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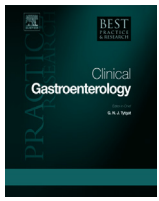

13

Intestinal microbiota in liver disease

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A B S T R A C T

The intestinal microbiota have emerged as a topic of intense interest in gastroenterology and hepatology. The liver is on the front line as the first filter of nutrients, toxins and bacterial metabolites from the intestines and we are becoming increasingly aware of interactions among the gut, liver and immune system as important mediators of liver health and disease. Manipulating the microbiota with therapeutic intent is a rapidly expanding field. In this review, we will describe what is known about the contribution of intestinal microbiota to liver homeostasis; the role of dysbiosis in the pathogenesis of liver disease including alcoholic and non-alcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma; and the therapeutic manifestations of altering intestinal microbiota via antibiotics, prebiotics, probiotics and fecal microbiota transplantation.

Introduction

The intestinal microbiota consist of the populations of bacteria, viruses, fungi and parasites that colonize the gastrointestinal tract from the mouth to the colon [1]. The vast majority of what is known about the microbiota comes from studies done on the 10^{14} mostly anaerobic bacteria which live in changing composition as we observe them from proximally to distally in the gut [2]. The composition

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of the microbiota varies with intestinal niche as well as host age, gender, ethnicity, diet and geographic location [1,3]. The microbiota play varied roles in health and disease; from symbiotic partner to colonizer to pathogen.

The liver receives the majority of its blood supply via the portal vein and thus becomes the first filter of nutrients absorbed by the intestines. The intestinal microbiota break down non-digestible carbohydrates into short chain fatty acids that can serve as an energy source for intestinal epithelium. Additionally, the liver is the first filter of microbiota generated by-products such as endotoxin (lipopolysaccharide or LPS), bacterial metabolites (peptidoglycans) and bacterial DNA, collectively referred to as pathogen associated molecular patterns (PAMPs). Disruptions in gut wall integrity may qualitatively and quantitatively influence the PAMPs to which the liver is exposed and influence the progression of various liver diseases.

The intestinal microbiota may be altered, intentionally or unintentionally, through dietary changes, antibiotic use or probiotic supplementation. Currently, antibiotics are frequently employed to treat or prophylax against several of the manifestations of end stage liver disease [4–6]. There is emerging evidence of the microbiota's role in obesity, non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH), alcohol induced liver disease and even hepatocellular carcinoma (HCC) and the potential for probiotics supplementation to mitigate these diseases' progression.

The intestinal microbiota in liver health

Energy homeostasis

The intestinal microbiota have developed a symbiotic relationship with its human host over the millennia and play a role in providing energy substrate for cells. Non digestible plant polysaccharides are fermented to short chain fatty acids (SCFA). SCFA serve as an energy source to host intestinal epithelium. Butyrate is the preferred energy substrate for colonocytes and its metabolism provides key substrates in cell metabolism [7]. SCFA also act as regulators of gut hormones like glucagon-like peptide 1 (GLP1) and peptide YY (PYY) that influence satiety. Increases in GLP1 and PYY improve oral glucose tolerance, insulin sensitivity, and leptin levels [8]. SCFA like butyrate, propionate, and acetate serve other diverse roles that regulate gut motility, inflammation, glucose homeostasis, and energy regulation [8,9]. Butyrate that enters the portal circulation and travels to the liver enters the citric acid cycle via the production of acetyl-CoA. Microbiota derived butyrate can enhance gylcogen synthesis, decrease glucose oxidation and increase hepatic glycogen storage, thus providing a link between dietary fiber consumption and improved glucose tolerance [7]. Each of these roles of the gut microbiota has an impact on liver homeostasis and health.

Gut barrier function

The microbiota exert an effect on immune mediated gut barrier function and thus control access of their products to the portal circulation and the liver [7]. Again, butyrate produced from gut microbiota is key here. Butyrate can enhance heat-shock proteins, provide cytoprotective effects and contribute to enterocyte and colonocyte proliferation [7]; all key components to mucosal integrity. Increased gut permeability may play a role in liver fibrosis in rats [10]. Restricting access of gut derived pathogens to the systemic circulation may protect against bacterial sepsis. The microbiota can also influence clearance of bacterial pathogens from the liver via Kupffer cell activation and/or induction of tolerance of portal venous antigens [11].

The intestinal microbiota in the pathogenesis of liver disease

The inflammatory cascade

The role of microbiota in liver disease largely derives from the inflammatory pathway that is triggered from the interaction between gut bacteria, the liver, and the immune system. At the heart of the process, is the interplay of the liver's macrophages, Kupffer cells, and PAMPs. One particular PAMP,