commentary

Lipids: a key player in the battle between the host and microorganisms[1]

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Products of gram negative bacteria (LPS), gram positive bacteria (lipoteichoic acid), fungi (zymosan), and viruses (RNA) are recognized by toll receptors on macrophages and other cells and thereby induce marked changes in lipid and lipoprotein metabolism (1). It is now increasingly recognized that lipids and lipoproteins play an important role in host defense as part of the innate immune system [for detailed review, see (1)]. For example, lipoproteins including HDL, chylomicrons, VLDL, and LDL can bind and neutralize LPS, lipoteichoic acid, and viruses. The binding of LPS by lipoproteins has been shown to protect animals from LPS induced death. Numerous studies have shown that animals that have elevations in serum lipid/lipoprotein levels are protected from the toxicity of LPS, whereas animals with low circulating lipid/lipoprotein levels are more sensitive to the toxic effects of LPS. Studies have shown that HDL may inhibit the ability of certain viruses to penetrate cells. Moreover, lipoproteins can block the adhesion of bacteria to host cells and reduce tissue invasion (2). Another example involves cell-to-cell communication between bacteria, which coordinates gene expression and the production of virulence factors (3). Studies have shown that *Staphylococcus aureus* produce an autoinducing peptide that binds to surface receptors on the bacteria increasing the production of toxins and invasive enzymes (3). Apo B-containing lipoproteins sequesters the autoinducing peptide and reduces the infectivity of *S. aureus* (3, 4).

Furthermore, lipoproteins have been shown to play an important role in defending against parasitic infections (1). Perhaps the best example is the resistance of humans to *Trypanosoma brucei brucei*, which is mediated by apo L-I and haptoglobin-related protein carried on HDL particles (5). Finally, alterations in lipid and lipoprotein metabolism during infection may allow for the redistribution of nutrients to cells that are important in host defense or tissue repair (1). For example, infection has been shown to decrease reverse cholesterol transport, which may help conserve cholesterol in macrophages and other cells that play key roles in host defense (6). Thus, in addition to their transport functions, there is abundant evidence that lipoproteins and lipids protect the host from the toxic effects of microorganisms.

Although lipids and lipoproteins play a key role in host defense, it needs to be recognized that microorganisms can coopt the lipid/lipoprotein system to facilitate their reproductive needs. Probably the best example of this is seen with the hepatitis C virus (HCV) (7–9). The HCV virus replicates in hepatic cells. In contrast to most viruses, the secretion of HCV occurs coupled to the secretion of VLDL particles. Inhibition of VLDL production and secretion with MTP inhibitors, RNA-mediated suppression of apoB synthesis, or inhibitors of acyl-CoA synthetase 3, an enzyme required for VLDL formation results in the inhibition of HCV particle secretion. Additionally, HCV infection stimulates the formation of VLDL by enhancing hepatic lipid synthesis and inhibitors of cholesterol or fatty acid synthesis also inhibit HCV replication. Thus, HCV has coopted the hepatic VLDL secretory system to facilitate its ability to exit hepatic cells. In the serum, HCV remains complexed with VLDL particles. This may protect HCV from immune recognition and may partially account for the inability to produce a vaccine that protects from HCV infection. To reenter hepatic cells for a new round of infection, the HCV complexed with VLDL utilizes both the LDL and SR-B1 receptor. The uptake of HCV by hepatic cells can be inhibited by VLDL or LDL competition. Thus, HCV utilizes the VLDL secretory and uptake pathways to facilitate its replication, secretion, and entry into cells (7–9).

Other examples of pathogens coopting the lipid/lipoprotein system are: *a*) certain human rhinoviruses utilize the LDL receptor and other LDL family members for entry into cells (10); *b*) *Chlamydia trachomatis* and *Chlamydia pneumoniae* bind to apo B-containing lipoproteins leading to the increased entry of chlamydial particles into cells (11); *c*) Ebola virus in the lysosomal compartment binds to NPC1, which facilitates its escape into the host cytoplasm (12, 13); *d*) the ability of *Mycobacterium tuberculosis* to catabolize cholesterol as an energy source, which might facilitate the ability of this microorganism to survive in macrophages

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(Of note, hypercholesterolemia increases the mortality of mice infected with *M. tuberculosis*) (14, 15); *e*) the utilization of host cholesterol by *Toxoplasma gondii* for growth and proliferation (16–18); and *f*) *Helicobacter pylori* is unable to synthesize cholesterol and therefore acquires exogenous cholesterol from the host (19). Glucosylated cholesterol is a major component of the cell wall of *H. pylori* and is required for cell proliferation (19).

In this issue of the *Journal of Lipid Research*, Ghosh et al. (20) present data demonstrating that hypercholesterolemia protects from *Leishmania donovani* infections in a mouse model. *L. donovani* causes visceral leishmaniasis (kala-azar), an important parasitic infection in Bangladesh, India, Nepal, Sudan, Ethiopia, and Brazil with approximately 500,000 new cases and 50,000 deaths each year (21). *L. donovani* is transmitted by sand fleas and is an obligate intracellular parasite surviving in macrophages (21). Inside the macrophages the parasite depletes cholesterol, disrupting lipid rafts leading to defective antigen presentation (22, 23). These abnormalities can be reversed by providing liposomal cholesterol to the macrophages. In the present study, Ghosh et al. (20) show that manipulating serum lipid levels can markedly affect the infectivity of *L. donovani* . Apo E-deficient mice, with elevated serum cholesterol and triglyceride levels, have a decreased parasite burden compared with control mice. That this is not due specifically to the absence of apo E is shown by the fact that increasing serum lipid levels (mainly serum cholesterol) in control mice by feeding an atherogenic diet also is protective against *L. donovani* infection. Conversely, lowering serum lipid levels by statin treatment increased parasite load. These results coupled with previous studies in hamsters demonstrating that liposomal cholesterol reduces *L. donovani* infectivity provides convincing evidence that serum cholesterol levels play an important role in modulating *L. donovani* infections in animal models (24).

In addition to demonstrating the importance of serum cholesterol levels, Ghosh et al. (20) provide mechanistic insights that might explain the protective effects of elevations in serum cholesterol levels. Macrophages from apo E-deficient mice have an increase in membrane cholesterol and *L. donovani* infection does not markedly deplete membrane cholesterol levels, which is in contrast to what happens with infection of macrophages from control animals. Associated with this maintenance of membrane cholesterol, macrophages from apo E-deficient mice that are infected with *L. donovani* are better antigen presenters than control macrophages infected with *L. donovani*, which may be due to the increased membrane cholesterol allowing for the persistence of lipid rafts, which are well recognized to play an important role in antigen presentation. This ability of macrophages from apo E-deficient mice to present antigens allows for the expansion of antileishmanial T cells that inhibit the growth of *L. donovani* limiting the infectivity. In fact, the authors demonstrate that the splenocytes from apo E-deficient mice produce a cytokine profile that is associated with protection from *L. donovani* infection, while splenocytes from control mice infected with *L. donovani* are unable to mount an effective host defense. Thus, *L. donovani* infection by depleting macrophages of cholesterol enhances its ability to be a successful pathogen. However, the host can negate this strategy and outwit the pathogen by increasing serum lipid levels, which prevents the degradation of macrophage immune function allowing for a robust host defense.

In the battle between microorganism and the host, microbes have often utilized the lipids/lipoproteins provided by the host to facilitate their proliferation. By recognizing these interactions, it might be possible to tip the scales in the favor of the host by appropriately altering lipid/lipoprotein metabolism. The studies of Ghosh et al. provide a potential novel approach to treating *L. donovani* infections. Similar to other infections, *L. donovani* infection leads to a decrease in serum cholesterol levels (25, 26). If serum cholesterol levels were maintained or even increased above normal, could this potentiate the host's normal defense mechanisms and allow for the control of this specific infection? A possible benefit of a Western, proatherogenic diet maybe protection from Leishmania! However, it is important to recognize that although a particular strategy may be beneficial for one specific host pathogen interaction, the same approach might be harmful for another host pathogen interaction. For example, although the present study demonstrates that elevated circulating cholesterol levels might be of benefit for *L. donovani* infections, other studies have shown that elevated lipid levels facilitate *M. tuberculosis* infections (14). A detailed knowledge of each host pathogen interaction will be required to design appropriate dietary or therapeutic strategies.

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