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The role of gut-derived oxidized lipids and bacterial lipopolysaccharide in systemic inflammation and atherosclerosis

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Purpose of review
This review explores mechanisms by which gut-derived bacterial lipopolysaccharide (LPS) and oxidized phospholipids contribute to chronic systemic inflammation and atherosclerosis.

Recent findings
Gut-derived LPS enters through the small intestine via two distinct pathways that involve high density lipoproteins (HDL) and chylomicrons. Gut-derived LPS can bind to the LPS-binding protein (LBP) and to HDL_3 in the small intestine and travel through the portal vein to the liver where it does not elicit an inflammatory reaction, and is inactivated or it can bind to HDL_2 and travel through the portal vein to the liver where it elicits an inflammatory reaction. Alternatively, in the small intestine, LPS can bind to LBP and chylomicrons and travel through the lymphatics to the systemic circulation and enhance inflammatory processes including atherosclerosis. Oxidized phospholipids formed in the small intestine regulate the levels and uptake of LPS in small intestine by regulating antimicrobial proteins such as intestinal alkaline phosphatase. Gut-derived LPS and oxidized phospholipids may be responsible for the persistent inflammation seen in some persons with human immunodeficiency virus on potent antiretroviral therapy with undetectable virus levels.

Summary
By targeting gut-derived oxidized phospholipids, the uptake of gut-derived LPS may be reduced to decrease systemic inflammation and atherosclerosis.

Keywords
apolipoprotein A-I mimetic peptides, atherosclerosis, human immunodeficiency virus, lipopolysaccharide, oxidized phospholipids

INTRODUCTION

Inflammation is recognized as a major contributor to the development of atherosclerosis [1]. Lipopolysaccharide (LPS) is a potent inducer of inflammation [2]. In humans, the major source of LPS is the gut, which contains 95% of the human microbiome [3]. LPS and its binding protein (LBP) are increased in persons at increased risk for atherosclerosis [4–15]. Most plasma LPS binds to lipoproteins [16–28,29▪▪]. LPS complexed to low-density lipoprotein (LDL) interacts with human monocyte-derived macrophages via the LDL receptor [16]. LPS that was not associated with lipoproteins disrupted the integrity of endothelial monolayers, while the monolayers remained intact if the same quantity of LPS was complexed to LDL (LPS-LDL). The LPS-LDL was transported across the intact monolayers, and increased monocyte-chemotactic activities in aortic endothelial cells and smooth muscle cells [30]. Thus, the formation of LPS-LDL complexes reduced acute toxicity in endothelial cells caused by LPS, but initiated a chronic inflammatory response in the artery wall cells.

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KEY POINTS

- Gut-derived oxidized phospholipids regulate the levels and uptake of gut-derived LPS.
- Gut-derived LPS can enter the circulation by either the portal vein or the chylomicron pathways.
- Intestinal alkaline phosphatase is an important regulator of the levels and uptake of biologically active gut-derived LPS.
- Gut-derived LPS and oxidized lipids may play an important role in the chronic inflammation that persists in some persons with HIV despite achieving undetectable virus levels on potent antiviral therapy.
- Oral apoA-I mimetic peptides decrease gut-derived oxidized phospholipids and gut-derived LPS.

GUT-DERIVED LIPOPOLYSACCHARIDE ENTERS VIA THE PORTAL VEIN OR CHYLOMICRON PATHWAYS

Approximately 30% of plasma high density lipoproteins (HDL) in mice is generated in the intestine by adenosine triphosphate (ATP)-binding cassette, subfamily A, member 1 (ABCA1) and is secreted directly into the circulation [31]. Han *et al.* [29▪▪] used a photoactivatable apoA-I knock-in mouse to trace HDL, and found in confirmation of the work of Brunham *et al.* [31] that HDL derived from small bowel enterocytes directly entered the portal vein and was not found in lymph until after the HDL passed through the liver and entered the systemic circulation. The major site of intestinal HDL formation was identified as being in the ileum [29▪▪]. Albumin levels in portal and systemic blood were similar, but apoA-I levels in the portal vein were ~60% of those in systemic plasma in mice and humans. Intestine-specific knockout of ABCA1 in mice reduced HDL-cholesterol levels in portal blood by >75%, while liver-specific ABCA1 knockout only decreased portal blood HDL-cholesterol levels by 25%, indicating that the main source of HDL in portal blood is enterically derived. HDL in the portal vein was mainly small sized HDL_3. Immunopurified HDL_3 was enriched in LBP that was lost during isolation by ultracentrifugation. In the presence of LBP, HDL_3 from mice or humans better inhibited LPS activity compared to HDL_2. LPS bound to HDL_2 readily transferred to LDL or VLDL, while most of the LPS bound to HDL_3 remained associated with HDL_3. LDL efficiently bound LPS, but in contrast with the findings of Vreugdenhil *et al.* [18], in the experiments of Han *et al.* [29▪▪], LDL did not bind LBP. Moreover, in contrast to HDL_3, LDL did not neutralize LPS bioactivity, nor did it dampen inflammatory responses in Kupffer cells [29▪▪]. It was determined that the binding of HDL_3 to LBP promoted the sequestration of LPS, but did not prevent acyloxyacyl hydrolase from inactivating LPS [29▪▪]. Thirty minutes after injection into the portal vein of biotin labelled LPS complexed to either HDL_3 or complexed to HDL_2, a time when the HDL had passed through the liver to enter the systemic circulation, most of the LPS associated with HDL_3 in the systemic circulation was inactive compared to LPS associated with HDL_2 or LDL [29▪▪]. Injection into the portal vein of LPS-loaded lipoproteins caused an acute increase in the levels of liver aspartate aminotransferase with LPS-HDL_3 eliciting the lowest increase [29▪▪]. The authors concluded that HDL_3 masks LPS, which prevents its binding to Kupffer cells, but HDL_3-associated LPS remains susceptible to inactivation by acyloxyacyl hydrolase [29▪▪].

In addition to gut-derived LPS entering via the portal vein, alternatively in the small intestine, it can enter via the chylomicron pathway [19,20]. In both the small and large intestine, the mucus layers constitute the interface between enterocytes and the bacteria in the lumen of the intestine. There are two mucus layers in the colon. The inner mucus layer is dense and provides a strong physical barrier to bacteria directly interacting with the enterocytes [32,33]. In the small intestine, there is much less of a dense protective layer, and in the case of the jejunum, the thin mucous layer is at times incomplete [34]. Because of the absence of a strong physical barrier such as that in the colon, the separation of bacteria from enterocytes in the small intestine is more dependent on an array of antibacterial peptides and proteins that are secreted into the mucus to regulate the number of bacteria and their interaction with the enterocytes [35].

Mukherjee *et al.* [36▪] compared feeding low-density lipoprotein receptor null ($Ldlr^{-/-}$) mice a low-fat, low-cholesterol chow diet versus feeding the mice a high-fat, high-cholesterol Western diet. Surprisingly, the Western diet contained less oxidized phospholipids compared to the chow diet. However, on feeding the diets to the mice, the content of oxidized phospholipids (measured as immunoreactivity to E06 antibodies) in the jejunum mucus increased on the Western diet compared to the chow diet, indicating that the metabolism of the Western diet promoted the formation of oxidized phospholipids [36▪]. On the Western diet, the mucus in the jejunum also contained higher levels of reactive oxygen species compared to mice fed the chow diet. The mucus in the jejunum on the Western diet had an altered taxonomic composition of bacteria; *Akkermansia muciniphila* virtually disappeared from the mucus. However,

overall bacteria numbers in the jejunum and the levels of bacterial LPS were increased in the jejunum mucus from the mice receiving the Western diet, and gut permeability increased on the Western diet. Gene and protein expression decreased in the jejunum of mice fed the Western diet for multiple peptides and proteins that are secreted into the mucus layer of the jejunum that act to limit bacteria numbers and limit their interaction with enterocytes. These included islet derived proteins, defensins, mucin 2, surfactant A, apoA-I, and others [36▪]. On feeding the mice the Western diet, gene, and protein expression in jejunum decreased for interleukin 36γ, interleukin 23 and interleukin 22, which are cytokines critical for antimicrobial activity. Feeding the Western diet decreased gene and protein expression for Notch signaling as well as for the basic helix-loop-helix transcription factor atonal homolog 1(*Atoh1*), which is required for the formation of functional goblet and Paneth cells. A zinc-finger protein family member, growth factor independent protein 1 is a direct target gene of *Atoh1* and is required for the formation of Paneth cells and goblet cells; its gene and protein expression were also decreased by the Western diet. Consistent with these changes, the number of goblet and Paneth cells were decreased in jejunum from mice fed the Western diet. These changes provided an explanation for the decreased mucin 2 and antimicrobial levels found in the jejunum of mice fed the Western diet [36▪]. The decreased antimicrobial defenses in the jejunum together with increased gut permeability were associated with increased levels of LPS in lymph draining from the jejunum, and in the plasma of the mice fed the Western diet [36▪].

Class A amphipathic helical apoA-I mimetic peptides containing 18 amino acids of which 4–6 are phenylalanine residues on the hydrophobic face of the peptides have been to shown to bind oxidized phospholipids with such high affinity that they cannot interact with cells [37–39]. Adding to the diet a concentrate of transgenic tomatoes expressing one of these peptides with 6 phenylalanine residues (Tg6F) ameliorated all of the Western diet-mediated changes [36▪]. Adding oxidized phospholipids *ex vivo* to the jejunum from mice fed a chow diet recapitulated the changes in gene expression *in vivo* that occurred when the mice were fed a Western diet, and these changes in gene expression were prevented with the addition of the 6F peptide [36▪]. These studies demonstrate that the metabolism of the Western diet leads to increased levels of oxidized phospholipids in the small intestine, which decrease antimicrobial defenses in the small intestine, and result in increased levels of LPS in the small intestine with increased gut-permeability that leads to increased levels of LPS in the lymph and blood [36▪]. Since Tg6F decreases levels of LPS in the mucus of the small intestine, it is likely that it would decrease the entry of LPS by both the portal vein and the chylomicron pathways.

INTESTINAL ALKALINE PHOSPHATASE

Ghosh *et al.* [40] reported that feeding a Western diet to *Ldlr*$^{-/-}$ mice reduced the activity of intestinal alkaline phosphatase, which led to decreased intestinal barrier function and increased plasma levels of LPS. Nonabsorbable antibiotics or curcumin ameliorated these parameters and reduced aortic atherosclerosis [40]. Mukherjee *et al.* [36▪] reported that jejunum gene expression for intestinal alkaline phosphatase (*Alp1*) was decreased in mice fed a Western diet, and the decrease was prevented by adding Tg6F to the diet. They also reported that on adding oxidized phospholipids *ex vivo* to jejunum taken from mice on a chow diet, *Alp1* gene expression decreased, and the decrease was prevented if the 6F peptide was added [36▪]. Intestinal alkaline phosphatase is secreted by enterocytes into the mucus and lumen of the intestine where it detoxifies LPS by catalysing the dephosphorylation of the Lipid A moiety [41]. Ghosh *et al.* [42] developed intestine-specific intestinal alkaline phosphatase transgenic mice expressing chimeric human intestinal alkaline phosphatase. The chimeric intestinal alkaline phosphatase was developed by Kiffer-Moreira *et al.* [43] and contains domains from human intestinal alkaline phosphatase and human placental alkaline phosphatase. The chimeric enzyme displays increased heat stability, increased Zn^{2+} binding affinity, increased transphosphorylation, a higher turnover number, narrower substrate specificity, and selectivity for bacterial LPS. In normal mice, the expression of intestinal alkaline phosphatase is highest in the duodenum and progressively declines along the length of the intestine such that there is minimal expression in the colon. In contrast, the transgene overexpressed uniformly along the entire length of the intestine including the colon, and improved barrier dysfunction and glucose intolerance in C57BL/6 mice [42].

Subsequently, Ghosh *et al.* [44▪▪] crossed these transgenic mice into a *Ldlr*$^{-/-}$ background. On feeding a Western diet, the transgenic mice gained less weight than the nontransgenic control mice. When the control mice were fed the Western diet there was disruption of the mucosal layer, which was not seen in the transgenic mice [44▪▪]. The transgenic mice demonstrated markedly lower levels of plasma LPS compared to the control mice on the Western diet, and the transgenic mice had lower plasma cholesterol levels and reduced lipid accumulation of

cholesteryl esters and triglycerides in the liver, but not in adipose tissue. The expression of macrophage inflammatory protein 1 alpha was significantly reduced in the livers of the transgenic mice [44▪▪]. The expression of fatty acid transporters CD36 and FTP4 and the cholesterol transporter, NPC1L1, were reduced in the small intestine of transgenic mice providing a possible explanation for the lower lipid levels in plasma and liver. Additionally, intracellular fatty acid binding proteins 1 and 2 were reduced in jejunum and the latter was also reduced in the ileum in the transgenic mice. Sterol carrier protein-2 was also reduced in the jejunum of the transgenic mice. Direct measurement showed that triglyceride absorption was reduced in the transgenic mice. The transgenic mice demonstrated a significant reduction in aortic atherosclerosis [44▪▪]. In an accompanying editorial [45], it was concluded that this study [44▪▪] supports the idea that targeting intestinal homeostasis may have therapeutic potential for the prevention and treatment of cardiometabolic disease.

GUT-DERIVED LIPOPOLYSACCHARIDE, OXIDIZED LIPIDS AND APOA-I MIMETC PEPTIDES IN CHRONIC TREATED HUMAN IMMUNODEFICIENCY VIRUS

Despite the introduction of potent antiretroviral therapy (ART), despite achieving undetectable virus levels in blood, many patients with chronic treated human immunodeficiency virus (HIV) have evidence of continued inflammation and increased risk of cardiovascular disease [46]. The continued inflammation is thought to be attributed to the persistence of intracellular virus (e.g. in rectal tissue) at levels that are so low that the virus is not detected in blood by the usual clinical laboratory techniques [47,48].

Kelesidis and colleagues [49▪,50▪,51▪] used two humanized mouse models of HIV infection, as well as gut explants from ten uninfected and ten HIV-infected men without evident morbidity to study the chronic inflammatory response in mice and humans on ART with no detectable HIV in blood. The mice were either infected with HIV or not, either treated with ART to reduce viral load to undetectable levels in blood or the mice did not receive ART, and either received a concentrate of transgenic tomatoes expressing the 6F peptide (Tg6F) that was added to their chow or they received a control transgenic tomato concentrate without the 6F peptide. Mu *et al.* [49▪] found that the HIV-infected mice treated with ART and the control transgenic tomato concentrate had higher levels of macrophage activation, more pronounced gut barrier dysfunction as determined with markers that included LPS and LBP levels, and higher plasma and gut tissue oxidized lipoprotein levels compared to HIV infected mice treated with ART plus Tg6F [49▪]. Ex vivo adding the 6F peptide or a related peptide (4F) improved measures of gut barrier dysfunction [49▪].

Daskou *et al.* [50▪] found that HIV infected humanized mice on ART and the control transgenic tomato concentrate had higher levels of plasma and gut bioactive lipids [particularly lipids derived from the cyclooxygenase (COX) pathway] compared to HIV infected humanized mice on ART and Tg6F. Ex vivo, the LPS stimulated production of COX-2 protein and associated secretion of bioactive lipids in gut explants from HIV infected persons on ART were reduced by the addition of 6F or 4F peptides [50▪].

Daskou *et al.* [51▪] also found that HIV infected humanized mice on ART and the control transgenic tomato concentrate had higher gut tissue cytokine levels (TNF-α and IL-6) and chemokines (CX3CL1) that are products of a disintegrin metalloprotease 17 (ADAM17) sheddase activity compared to HIV infected humanized mice on ART and Tg6F. ADAM17 is an inflammation-inducible enzyme that is responsible for the protease-driven shedding of TNF-α, CX3CL1 and plasma soluble CD163 (sCD163). The latter, sCD163, is one the most robust biomarkers of innate immune activation that is associated with mortality in chronic treated HIV [52]. Adding oxidized lipoproteins and LPS *ex vivo* to gut explants from the HIV infected men on ART increased levels of ADAM17 in myeloid and intestinal cells, which increased TNF-α, CX3CL1; the apoA-I mimetic peptides 4F and 6F attenuated these changes [51▪].

CONCLUSION

Oxidized phospholipids in the intestine regulate the levels and uptake of gut-derived LPS, which stimulates systemic inflammation and atherosclerosis. By targeting the levels of oxidized phospholipids in intestine, gut-derived LPS levels may be reduced to decrease systemic inflammation and atherosclerosis.

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Conflicts of interest

S.T.R. and A.M.F. are principals in Bruin Pharma and A. M.F. is an officer in Bruin Pharma.

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