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 Zn²⁺ 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.

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.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Libby P. The changing landscape of atherosclerosis. Nature 2021; 592:524–533.
2. Mohr AE, Crawford M, Jasbi P, *et al.* Lipopolysaccharide and the gut microbiota: considering structural variation. FEBS Lett 2022; 596:849–875.
3. Dupont HL, Jiang Z-D, Utay NS. The intestinal microbiome in human health and disease. Trans Am Clin Climatol Assoc 2020; 131:178–197.
4. Wiedermann CJ, Kiechl S, Dunzendorfer S, *et al.* Association of endotoxemia with carotid atherosclerosis and cardiovascular disease. Prospective results from the Bruneck Study. J Am Coll Cardiol 1999; 34:1975–1981.
5. Niebaure J, Volk HD, Kemp M, *et al.* Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet 1999; 353:1838–1842.
6. Kiechl S, Egger G, Mayr M, *et al.* Chronic infections and the risk of carotid atherosclerosis. Prospective results from a large population study. Circulation 2001; 103:1064–1070.
7. Peschel T, Schonauer M, Thiele H, *et al.* Invasive assessment of bacterial endotoxin and inflammatory cytokines in patients with acute heart failure. Eur J Heart Fail 2003; 5:609–614.
8. Lepper PM, Schumann C, Triantafilou K, *et al.* Association of lipopolysaccharide-binding protein and coronary artery disease in men. J Am Coll Cardiol 2007; 50:25–31.
9. Serrano M, Moreno-Navarrete JM, Puig J, *et al.* Serum lipopolysaccharide-binding protein as a marker of atherosclerosis. Atherosclerosis 2013; 230:223–227.
10. Gonzalez-Quintela A, Alonso M, Campos J, *et al.* Determinants of serum concentrations of lipopolysaccharide-binding protein (LBP) in the adult population. The role of obesity. PLoS One 2013; 8:e54600.
11. Tilves CM, Zmuda JM, Kuipers AL, *et al.* Association of lipopolysaccharide-binding protein with aging-related adiposity change and prediabetes among African ancestry men. Diabetes Care 2016; 39:385–391.
12. Pastori D, Carnevale R, Nocella C, *et al.* Gut-derived serum lipopolysaccharide is associated with enhanced risk of major adverse cardiovascular events in atrial fibrillation: effect of adherence to Mediterranean diet. J Am Heart Assoc 2017; 6:e005784.
13. Carnevale R, Nocella C, Petrozza V, *et al.* Localization of lipopolysaccharide from Escherichia Coli into human atherosclerotic plaque. Sci Rep 2018; 8:3598.
14. Asada M, Oishi E, Sakata S, *et al.* Serum lipopolysaccharide-binding protein levels and the incidence of cardiovascular disease in a general Japanese population. The Hisayama Study. J Am Heart Assoc 2019; 8:e013628.
15. Hakoupian M, Ferino E, Jickling GC, *et al.* Bacterial lipopolysaccharide is associated with stroke. Sci Rep 2021; 11:6570.
16. Van Lenten BJ, Fogelman AM, Haberland ME, Edwards PA. The role of lipoproteins and receptor mediated-endocytosis in the transport of bacterial lipopolysaccharide. Proc Natl Acad Sci USA 1986; 83:2704–2708.
17. Kitchens RL, Wolfbauer G, Albers JJ, Munford RS. Plasma lipoproteins promote the release of bacterial lipoprotein from the monocyte cell surface. J Biol Chem 1999; 274:34116–34122.
18. Vreugdenhil ACE, Snoek AMP, van't Veer C, *et al.* LPS-binding protein circulates in association with apoB-containing lipoproteins and enhances endotoxin-LDL/VLDL interaction. J Clin Invest 2001; 107:225–234.
19. Ghoshal S, Witta J, Zhong J, *et al.* Chylomicrons promote intestinal absorption of lipopolysaccharides. J Lipid Res 2009; 50:90–97.
20. Grunfeld C, Feingold KR. Endotoxin in the gut and chylomicrons: translocation or transportation? J Lipid Res 2009; 50:1–2.
21. Verges B, Duvillard L, Lagrost L, *et al.* Changes in lipoprotein kinetics associated with Type 2 diabetes affect the distribution of lipopolysaccharides among lipoproteins. J Clin Endocrinol Metab 2014; 99:E1245–E1253.
22. Vors C, Pineau G, Drai J, *et al.* Postprandial endotoxemia linked with chylomicrons and lipopolysaccharides handling in obese versus lean men: a lipid dose-effect trial. J Clin Endocrinol Metab 2015; 100:3427–3435.
23. Gueville M, Boudry G. Gastrointestinal and hepatic mechanisms limiting entry and dissemination of lipopolysaccharide into the systemic circulation. Am J Physiol Gastrointest Liver Physiol 2016; 311:G1–G15.
24. Topchiy E, Cirstea M, Kong H-JJ, *et al.* Lipopolysaccharide is cleared from the circulation by hepatocytes via the low density lipoprotein receptor. PLoS One 2016; 11:e0155030.
25. Hersoug L-G, Moller P, Loft S. Role of microbiota-derived lipopolysaccharide in adipose tissue inflammation, adipocyte size and pryoptosis during obesity. Nutr Res Rev 2018; 31:153–163.
26. Grin PM, Dwivedi DJ, Chathely KM, *et al.* Low-density lipoprotein (LDL)-dependent uptake of lipoteichoic acid and gram-negative lipopolysaccharide occurs through LDL receptor. Sci Rep 2018; 8:10496.
27. Dargent A, de Barros J-PP. Saheb S, *et al.* LDL apheresis as an alternate method for plasma LPS purification in healthy volunteers and dyslipidemic and septic patients. J Lipid Res 2020; 61:1776–1783.
28. Rehues P, Rodriguez M, Alvarez J, *et al.* Characterization of the LPS 3OHFA contents in the lipoprotein fractions and lipoprotein particles of healthy men. Biomolecules 2022; 12:47.
29. Han Y-H, Onufer EJ, Huang L-H, *et al.* Enterically derived high-density
■■ lipoprotein restrains liver injury through the portal vein. Science 2021; 373:eabe6729.
This study describes the role of HDL_3 in the intestine in delivering LPS via the portal vein in a state that prevents LPS from inducing an inflammatory reaction while allowing LPS to be inactivated by acyloxyacyl hydrolase in the liver.
30. Navab M, Hough GP, Van Lenten BJ, *et al.* Low density lipoproteins transfer bacterial lipopolysaccharides across endothelial monolayers in a biologically active form. J Clin Invest 1988; 81:601–605.
31. Brunham LR, Kruit JK, Iqbal J, *et al.* Intestinal ABCA1 directly contributes to HDL biogenesis in vivo. J Clin Invest 2006; 116:1052–1062.
32. Johansson MEV, Phillipson M, Petersson J, *et al.* The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. Proc Natl Acad Sci U S A 2008; 105:15064–15069.
33. Johansson MEV, Holmen Larsson JM, Hansson GC. The two mucus layers of colon are organized by the Muc2 mucin, whereas the outer layer is a legislator of host-microbial interactions. Proc Natl Acad Sci U S A 2011; 108:4659–4665.
34. Atuma C, Strugala V, Allen A, Holm L. The adherent gastrointestinal mucus gel layer: thickness and physical state in vivo. Am J Physiol Gastrointest Liver Physiol 2001; 280:G922–G929.
35. Ermund A, Schutte A, Johansson MEV, *et al.* Studies of mucus in mouse stomach, small intestine and colon. I. Gastrointestinal mucus layers have different properties depending on location as well as over the Peyer's patches. Am J Physiol Gastrointest Liver Physiol 2013; 305: G341–G347.
36. Mukherjee P, Chattopadhyay A, Grijalva V, *et al.* Oxidized phospholipids
■ cause changes in jejunum mucus that induce dysbiosis and systemic inflammation. J Lipid Res 2022; 63:100153.
This study demonstrates that oxidized phospholipids in the small intestine regulate the levels and uptake of gut-derived LPS and also demonstrates the ability of an oral apoA-I mimetic peptide to ameliorate these processes.
37. Datta G, Chaddha M, Hama S, *et al.* Effects of increasing hydrophobicity on the physical-chemical and biological properties of a class A amphipathic helical peptide. J Lipid Res 2001; 42:1096–1104.
38. Van Lenten BJ, Wagner AC, Jung C-L, *et al.* Anti-inflammatory apoA-I-mimetic peptides bind oxidized lipids with much higher affinity than human apoA-I. J Lipid Res 2008; 49:2302–2311.
39. Chattopadhyay A, Navab M, Hough G, *et al.* A novel approach to oral apoA-I mimetic therapy. J Lipid Res 2013; 54:995–1010.
40. Ghosh SS, Bie J, Wang J, Ghosh S. Oral supplementation with nonabsorbable antibiotics or curcumin attenuates Western diet-induced atherosclerosis and glucose intolerance in LDLR-/- mice - role of intestinal permeability and macrophage activation. PLoS One 2014; 9:e108577.
41. Ghosh SS, Wang J, Yannie PJ, Ghosh S. Intestinal barrier dysfunction, LPS translocation, and disease development. J Endocr Soc 2020; 4:1–15.
42. Ghosh SS, He H, Wang J, *et al.* Intestine-specific expression of human chimeric intestinal alkaline phosphatase attenuates Western diet-induced barrier dysfunction and glucose intolerance. Phys Rep 2018; 6: e13790.
43. Kiffer-Moreira T, Sheen CR, Gasque C, *et al.* Catalytic signature of a heat-stable, chimeric human alkaline phosphatase with therapeutic potential. PLoS One 2014; 9:e89374.
44. Ghosh SS, Wang J, Yannie PJ, *et al.* Over-expression of intestinal
■■ alkaline phosphatase attenuates atherosclerosis. Cir Res 2021; 128: 1646–1659.
This study demonstrates the important role that intestinal alkaline phosphatase plays in regulating the levels and uptake of gut-derived biologically active LPS, which contributes to dyslipidemia and atherosclerosis.
45. de Aguiar Vallim TQ, Tarling EJ. mInd the gAP Inestinal alkaline phosphatase puts the breaks on atherosclerosis. Circ Res 2021; 128:1660–1662.
46. Pyarali F, Iordanov R, Ebner B, *et al.* Cardiovascular disease and prevention among people living with HIV in South Florida. Medicine (Baltimore) 2021; 100:e26631.
47. Khoury G, Fromentin R, Solomon A, *et al.* Human immunodeficiency virus persistence and T-cell activation in blood, rectal and lymph node tissue in human immunodeficiency virus-infected individuals receiving suppressive antiretroviral therapy. J Infect Dis 2017; 215:911–919.
48. McLaughlin MM, Ma Y, Scherzer R, *et al.* Association of viral persistence and atherosclerosis in adults with treated HIV infection. JAMA Netw Open 2020; 3:e2018099.

Atherosclerosis: cell biology and lipoproteins

49. Mu W, Sharma M, Heymans R, *et al.* Apolipoprotein A-I mimetics
■   attenuate macrophage activation in chronic treated HIV. AIDS 2021;
    35:543–553.
This study demonstrates the ability of apoA-I mimetic peptides to prevent macro-
phage activation induced by gut-derived LPS and oxidized lipids in
humanized mouse models, and *ex vivo* in gut explants from HIV infected subjects
successfully treated with potent antiretroviral therapy to achieve undetectable
levels of virus.

50. Daskou M, Sharma M, Mu W, *et al.* ApoA-I mimetics favorably impact
■   cyclooxygenase 2 and bioactive lipids that may contribute to cardiometabolic
    syndrome in chronic HIV. Metab Clin Exp 2021; 124:154888.
This study demonstrates the ability of apoA-I mimetic peptides to prevent the
formation of increased COX2 bioactive lipids induced by gut-derived LPS and

oxidized lipids in humanized mouse models, and *ex vivo* in gut explants from HIV
infected subjects successfully treated with potent antiretroviral therapy to achieve
undetectable levels of virus.

51. Daskou M, Wu W, Sharma M, *et al.* ApoA-I mimetics reduce systemic
■   and gut inflammation in chronic treated HIV. PLoS Pathog 2022; 18:
    e1010160.
This study demonstrates the ability of apoA-I mimetic peptides to prevent ADAM17
sheddase activity induced by gut-derived LPS and oxidized lipids in humanized
mouse models, and *ex vivo* in gut explants from HIV infected subjects successfully
treated with potent antiretroviral therapy to achieve undetectable levels of virus.

52. Knudsen TB, Ertner G, Petersen J, *et al.* Plasma soluble CD163 level
    independently predicts all-cause mortality in HIV-1-infected individuals. J
    Infect Dis 2016; 214:1198–1204.