REVIEW ARTICLE

Targeting gut-liver axis for the treatment of nonalcoholic steatohepatitis: translational and clinical evidence

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Nonalcoholic fatty liver disease (NAFLD) is widely emerging as the most prevalent liver disorder and is associated with increased risk of liver-related and cardiovascular mortality. Recent experimental and clinical studies have revealed the pivotal role played by the alteration of gut-liver axis in the onset of fatty liver and related metabolic disturbances. Gut-liver cross talk is implicated not only in the impairment of lipid and glucose homeostasis leading to steatogenesis, but also in the initiation of inflammation and fibrogenesis, which characterize nonalcoholic steatohepatitis (NASH), the evolving form of NAFLD. The gut microbiota has been recognized as the key player in the gut-liver *liaison* and because of its complexity can act as a villain or a victim. Gut microbiota not only influences absorption and disposal of nutrients to the liver, but also conditions hepatic inflammation by supplying toll-like receptor ligands, which can stimulate liver cells to produce proinflammatory cytokines. Thus, the modification of intestinal bacterial flora by specific probiotics has been proposed as a therapeutic approach for the treatment of NASH. In this review, we summarized the evidence regarding the role of gut-liver axis in the pathogenesis of NASH and discussed the potential therapeutic role of gut microbiota modulation in the clinical setting. (Translational Research 2015;■:1–9)

Abbreviations: ALT = alanine aminotransferase; BMP = bone morphogenetic protein; BT = bacterial translocation; CFU = colony-forming unit; DAMP = damage associated molecular patterns; FIAF = fasting-induced adipose factor; HSCs = hepatic stellate cells; IM = intestinal microbiota; IP = intestinal permeability; LPS = lipopolysaccharide; MetS = metabolic syndrome; NAFLD = nonalcoholic fatty liver disease; NASH = , nonalcoholic steatohepatitis; NF-kB = nuclear transcriptional factor kappa-B; PAMPs = pathogen-associated molecular patterns; RES = reticulumendothelial system; SIBO = small intestinal bacteria overgrowth; TGF-β = transforming growth factor β; TJ = tight junction; TLR = toll-like receptors; TNF-α = tumor necrosis factor alpha

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of increased liver enzymes both in western and eastern countries and can be considered as global epidemics.[1] NAFLD has been traditionally considered the hepatic manifestation of the metabolic syndrome (MetS) because of its association with insulin resistance and the components of the MetS in cross-sectional studies[2]; however, several prospective studies have shown that liver fat accumulation per se precedes the onset of MetS.[3] For this reason, it has been proposed to consider NAFLD the hepatic trigger of the MetS rather than its component.[4] Although in most patients liver steatosis is not associated with progressive liver damage (nonalcoholic fatty liver, NAFL), a subset of patients develops liver inflammation and progressive fibrosis,[5] that is, nonalcoholic steatohepatitis (NASH), which is now emerging as a main indication to liver transplantation because of evolution to cirrhosis and hepatocellular carcinoma.[6]

Hepatic lipid accumulation, the hallmark of NAFLD, is preceded by an excess in the dietary intake of fructose, saturated fat, and cholesterol leading to impaired β-oxidation and increased lipogenesis.[7] However, the molecular events that cause transition of fatty liver to NASH have not been fully elucidated. Historically, the pathogenesis of NASH has been linked to the 2-hit hypothesis[8] that for many years has been overtaken by the multiple parallel hits hypothesis.[9] Among multiple hits, increasing clinical and experimental evidence indicates that gut-liver liver axis is implicated in NASH onset and progression and the gut microbiota has been recognized as the key player in the gut-liver cross talk. For this reason, the modification of intestinal bacterial flora by prebiotics and specific probiotics has been proposed as a therapeutic approach for the treatment of NASH.

In this review, we will focus on the role of gut-liver axis as a triggering factor for the transition from fatty liver to NASH and its role on priming hepatic fibrosis. Subsequently, we will discuss the potential therapeutic role of gut microbiota modulation for the treatment of NASH.

INTESTINAL MICROBIOTA

The possible role of intestinal microbiota (IM) and the therapeutic or preventive application of probiotics in several disorders has received an increasing attention in the past years.

The IM is a complex ecological system consisting of at least 500 different bacterial species with anatomic variations in composition and numbers: in the stomach a small number of bacteria have been found, predominantly consisting of lactobacilli, streptococci, staphylococci, enterobacteriaceae, and yeasts. This small number is mainly because of low intragastric pH. In the subsequent gastrointestinal tracts, there is a quantitative increase from $0–10^5$ colony-forming unit/g (CFU/g) in the duodenum to 10^8 CFU/g in the ileum and 10^{10} CFU/g in the colon because of neutral intestinal pH, slower transit time, and the availability of nutrients. In the colon more than 99% of the micro-organisms are strictly anaerobic, such as bifidobacteria, Bacteroides spp, Clostridium spp, Eubacterium spp, Fusobacterium spp, and peptstreptococci.[10,11]

The IM performs several important functions for the host, including the conversion of procarcinogenic substances, production of vitamins, degradation of bile acids, and digestion of nutrients. In particular, saccharolytic fermentation of unabsorbed and indigestible carbohydrates by intestinal bacteria, occurring mostly in the proximal colon, is important for the production of short-chain fatty acids (ie, acetate, propionate, and butyrate).[12] Butyrate, the major energy source for intestinal epithelial cells, affects cell proliferation and differentiation, increases mucus secretion, and decreases inflammation.[13] Proteolytic bacterial fermentation usually takes place in the more distal colon, where carbohydrates are no longer available, and determines the production of toxic compounds such as ammonia, phenols, cresols, and paracresols.[14] The colonization of the intestine by commensal bacteria is also important for the development and functioning of the immune system. For example, in germ-free raised animals, fewer lymphocytes, plasma cells, and mononuclear cells, as well as a reduced development of lymphoid structures are found. In addition, lower IgA and mucin production have been observed.[10-15] Finally, together with the intestinal mucosa, the endogenous intestinal flora forms an important barrier against pathogens by the mechanism of metabolic competition that impedes the development of pathogenic species.

Several functions of the IM may be beneficially influenced by probiotics. Although probiotics exert their healthful effects via different mechanisms, their ability to increase intestinal barrier function and prevent bacterial translocation is more relevant than their role in liver disease.[16-18]

Together with its important physiological functions, the microbiota may also exert harmful actions on the liver. In fact, gut-derived endotoxins may contribute to the shift of NAFLD to NASH and fibrosis, as well as to the onset of portal hypertension.[19-24] In some studies, it has been demonstrated that the treatment with oral poorly absorbed antibiotics or probiotics may inhibit the shift of NAFLD to NASH in animals with obesity and improve the hemodynamics of portal circulation in patients with portal hypertension.[25-27]