

Endotoxin in the gut and chylomicrons: translocation or transportation?¹

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The intestine contains trillions of microorganisms and massive amounts of endotoxin, which if absorbed from the intestinal lumen into the body would result in overwhelming septic shock and death. Recently there has been an increasing appreciation of the role of gut microorganisms and their translocation into the systemic circulation in promoting metabolic disorders including obesity and insulin resistance, as well as in the pathogenesis of very different disorders, such as inflammatory bowel disease, HIV infection, ethanol-induced liver disease, and hemorrhagic shock.

Germ-free mice are protected against obesity induced by a high-fat, sugar-rich diet compared with conventional mice and experimental colonization of the intestine of germ-free mice with microorganism from the cecum of conventional mice induced increased rates of weight gain (1, 2). Similarly, antibiotic treatment that alters intestinal flora also has beneficial effects on metabolic parameters (3, 4). Moreover, the intestinal flora of obese ob/ob mice differ from control lean mice, and when the intestinal flora of ob/ob mice are transplanted into germ-free mice, there is a greater increase in adiposity than when flora from control mice are transplanted (5, 6). A number of different mechanisms might account for the link between intestinal microflora and metabolic disorders, including intestinal microorganisms increasing the absorbable caloric content of food by breaking down primarily plant-based nutrients that mammals are not equipped to metabolize, and intestinal microorganisms modulating host genes, particularly in the intestinal mucosa, that then have local and systemic effects on energy metabolism (1, 2).

However, additional studies link the absorption of endotoxin from the gastrointestinal tract into the circulation with the weight gain and insulin resistance induced by diet. A diet enriched in energy, either a high-fat or high-carbohydrate diet, induces an increase in plasma endotoxin levels in mice (7). Moreover, the high-fat diet resulted in a much greater increase in plasma endotoxin levels than either the control diet or the high-carbohydrate diet (2–3-fold increase). Similarly, in humans, there is a positive correlation between plasma endotoxin levels and energy or fat intake (correlations were observed for saturated, mono-

unsaturated, and polyunsaturated fat intake) (8). Circulating endotoxin levels are also increased in patients with type 2 diabetes (9). Finally, in humans a single high-fat meal acutely increased plasma endotoxin levels (10). Taken together, these results indicate that a high-fat diet produces an increase in circulating endotoxin levels. Animal studies have shown that chronic endotoxemia induces obesity, insulin resistance, and diabetes (6).

Increased translocation of endotoxin from the gut to the interior of the body is found in inflammatory bowel disease, ethanol induced liver disease, HIV infection, and hemorrhagic shock (11–14). The resulting systemic inflammation plays a role in the pathophysiology of those diseases. For example, translocation of endotoxin is associated with more rapid progression of HIV infection (13). In contrast to the deleterious metabolic effects of high-fat diets previously described, dietary fat protects against endotoxin toxicity during hemorrhagic shock by decreasing the translocation of endotoxin (15, 16) and has been shown to protect from disease-induced disruption of the gut barrier (16, 17). Indeed, chylomicrons have previously been shown to decrease the toxicity of endotoxin (18, 19).


The ability of enteral fat to sustain the gut barrier and decrease the translocation of macromolecules (16, 17) raises questions regarding the mechanism accounting for how dietary fat leads to increased circulating endotoxin and what the consequences are. The paper of Ghoshal et al. (20) in this issue of the *Journal of Lipid Research* addresses these important questions. Using both animal models and polarized, cultured gut cells, they show that endotoxin, which is internalized into gut cells, is secreted into the circulation during the formation and secretion of chylomicrons. Intra-gastric lavage with triolein (which forms chylomicrons) increases plasma endotoxin, whereas gavage with tributyrin (whose fatty acids enter the circulation without chylomicron formation) does not increase endotoxemia. Polarized CaCo-2 cells secrete endocytosed endotoxin when incubated with oleate, which forms chylomicrons in those cells, but not when incubated with buty-

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rate, which does not. Importantly, Pluronic L-81, an inhibitor of chylomicron formation, blocked the effect of oleate. Thus endotoxin is transported into the circulation in conjunction with chylomicron formation and secretion, not just translocated due to breakdown of the intestinal barrier.

Ghoshal et al. (20) also provide data that are important to our understanding of the inflammatory response. They show that mesenteric lymph nodes are activated by the endotoxin on chylomicrons. Mesenteric lymph nodes likely play an important role of scavenging the loosely attached endotoxin and decreasing the amount that reaches the systemic circulation. But scavenging means activating the cells in the lymph nodes to secrete cytokines, hence inducing systemic inflammation. What happens when the mesenteric lymph nodes are defective, for example in a disease such as in HIV infection where mesenteric lymph nodes are depleted early in the disease and do not return to normal at the time of repletion of circulating CD4 cells (21, 22)? The likely answer is more endotoxin makes it into the circulation even in healthy patients with HIV infection, with ensuing inflammation and metabolic disturbances (13).

From a broader perspective, a large body of evidence has shown that lipoproteins play an important role in host defense as part of the innate immune system (for review see Ref. 18) in addition to their well-known function in the transport of lipids. Systemic administration of chylomicrons and chylomicron-like particles have been shown to bind endotoxin and not only protect from the toxicity of administered endotoxin (19), but also to protect from cecal ligation and puncture (23), a model of gut sepsis that even anticytokine agents fail to block. The novel findings reported in the paper of Ghoshal et al. (20) in this issue of the *Journal of Lipid Research* brings these two functions of lipoproteins together. One can speculate that the transportation of endotoxin in chylomicrons is a protective mechanism designed to reduce the toxicity of absorbed endotoxin. They have shown that the price paid for this protection is activation of the systemic inflammatory response. It will be important to determine the degree to which long-term endotoxemia induced by increased food intake contributes to inflammation and metabolic disorders such as obesity, insulin resistance, diabetes, and atherosclerosis. Another interesting question to ponder is whether decreasing endotoxin transport will make a difference to those who have metabolic disorders. 

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