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Reprint requests
Address requests for reprints to: Alessio Aghemo, MD, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Via F. Sforza 35, 20122 Milan, Italy. e-mail: alessio.aghemo@policlinico.mi.it.

Conflicts of interest
The authors disclose the following: Alessio Aghemo is on the Advisory Board of Gilead Sciences, Janssen, and AbbVie; and on the Speakers Bureau of Merck, Janssen, Gilead Sciences, and AbbVie. Maria Francesca Donato is a member of the Speaker Bureau for Janssen and Gilead Sciences.

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Dietary Saturated Lipids in Alcoholic Liver Disease: New Microbiota-Targeting Bullets?

See "Supplementation of saturated long-chain fatty acids maintains intestinal eubiosis and reduces ethanol-induced liver injury in mice," by Chen P, Torralba M, Tan J, et al, on page 203.

The human intestinal tract harbors an incredible number of microorganisms consisting of $>10^{14}$ bacteria, archaea, and viruses. Their combined genomes exceed the human genome by >100-fold.[1] Although early studies have revealed that these genes mainly encode functions that affect the digestion of complex carbohydrates, recent studies suggest that the microbiota might be also involved in fat metabolism, and regulate numerous immune, inflammatory, and metabolic pathways throughout the organism, contributing to the pathogenesis of various types of diseases, including liver disease.[2] For example, an important role of gut bacteria-derived endotoxin in the pathogenesis of alcoholic liver disease (ALD) was well documented many years ago, which is owing to ethanol-mediated increase of gut permeability.[3,4] Recently, several studies demonstrated that chronic alcohol consumption causes intestinal bacterial overgrowth and enteric dysbiosis, contributing to ALD.[5,6] Targeting dysbiosis by administration of the probiotic *Lactobacillus rhamnosus GG* restores intestinal integrity and ameliorates ALD in mice.[7,8] In this issue of *Gastroenterology*, Chen et al[9] identify a novel mechanism underlying the complex interaction of gut microbiota and ALD (Figure 1), demonstrating that chronic ethanol consumption inhibits synthesis of saturated long-chain fatty acids (LCFA) by gut bacteria and subsequently reduces the proportion of LCFA-dependent and hepatoprotective functions of *Lactobacilli*. Administration of saturated LCFA increased the intestinal content of *Lactobacilli* and alleviated intestinal epithelial barrier dysfunction and liver injury in a murine model of ALD.

Dysbiosis, an impaired intestinal barrier and a consecutive leaky gut, have been suggested to play a major role in various types of liver diseases.[2] Gut bacteria-derived factors, such as endotoxin and inflammatory cytokines, are critically involved in many types of acute and chronic liver diseases.[2,10] An important role for the gut microbiota in experimental ALD has been well-documented in several earlier studies. Mice deficient in Toll-like receptor 4 or treated with antibiotics are resistant to experimental ALD, highlighting the key role of endotoxin in this disease.[3] In patients with alcoholic hepatitis, plasma endotoxin levels are markedly elevated and have been implicated in the pathogenesis of ALD in patients,[11] and anti-endotoxin therapy is currently under consideration for the treatment of alcoholic hepatitis.[12] Chronic alcohol consumption increases gut permeability in a dose-dependent manner, resulting in gut leakiness and cytokine activation.[3] Involved mechanisms remain unclear, but may include disruption of intercellular junctions by acetaldehyde, the first degradation product of ethanol.[13] Moreover, length heterogeneity polymerase chain reaction fingerprinting analyses revealed that daily alcohol consumption for 10 weeks was able to affect colonic microbiome composition in rats.[14] Interestingly, mainly mucosa-associated microbiota was affected, and administration of a probiotic (*Lactobacillus rhamnosus GG*) and a prebiotic (oats) prevented these changes in this rat model.[14] Recently, in a murine model of ALD, Yan et al[5] investigated bacterial translocation, changes in the gut microbiome, and its regulation by mucosal antimicrobial proteins. These authors found that bacterial translocation preceded changes in the microbiome, suggesting that an impaired barrier might be an early event after alcohol exposure. High-throughput sequencing of 16S ribosomal RNA genes showed a relative abundance of *Bacteroidetes* and *Verrucomicrobia* in mice fed alcohol compared with a relative predominance of *Firmicutes* in pair-fed mice. Furthermore, alcohol consumption decreased gene and protein expression of bactericidal c-type lectins regenerating islet-derived protein 3 (Reg3)b and Reg3g in the small intestine. Substantial aspects of this phenotype such as decreased Reg3g protein levels, intestinal bacterial overgrowth, and liver inflammation could be reversed by the treatment with a prebiotic (eg. fructooligosaccharide).[5] In summary, the intestinal microbiome has evolved as a major player in the pathophysiology of ALD.

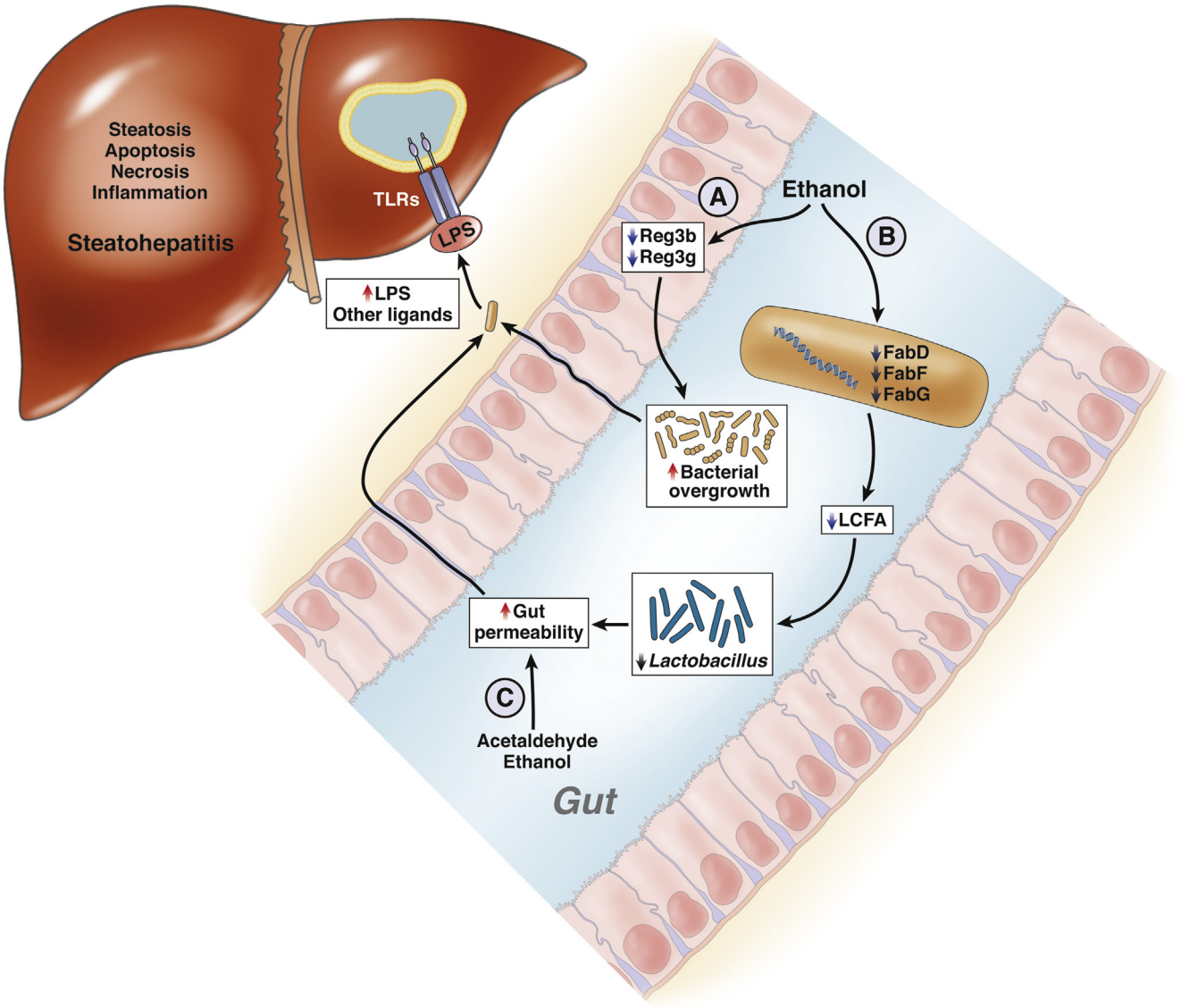

Figure 1. Interplay between ethanol, diet, microbiota, and immunity in the gut during chronic alcoholic liver disease (ALD). Chronic ethanol consumption promotes ALD via 3 ways of modulation of the gut microbiota and epithelial integrity. First, ethanol down-regulates expression of bactericidal protein Reg3b and Reg3g, resulting in dysbiosis and bacterial overgrowth. Second, ethanol inhibits expression of bacterial genes (eg, FabD, FabF, and FabG) involved in the biosynthesis of long-chain fatty acids (LCFA) and subsequently decreases LCFA-dependent *Lactobacilli*, a group of bacteria that play an important role in restricting gut permeability. Third, acetaldehyde directly damages gut epithelial integrity. All of these changes cause an increase of bacteria-derived factors in the circulation and finally the liver, which promote liver inflammation and ALD. FabD, malonyl CoA:ACP acyltransferase; FabF, 3-oxoacyl-[acyl-carrier-protein] synthase 2, FabG: 3-oxoacyl-[acyl-carrier-protein] reductase; Reg3, regenerating islet-derived protein 3.

Diet has been demonstrated to be a major confounder of the gut microbiota.[15] There is growing evidence that a high-fat/high-sugar Western diet substantially affects the human gut microbiome, including the genetic composition and metabolic behavior.[16] Chronic alcohol feeding also affects the gut microbiome by inducing intestinal bacterial overgrowth paralleled by bacterial translocation to mesenteric lymph nodes and to the blood and increased endotoxin serum levels.[5] The current study[9] demonstrated that alcohol consumption reduces the capacity of the microbiome to synthesize LCFA in mice and humans. The authors observed that ethanol administration resulted in a remarkably decreased synthesis of almost all known LCFA (C13:0-C18:0) paralleled by a reduction in *Lactobacilli*. Palmitic acid (C16:0) and stearic acid (C18:0) constitute the dominant LCFA in the cecal contents of mice and both were suppressed significantly by ethanol. Other LCFA that can only be synthesized by the microbiota such as pentadecanoic acid (C15:0) or heptadecanoic acid (C17:0) were reduced profoundly also. Importantly, dietary administration of LCFA (12% palmitic acid and 85% stearic acid) resulted in eubiosis, reconstituted the impaired intestinal