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Review Article

Targeting the gut barrier for the treatment of alcoholic liver disease☆

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ABSTRACT

Alcohol consumption remains one of the predominant causes of liver disease and liver-related death worldwide. Intriguingly, dysregulation of the gut barrier is a key factor promoting the pathogenesis of alcoholic liver disease (ALD). A functional gut barrier, which consists of a mucus layer, an intact epithelial monolayer and mucosal immune cells, supports nutrient absorption and prevents bacterial penetration. Compromised gut barrier function is associated with the progression of ALD. Indeed, alcohol consumption disrupts the gut barrier, increases gut permeability, and induces bacterial translocation both in ALD patients and in experimental models with ALD. Moreover, alcohol consumption also causes enteric dysbiosis with both numerical and proportional perturbations. Here, we review and discuss mechanisms of alcohol-induced gut barrier dysfunction to better understand the contribution of the gut-liver axis to the pathogenesis of ALD. Unfortunately, there is no effectual Food and Drug Administration-approved treatment for any stage of ALD. Therefore, we conclude with a discussion of potential strategies aimed at restoring the gut barrier in ALD. The principle behind antibiotics, prebiotics, probiotics and fecal microbiota transplants is to restore microbial symbiosis and subsequently gut barrier function. Nutrient-based treatments, such as dietary supplementation with zinc, niacin or fatty acids, have been shown to regulate tight junction expression, reduce intestinal inflammation, and prevent endotoxemia as well as liver injury caused by alcohol in experimental settings. Interestingly, saturated fatty acids may also directly control the gut microbiome. In summary, clinical and experimental studies highlight the significance and efficacy of the gut barrier in treating ALD.

1. Introduction

Long-term excessive alcohol consumption causes liver disease, namely alcoholic liver disease (ALD). ALD is one of the major causes of liver-related mortality worldwide. Alcohol-related deaths account for up to 48% of liver-related deaths in the United States,[1] whereas it has been estimated that 60%–80% of liver-related deaths in Europe are due to excessive alcohol consumption.[2] Unfortunately, effective therapies for ALD are currently unavailable. The major obstacle is the limited understanding of the pathogenesis of ALD. The spectrum of ALD involves three progressive stages: alcoholic steatosis (fatty liver), hepatitis and cirrhosis.[1,3] Alcoholic steatosis, characterized by macrovesicular and/or microvesicular lipid droplet accumulation in hepatocytes, is the earliest manifestation of ALD and is generally reversible with abstinence. Alcoholic hepatitis features inflammation and necrosis in the liver, which encompasses a spectrum of severity ranging from asymptomatic dysregulation of biochemistries to fulminant liver failure. Alcoholic cirrhosis, the most advanced form of ALD, refers to the replacement of functional liver tissue with nonfunctional fibrotic tissue and regenerative nodules, and may result in clinical manifestations of portal hypertension and liver failure. It is noteworthy that not all heavy drinkers develop alcoholic hepatitis, and the disease can occur in people who drink only moderately. Indeed, approximately 90%–95% of people who consume large quantities of alcohol develop steatosis, of which only 10%–40% eventually develop liver fibrosis.[4] Despite the correlation between the per capita alcohol consumption and mortality rates from hepatic cirrhosis,[5] there is little evidence suggesting that alcohol itself is able to cause

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permanent damage to the liver. Thus, factors other than alcohol intake influence the development and progression of ALD.

Early studies in ALD identified increased levels of lipopolysaccharide (LPS), a bacterial endotoxin, in the plasma of both ALD patients and experimental animal models of ALD (namely endotoxemia).[6–9] Experimentally-induced endotoxemia indicates that it is a key factor in the development of ALD.[10,11] In addition to LPS, increasing evidence from recent studies supports an emerging role for bacterial pathogen-associated molecular patterns (PAMPs) in ALD.[12–14] Clinical studies have shown that only alcoholics with gut leakiness develop liver injury,[15] suggesting a pivotal role of gut-derived toxins and the gut barrier in ALD. This review focuses on the gut barrier and gut-derived PAMPs in the pathogenesis of ALD. Potential therapeutic approaches targeting the gut for the treatment of ALD will also be discussed.

2. Gut barrier

The primary function of the gastrointestinal tract is to digest food and absorb nutrients. It has the largest surface where the body exposes to the external environment, which puts the gastrointestinal tract at risk from exogenous pathogenic microorganisms such as bacteria, fungi and viruses.[16–18] Therefore, another essential function of the gastrointestinal tract is to act as a barrier preventing the invasion of the circulation by microorganisms. The gut barrier is a multi-layer system, and has both physical and immune defense functions. It consists of three major components, including mucus, epithelial cells and immune cells (Fig. 1A).[19–21] While the mucus and epithelial cells act basically as physical barriers, all three layers contribute to the immune barrier function.

2.1. Mucus layer

The first line of defense is the stratified mucus layer, which together with the glycocalyx of the epithelial cells, provides a protective spacer against physical and chemical injury caused by ingested food, microbes and microbial products.[20,21] The organization of the mucus system varies markedly along the gastrointestinal tract; the small intestine has a single unattached mucus layer which limits bacteria reaching the intestinal epithelium, whereas the stomach and colon have a two-layered mucus, namely inner and outer layers. The inner colonic mucus layer is dense and firmly attached to the epithelial cells, and does not allow bacterial penetration. The outer colonic mucus layer is loose and unattached, and it is the natural habitat of commensal bacteria.[22]

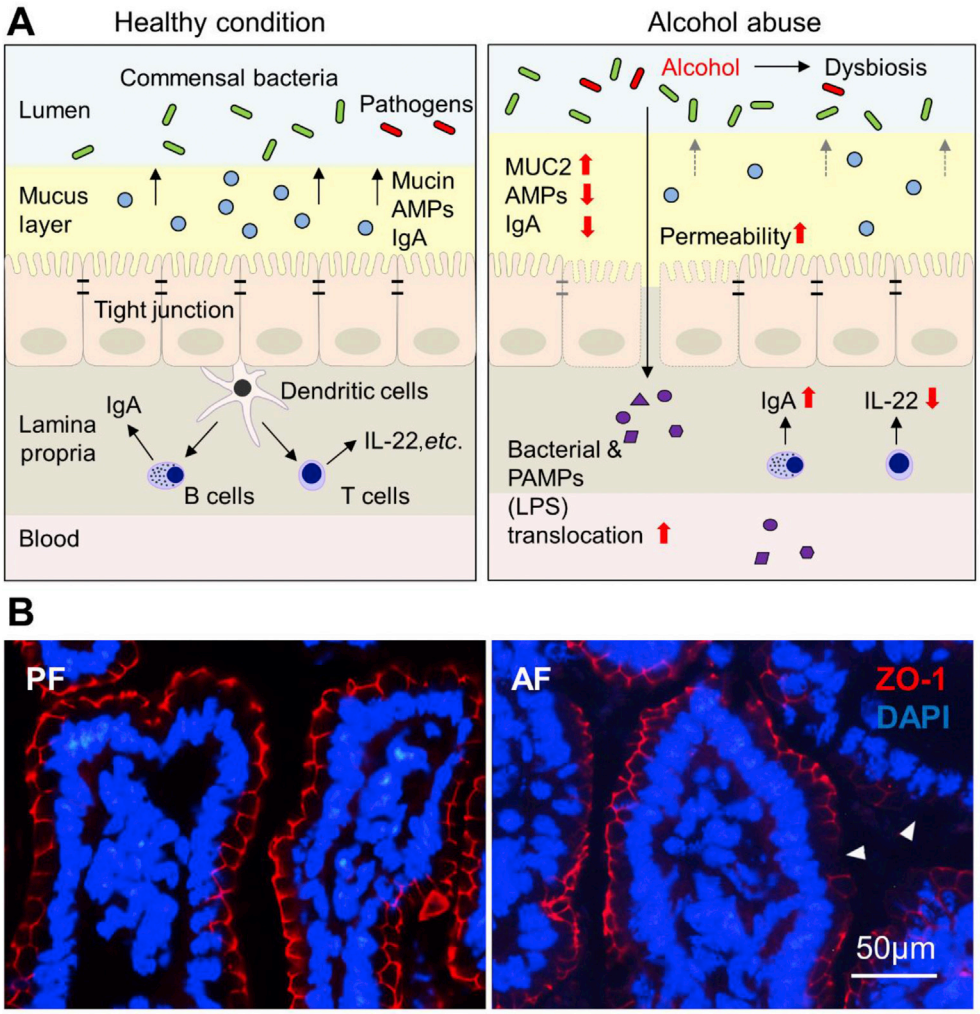

Fig. 1. Alcohol-induced gut barrier dysfunction. **(A)** Schematic diagrams of the gut barrier under healthy and alcohol-intoxicated conditions. **(B)** Immunofluorescence of ileal tight junction protein ZO-1. Arrowheads indicate dissociated ZO-1. Abbreviations: AMP, antimicrobial peptide; LPS, lipopolysaccharide; PF, pair-fed; AF, alcohol-fed; ZO-1, zonula occludens-1; DAPI, 4′,6-diamidino-2-phenylindole.