL and there is a similarity between apo(a) and Plg. However, the physiological role of Lp(a) remains elusive. Some authors suggest that Lp(a) might promote or accelerate wound healing and repair of tissue injuries (68). Apo(a), independent of its interaction with Plg, has recently been demonstrated to inhibit neutrophil recruitment in some peritoneal inflammatory models of apo(a) transgenic mice. This suggests that apo(a) might play a beneficial role in humans by suppressing inflammation (69).

It has been reported that a vast number of pathogens, including a number of Gram-negative and Gram-positive bacteria, recruit human plasmin(ogen) through the lysine residue in their surface Plg receptors, and some even produce Plg activators to penetrate tissue barriers (70). Activation and regulation of plasmin(ogen) may play an important role in the invasion of pathogens (71, 72). For example, streptokinase secreted from GAS is highly specific for activation of human Plg, and human Plg-transgenic mice are highly susceptible to GAS (73). Additionally, the PAM-positive M type 53 of GAS causes a 60% increase in mortality in transgenic mice when compared with control mice, whereas the PAM-negative isogenic mutant of this

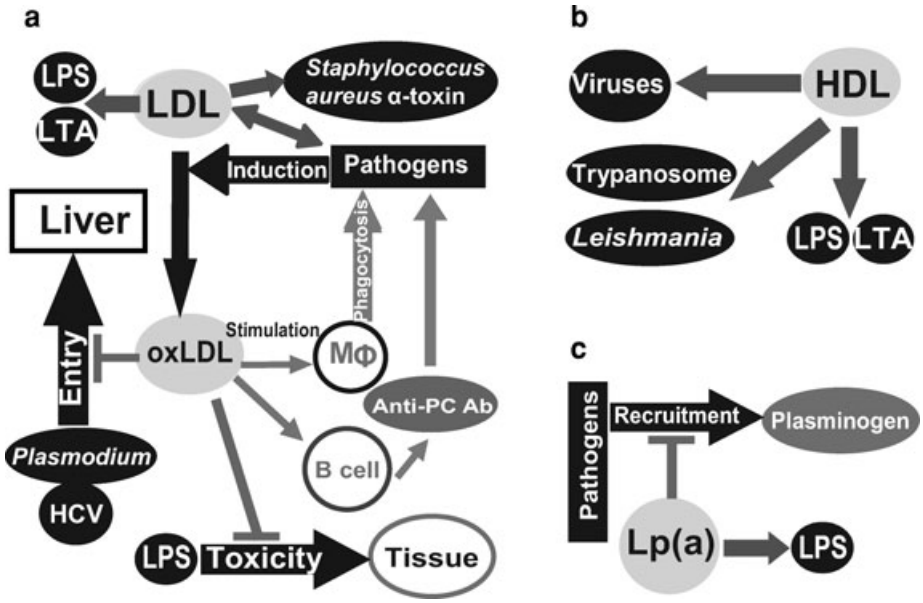

Fig. 1. The anti-infective immunity of plasma lipoproteins. (a), (b) and (c) delineate LDL, HDL and Lp(a)-related anti-infective mechanisms, respectively. LDL, HDL and Lp(a) can detoxify LPS and LTA. LDL directly interacts with pathogens, including inactivating *S. aureus* α-toxin. Infections may induce oxidation of LDL. OxLDL plays important anti-infective roles in an indirect way via oxLDL-activated macrophage and oxLDL-elicited anti-PC antibody. OxLDL also directly serves a protective role in endotoxin-induced tissue damage. In addition, oxLDL may inhibit the entry of hepatic C virus into liver cells. *Plasmodium* sporozoite invasion of host hepatocytes is significantly reduced by ox-LDL, but not by LDL or HDL. HDL broadly, but mildly, prevents virus infections. Trypanosome lytic factors not only completely protect humans from infection by most species of African trypanosomes but also inhibit intracellular infection by *Leishmania*. Lp(a) might compete for the binding of Plg to pathogens and reduce the amount of Plg immobilized on the pathogen surface. Thus, Lp(a) might play an important role in preventing infections.

strain shows only minimal virulence in both wild-type and transgenic mice. Therefore, many infections may be inhibited or prevented to some extent if recruitment and activation of host Plg by pathogens is blocked or inhibited (73). We consider that Lp(a) might constitute part of the host defense system for inhibiting pathogens by recruiting host plasmin(ogen), since it has an anti-fibrinolytic activity (74). In fact, one *in vitro* experiment has shown that Lp(a) inhibits Plg activation by streptokinase (75). We have also reported that Lp(a) inhibits binding between *S. aureus* CMCC26003 and Plg, and subsequently decreases urokinase-type Plg activator-activated fibrinolytic activity on streptococcal cells *in vitro* (presented at the Ninth National Conference on Plasma Lipoprotein, Xining, China, October 24, 2008). Thus, further research on the interaction of Lp(a) with other pathogens is warranted.

In addition, Lp(a) is as potent as LDL in inhibiting LPS-stimulated tumor necrosis factor synthesis by human mononuclear cells (76). This implies that Lp(a) may be an important factor in determining the amplitude of the response to LPS in humans, as there is a great variation in Lp(a) concentrations among individuals (76). Therefore Lp(a), with its combination of apo(a) and LDL, might be a potent anti-infective molecule in humans.

CONCLUSION

Taken together we suggest that, besides their primary role in lipid transport, lipoproteins participate in innate immunity since they have broad preventive effects against bacterial, viral and parasitic infections (summarized in Fig. 1 and Table 1). Many experiments have been conducted using mouse models. However, the effects of infection and inflammation on cholesterol metabolism differ between primates and rodents (3); in the latter HDL seems to have the same role as LDL in humans and vice versa (77). Therefore, data from studies with mouse models may not be fully applicable to the situation in humans, but plasma lipoproteins are doubtlessly important components of the immune system in both groups. Lipoproteins are complicated supermolecular complexes and their multi-functional characteristics warrant further experiments and clinical trials.

In addition, the cumulative evidence suggests that infections may induce or promote atherosclerosis (21, 41,

Table 1. The complex interplay between plasma lipoproteins and infections

Pathogen	HDL	LDL	oxLDL[a]
Hepatitis C virus	$-^{t,h}$ (23, 24)	$n^{t,h}$ (59)	$+^{t,h}$ (59)
Hepatotropic lymphocytic choriomeningitis virus	n	$-^{m}$ (36)	n
Rabies, vesicular stomatitis, Japanese encephalitis, rubella, and SA-11 rota- viruses.	$+^{t,h}$ (19, 20)	$+^{t,h}$ (20, 83, 84)	n
Epstein-Barr, herpes simplex, HIV, xenotropic, Sindbis, vaccinia, Coxsackie, polio, Mengo, and influenza viruses.	$+^{t,h}$ (18, 19)	$n^{t,h}$ (19)	n
Streptococcus pyogenes	$?^{t,h}$ (31)	$?^{t,h}$ (17)	n
Staphylococcus aureus	n	$+^{t,h}$ (8)	n
Salmonella typhimurium	n	$+^{m}$ (29)	n
Vibrio vulnificus	n	$+^{m}$ (34)	n
Yersinia pestis	n	$?^{t,h}$ (30)	n
Klebsiella pneumoniae	$+^{m}$ (28)	$?^{m}$ (27)	n
Listeria monocytogenes	$?^{m}$ (32)	$?^{m}$ (32)	n
Mycobacterium tuberculosis	$?^{m}$ (33)	n^{m} (33)	n
Streptococcus pneumoniae,	n	n	$+^{m}$ (50, 51), $^{t,h;m}$ (53)
Haemophilus influenzae	n	n	$+^{m}$ (51), $^{t,h;m}$ (53); $-^{t,h}$ (55, 57)
Actinobacillus actinomycetemcomitans	n	n	$+^{t,h}$ (54)
Candida albicans	$-^{v,h}$ (25)	$-^{m}$ (37, 38)	$-^{t,h}$ (63)
Trypanosoma brucei and *Leishmania*	$+^{t,h;m}$ (16)	n	n
Plasmodium sporozoite	$n^{t,h;m}$ (60)	$n^{t,h;m}$ (60)	$+^{t,h;m}$ (60)

[a], including oxLDL and oxLDL-elicited anti-PC antibody; [h], human lipoprotein(s) are involved; [m], animal study with mice; n, an anti-infectious of the lipoprotein has not been observed or reported; [t], *in vitro* study; [v], *in vivo* study; –, the lipoprotein enhances infection by the pathogen; +, the lipoprotein protects against infection by the pathogen; ?, further studies to test whether the lipoprotein is a friend to, or foe of, the pathogen are required.

78–82). From our point of view, scientists might readily explain the correlation between infections and atherosclerosis on the basis of the double-edged sword property of the anti-infective immune effects of lipoproteins, and might be able to design more rational and systemic experiments to test this correlation.

CONFLICTS OF INTEREST

The author declares that there are no competing financial interests.

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REFERENCES

1. Ravnskov U. (2003) High cholesterol may protect against infections and atherosclerosis. *QJM* **96:** 927–34.
2. Van Amersfoort E.S., Van Berkel T.J., Kuiper J. (2003) Receptors, mediators, and mechanisms involved in bacterial sepsis and septic shock. *Clin Microbiol Rev* **16:** 379–414.
3. Khovidhunkit W., Kim M.S., Memon R.A., Shigenaga J.K., Moser A.H., Feingold K.R., Grunfeld C. (2004) Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res* **45:** 1169–96.
4. Wendel M., Paul R., Heller A. (2007) Lipoproteins in inflammation and sepsis. II. Clinical aspects. *Intensive Care Med* **33:** 25–35.
5. Murch O., Collin M., Hinds C., Thiemermann C. (2007) Lipoproteins in inflammation and sepsis. I. Basic science. *Intensive Care Med* **33:** 13–24.
6. Pajkrt D., Lerch P.G., Van Der Poll T., Levi M., Illi M., Doran J.E., Arnet B., Van Den Ende A., Ten Cate J.W., Van Deventer S.J. (1997) Differential effects of reconstituted high-density lipoprotein on coagulation, fibrinolysis and platelet activation during human endotoxemia. *Thromb Haemost* **77:** 303–7.
7. Arnaud G., Dominique T., Khalid A.T., Marika R., Morvarid Shir M., Dominique B.-R., Hind B., Annie B., Zera T., Cécile G., Nicolas C., Eric O.-D., Richard M., Didier L. (2009) *Ex vivo* effects of high-density lipoprotein exposure on the lipopolysaccharide-induced inflammatory response in patients with severe cirrhosis. *Hepatology* **49:** 175–84.

8. Bhakdi S., Tranum-Jensen J., Utermann G., Fussle R. (1983) Binding and partial inactivation of *Staphylococcus aureus* alpha-toxin by human plasma low density lipoprotein. *J Biol Chem* **258:** 5899–904.
9. Feingold K.R., Funk J.L., Moser A.H., Shigenaga J.K., Rapp J.H., Grunfeld C. (1995) Role for circulating lipoproteins in protection from endotoxin toxicity. *Infect Immun* **63:** 2041–46.
10. Shiflett A.M., Bishop J.R., Pahwa A., Hajduk S.L. (2005) Human high density lipoproteins are platforms for the assembly of multi-component innate immune complexes. *J Biol Chem* **280:** 32578–85.
11. Memon R.A., Staprans I., Noor M., Holleran W.M., Uchida Y., Moser A.H., Feingold K.R., Grunfeld C. (2000) Infection and inflammation induce LDL oxidation *in vivo*. *Arterioscler Thromb Vasc Biol* **20:** 1536–42.
12. Bochkov V.N., Kadl A., Huber J., Gruber F., Binder B.R., Leitinger N. (2002) Protective role of phospholipid oxidation products in endotoxin-induced tissue damage. *Nature* **419:** 77–81.
13. Miller Y.I., Viriyakosol S., Binder C.J., Feramisco J.R., Kirkland T.N., Witztum J.L. (2003) Minimally modified LDL binds to CD14, induces macrophage spreading via TLR4/MD-2, and inhibits phagocytosis of apoptotic cells. *J Biol Chem* **278:** 1561–68.
14. Walton K.A., Cole A.L., Yeh M., Subbanagounder G., Krutzik S.R., Modlin R.L., Lucas R.M., Nakai J., Smart E.J., Vora D.K., Berliner J.A. (2003) Specific phospholipid oxidation products inhibit ligand activation of Toll-like receptors 4 and 2. *Arterioscler Thromb Vasc Biol* **23:** 1197–203.
15. Bochkov V.N., Mechtcheriakova D., Lucerna M., Huber J., Malli R., Graier W.F., Hofer E., Binder B.R., Leitinger N. (2002) Oxidized phospholipids stimulate tissue factor expression in human endothelial cells via activation of ERK/EGR-1 and Ca++/NFAT. *Blood* **99:** 199–206.
16. Samanovic M., Molina-Portela M.P., Chessler A.D., Burleigh B.A., Raper J. (2009) Trypanosome lytic factor, an antimicrobial high-density lipoprotein, ameliorates *Leishmania* infection. *PLoS Pathog* **5:** e1000276.
17. Courtney H.S., Zhang Y.-M., Frank M.W., Rock C.O. (2006) Serum opacity factor, a streptococcal virulence factor that binds to apolipoproteins A-I and A-II and disrupts high density lipoprotein structure. *J Biol Chem* **281:** 5515–21.
18. Owens B.J., Anantharamaiah G.M., Kahlon J.B., Srinivas R.V., Compans R.W., Segrest J.P. (1990) Apolipoprotein A-I and its amphipathic helix peptide analogues inhibit human immunodeficiency virus-induced syncytium formation. *J Clin Invest* **86:** 1142–50.
19. Singh I.P., Chopra A.K., Coppenhaver D.H., Ananatharamaiah G.M., Baron S. (1999) Lipoproteins account for part of the broad non-specific antiviral activity of human serum. *Antiviral Res* **42:** 211–8.
20. Superti F., Seganti L., Marchetti M., Marziano M.L., Orsi N. (1992) SA-11 rotavirus binding to human serum lipoproteins. *Med Microbiol Immunol* **181:** 77–86.
21. Van Lenten B.J., Wagner A.C., Anantharamaiah G.M., Garber D.W., Fishbein M.C., Adhikary L., Nayak D.P., Hama S., Navab M., Fogelman A.M. (2002) Influenza infection promotes macrophage traffic into arteries of mice that is prevented by D-4F, an apolipoprotein A-I mimetic peptide. *Circulation* **106:** 1127–32.
22. Bartosch B., Verney G., Dreux M., Donot P., Morice Y., Penin F., Pawlotsky J.M., Lavillette D., Cosset F.L. (2005) An interplay between hypervariable region 1 of the hepatitis C virus E2 glycoprotein, the scavenger receptor BI, and high-density lipoprotein promotes both enhancement of infection and protection against neutralizing antibodies. *J Virol* **79:** 8217–29.
23. Voisset C., Callens N., Blanchard E., Op De Beeck A., Dubuisson J., Vu-Dac N. (2005) High density lipoproteins facilitate hepatitis C virus entry through the scavenger receptor class B type I. *J Biol Chem* **280:** 7793–9.
24. Dreux M., Pietschmann T., Granier C., Voisset C., Ricard-Blum S., Mangeot P.E., Keck Z., Foung S., Vu-Dac N., Dubuisson J., Bartenschlager R., Lavillette D., Cosset F.L. (2006) High density lipoprotein inhibits hepatitis C virus-neutralizing antibodies by stimulating cell entry via activation of the scavenger receptor BI. *J Biol Chem* **281:** 18285–95.
25. Netea M.G., Curfs J.H., Demacker P.N., Meis J.F., Van Der Meer J.W., Kullberg B.J. (1999) Infusion of lipoproteins into volunteers enhances the growth of *Candida albicans*. *Clin Infect Dis* **28:** 1148–51.
26. Thompson P.A., Berbee J.F., Rensen P.C., Kitchens R.L. (2008) Apolipoprotein A-II augments monocyte responses to LPS by suppressing the inhibitory activity of LPS-binding protein. *Innate Immun* **14:** 365–74.
27. Netea M.G., Demacker P.N., Kullberg B.J., Boerman O.C., Verschueren I., Stalenhoef A.F., Van Der Meer J.W. (1996) Low-density lipoprotein receptor-deficient mice are protected against lethal endotoxemia and severe gram-negative infections. *J Clin Invest* **97:** 1366–72.
28. De Bont N., Netea M.G., Demacker P.N., Verschueren I., Kullberg B.J., Van Dijk K.W., Van Der Meer J.W., Stalenhoef A.F. (1999) Apolipoprotein E knock-out mice are highly susceptible to endotoxemia and *Klebsiella pneumoniae* infection. *J Lipid Res* **40:** 680–5.
29. Netea M.G., Joosten L.A., Keuter M., Wagener F., Stalenhoef A.F., Van Der Meer J.W., Kullberg B.J. (2009) Circulating lipoproteins are a crucial component of host defense against invasive *Salmonella typhimurium* infection. *PLoS ONE* **4:** e4237.
30. Makoveichuk E., Cherepanov P., Lundberg S., Forsberg A., Olivecrona G. (2003) pH6 antigen of *Yersinia pestis* interacts with plasma lipoproteins and cell membranes. *J Lipid Res* **44:** 320–30.
31. Han R., Caswell C.C., Lukomska E., Keene D.R., Pawlowski M., Bujnicki J.M., Kim J.K., Lukomski S. (2006) Binding of the low-density lipoprotein by streptococcal collagen-like protein Scl1 of *Streptococcus pyogenes*. *Mol Microbiol* **61:** 351–67.
32. Roselaar S.E., Daugherty A. (1998) Apolipoprotein E-deficient mice have impaired innate immune responses to *Listeria monocytogenes in vivo*. *J Lipid Res* **39:** 1740–3.
33. Martens G.W., Arikan M.C., Lee J., Ren F., Vallerskog T., Kornfeld H. (2008) Hypercholesterolemia impairs immunity to tuberculosis. *Infect Immun* **76:** 3464–72.
34. Park K.H., Kim J.S., Lee Y.R., Moon Y.J., Hur H., Choi Y.H., Kim C.H., Kim U.H., Song E.K., Yoo W.H., Lee C.S., Kim B.S., Lee S.H., Ryu P.Y., Han M.K. (2007) Low-density lipoprotein protects *Vibrio vulnificus*-induced lethality through blocking lipopolysaccharide action. *Exp Mol Med* **39:** 673–8.
35. Sprong T., Netea M.G., Van Der Ley P., Verver-Jansen T.J.G., Jacobs L.E.H., Stalenhoef A., Van Der Meer J.W.M., Van Deuren M. (2004) Human lipoproteins have divergent neutralizing effects on *E. coli* LPS, *N. meningitidis* LPS, and complete Gram-negative bacteria. *J Lipid Res* **45:** 742–49.
36. Ludewig B., Jaggi M., Dumrese T., Brduscha-Riem K., Odermatt B., Hengartner H., Zinkernagel R.M. (2001) Hypercholesterolemia exacerbates virus-induced immunopathologic liver disease via suppression of antiviral cytotoxic T cell responses. *J Immunol* **166:** 3369–76.
37. Netea M.G., Demacker P.N., De Bont N., Boerman O.C., Stalenhoef A.F., Van Der Meer J.W., Kullberg B.J. (1997) Hyperlipoproteinemia enhances susceptibility to acute disseminated *Candida albicans*

infection in low-density-lipoprotein-receptor-deficient mice. *Infect Immun* **65:** 2663–7.
38. Vonk A.G., De Bont N., Netea M.G., Demacker P.N., Van Der Meer J.W., Stalenhoef A.F., Kullberg B.J. (2004) Apolipoprotein-E-deficient mice exhibit an increased susceptibility to disseminated candidiasis. *Med Mycol* **42:** 341–8.
39. Murphy J.E., Tedbury P.R., Homer-Vanniasinkam S., Walker J.H., Ponnambalam S. (2005) Biochemistry and cell biology of mammalian scavenger receptors. *Atherosclerosis* **182:** 1–15.
40. Lehtiniemi J., Karhunen P.J., Goebeler S., Nikkari S., Nikkari S.T. (2005) Identification of different bacterial DNAs in human coronary arteries. *Eur J Clin Invest* **35:** 13–6.
41. Ott S.J., El Mokhtari N.E., Musfeldt M., Hellmig S., Freitag S., Rehman A., Kuhbacher T., Nikolaus S., Namsolleck P., Blaut M., Hampe J., Sahly H., Reinecke A., Haake N., Gunther R., Kruger D., Lins M., Herrmann G., Folsch U.R., Simon R., Schreiber S. (2006) Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. *Circulation* **113:** 929–37.
42. Bengtsson T., Karlsson H., Gunnarsson P., Skoglund C., Elison C., Leanderson P., Lindahl M. (2008) 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* **263:** 558–71.
43. Chou M.Y., Hartvigsen K., Hansen L.F., Fogelstrand L., Shaw P.X., Boullier A., Binder C.J., Witztum J.L. (2008) Oxidation-specific epitopes are important targets of innate immunity. *J Intern Med* **263:** 479–88.
44. Baumgarth N., Tung J.W., Herzenberg L.A. (2005) Inherent specificities in natural antibodies: a key to immune defense against pathogen invasion. *Springer Semin Immunopathol* **26:** 347–62.
45. Gillespie S.H., Mcwhinney P.H., Patel S., Raynes J.G., Mcadam K.P., Whiley R.A., Hardie J.M. (1993) Species of alpha-hemolytic streptococci possessing a C-polysaccharide phosphorylcholine-containing antigen. *Infect Immun* **61:** 3076–7.
46. Kolberg J., Hoiby E.A., Jantzen E. (1997) Detection of the phosphorylcholine epitope in streptococci, *Haemophilus* and pathogenic *Neisseriae* by immunoblotting. *Microb Pathog* **22:** 321–9.
47. Weiser J.N., Goldberg J.B., Pan N., Wilson L., Virji M. (1998) 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* **66:** 4263–7.
48. Harnett W., Harnett M.M. (1999) Phosphorylcholine: friend or foe of the immune system? *Immunol Today* **20:** 125–9.
49. Serino L., Virji M. (2002) Genetic and functional analysis of the phosphorylcholine moiety of commensal Neisseria lipopolysaccharide. *Mol Microbiol* **43:** 437–48.
50. Mold C., Rodic-Polic B., Du Clos T.W. (2002) Protection from *Streptococcus pneumoniae* infection by C-reactive protein and natural antibody requires complement but not Fc gamma receptors. *J Immunol* **168:** 6375–81.
51. Tanaka N., Fukuyama S., Fukuiwa T., Kawabata M., Sagara Y., Ito H.O., Miwa Y., Nagatake T., Kiyono H., Kurono Y. (2007) Intranasal immunization with phosphorylcholine induces antigen specific mucosal and systemic immune responses in mice. *Vaccine* **25:** 2680–7.
52. Binder C.J., Horkko S., Dewan A., Chang M.K., Kieu E.P., Goodyear C.S., Shaw P.X., Palinski W., Witztum J.L., Silverman G.J. (2003) Pneumococcal vaccination decreases atherosclerotic lesion formation: molecular mimicry between *Streptococcus pneumoniae* and oxidized LDL. *Nat Med* **9:** 736–43.
53. Goldenberg H.B., Mccool T.L., Weiser J.N. (2004) Cross-reactivity of human immunoglobulin G2 recognizing phosphorylcholine and evidence for protection against major bacterial pathogens of the human respiratory tract. *J Infect Dis* **190:** 1254–63.
54. Purkall D., Tew J.G., Schenkein H.A. (2002) Opsonization of *Actinobacillus actinomycetemcomitans* by immunoglobulin G antibody reactive with phosphorylcholine. *Infect Immun* **70:** 6485–8.
55. Lysenko E.S., Gould J., Bals R., Wilson J.M., Weiser J.N. (2000) Bacterial phosphorylcholine decreases susceptibility to the antimicrobial peptide LL-37/hCAP18 expressed in the upper respiratory tract. *Infect Immun* **68:** 1664–71.
56. Weiser J.N., Pan N., Mcgowan K.L., Musher D., Martin A., Richards J. (1998) 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* **187:** 631–40.
57. Lysenko E., Richards J.C., Cox A.D., Stewart A., Martin A., Kapoor M., Weiser J.N. (2000) The position of phosphorylcholine on the lipopolysaccharide of *Haemophilus influenzae* affects binding and sensitivity to C-reactive protein-mediated killing. *Mol Microbiol* **35:** 234–45.
58. Shaw P.X., Horkko S., Chang M.K., Curtiss L.K., Palinski W., Silverman G.J., Witztum J.L. (2000) Natural antibodies with the T15 idiotype may act in atherosclerosis, apoptotic clearance, and protective immunity. *J Clin Invest* **105:** 1731–40.
59. Von Hahn T., Lindenbach B.D., Boullier A., Quehenberger O., Paulson M., Rice C.M., Mckeating J.A. (2006) Oxidized low-density lipoprotein inhibits hepatitis C virus cell entry in human hepatoma cells. *Hepatology* **43:** 932–42.
60. Rodrigues C.D., Hannus M., Prudencio M., Martin C., Goncalves L.A., Portugal S., Epiphanio S., Akinc A., Hadwiger P., Jahn-Hofmann K., Rohl I., Van Gemert G.J., Franetich J.F., Luty A.J., Sauerwein R., Mazier D., Koteliansky V., Vornlocher H.P., Echeverri C.J., Mota M.M. (2008) Host scavenger receptor SR-BI plays a dual role in the establishment of malaria parasite liver infection. *Cell Host Microbe* **4:** 271–82.
61. 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. (2008) Impact of plasma oxidized low-density lipoprotein removal on atherosclerosis. *Circulation* **118:** 75–83.
62. Shoenfeld Y., Wu R., Dearing L.D., Matsuura E. (2004) Are anti-oxidized low-density lipoprotein antibodies pathogenic or protective? *Circulation* **110:** 2552–58.
63. Giordani L., Mattioli B., Quaranta M.G., Giacomini E., Libri I., Vari R., Masella R., Viora M. (2005) Mildly oxidized low-density lipoprotein inhibits the *in vitro* induction of the specific antibody response to *Candida albicans*. *Free Radic Biol Med* **39:** 960–9.
64. Mccormick S.P. (2004) Lipoprotein(a): biology and clinical importance. *Clin Biochem Rev* **25:** 69–80.
65. Berglund L., Ramakrishnan R. (2004) Lipoprotein(a): an elusive cardiovascular risk factor. *Arterioscler Thromb Vasc Biol* **24:** 2219–26.
66. Koschinsky M.L. (2006) Novel insights into Lp(a) physiology and pathogenicity: more questions than answers? *Cardiovasc Hematol Disord Drug Targets* **6:** 267–78.
67. Anuurad E., Boffa M.B., Koschinsky M.L., Berglund L. (2006) Lipoprotein(a): a unique risk factor for cardiovascular disease. *Clin Lab Med* **26:** 751–72.
68. Lippi G., Guidi G. (2000) Lipoprotein(a): from ancestral benefit to modern pathogen? *QJM* **93:** 75–84.

69. Hoover-Plow J., Hart E., Gong Y., Shchurin A., Schneeman T. (2009) A physiological function for apolipoprotein(a): a natural regulator of the inflammatory response. *Exp Biol Med* **234:** 28–34.
70. Lahteenmaki K., Kuusela P., Korhonen T.K. (2001) Bacterial plasminogen activators and receptors. *FEMS Microbiol Rev* **25:** 531–52.
71. Lahteenmaki K., Edelman S., Korhonen T.K. (2005) Bacterial metastasis: the host plasminogen system in bacterial invasion. *Trends Microbiol* **13:** 79–85.
72. Sun H. (2006) The interaction between pathogens and the host coagulation system. *Physiology (Bethesda)* **21:** 281–8.
73. Sun H., Ringdahl U., Homeister J.W., Fay W.P., Engleberg N.C., Yang A.Y., Rozek L.S., Wang X., Sjobring U., Ginsburg D. (2004) Plasminogen is a critical host pathogenicity factor for group A streptococcal infection. *Science* **305:** 1283–6.
74. Han R. (2009) Plasma lipoproteins are important components of the host defense system? *J Immunol* **182:** 134.74.
75. Edelberg J.M., Gonzalez-Gronow M., Pizzo S.V. (1989) Lipoprotein a inhibits streptokinase-mediated activation of human plasminogen. *Biochemistry* **28:** 2370–4.
76. Netea M.G., De Bont N., Demacker P.N., Kullberg B.J., Jacobs L.E., Verver-Jansen T.J., Stalenhoef A.F., Van Der Meer J.W. (1998) Lipoprotein(a) inhibits lipopolysaccharide-induced tumor necrosis factor alpha production by human mononuclear cells. *Infect Immun* **66:** 2365–7.
77. Rhainds D., Brissette L. (2004) The role of scavenger receptor class B type I (SR-BI) in lipid trafficking: Defining the rules for lipid traders. *Int J Biochem Cell Biol* **36:** 39–77.
78. Buyukhatipoglu H., Tiryaki O., Tahta K., Usalan C. (2007) Inflammation as a risk factor for carotid intimal-medial thickening, a measure of subclinical atherosclerosis in haemodialysis patients: the role of chlamydia and cytomegalovirus infection. *Nephrology (Carlton)* **12:** 25–32.
79. Westerterp M., Berbee J.F., Pires N.M., Van Mierlo G.J., Kleemann R., Romijn J.A., Havekes L.M., Rensen P.C. (2007) Apolipoprotein C-I is crucially involved in lipopolysaccharide-induced atherosclerosis development in apolipoprotein E-knockout mice. *Circulation* **116:** 2173–81.
80. Milioti N., Bermudez-Fajardo A., Penichet M.L., Oviedo-Orta E. (2008) Antigen-induced immunomodulation in the pathogenesis of atherosclerosis. *Clin Dev Immunol* **2008:** 723539.
81. Mayr M., Kiechl S., Tsimikas S., Miller E., Sheldon J., Willeit J., Witztum J.L., Xu Q. (2006) Oxidized low-density lipoprotein autoantibodies, chronic infections, and carotid atherosclerosis in a population-based study. *J Am Coll Cardiol* **47:** 2436–43.
82. Mattila K.J., Pussinen P.J., Paju S. (2005) Dental infections and cardiovascular diseases: a review. *J Periodontol* **76:** 2085–8.
83. Seganti L., Grassi M., Mastromarino P., Pana A., Superti F., Orsi N. (1983) Activity of human serum lipoproteins on the infectivity of rhabdoviruses. *Microbiologica* **6:** 91–9.
84. Shortridge K.F., Ho W.K. (1976) Comparison of the activities in inhibition of haemagglutination by different togaviruses for human serum lipoproteins and their constituents. *J Gen Virol* **33:** 523–7.