Journal of Functional Foods 17 (2015) 137–151

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/jff

Current evidence on the use of probiotics in liver diseases

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ARTICLE INFO

Article history:
Received 27 January 2015
Received in revised form 29 April 2015
Accepted 1 May 2015
Available online

Keywords:
Bacterial translocation
Cirrhosis
Hepatitis
Liver diseases
Microbiota
Probiotics

ABSTRACT

The human gastrointestinal tract contains bacterial species that, among other functions, maintain a microbial barrier against potential pathogens and help regulate the immune response in the human body. The composition of gut microbiota and its variations hold an important role in the development of liver diseases. Under pathological conditions, bacterial components are released into the liver–gut axis and cause proinflammatory and autoimmune responses in the liver; these responses can initiate direct damage to liver cells. Probiotics have been shown to have favorable effects when used to treat several liver diseases by reducing the production of bacterial toxins and by modulating autoimmune responses, intestinal permeability, and the inflammatory response. This review discusses current data concerning the role of gut microbiota and its relationship with the immune system and the progression of liver diseases, as well as the use of different strains of bacteria for treatments of such diseases.

Contents

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Abbreviations: GI, gastrointestinal; BECs, biliary epithelial cells; TLRs, Toll-like receptors; IL, interleukin; TNF, tumor necrosis factor; LPS, lipopolysaccharide; NF-κβ, nuclear factor kappa β; NASH, nonalcoholic steatohepatitis; ALD, alcoholic liver disease; TJ, tight junction; IBD, inflammatory bowel disease; BT, bacterial translocation; Ig, immunoglobulin; NAFLD, nonalcoholic fatty liver disease; SREBP, sterol regulatory element-binding protein; O, occludin; ZO, zonula occludens; RCT, randomized clinical trial; CHB, chronic hepatitis B; HBV, hepatitis B virus; HCV, hepatitis C virus; Mx, myxovirus; HVGP, hepatic venous pressure gradient; SBP, spontaneous bacterial peritonitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AMA, antimitochondrial antibodies

http://dx.doi.org/10.1016/j.jff.2015.05.009
1756-4646/

1. Introduction

Probiotics are defined as "live microorganisms that confer a health benefit to the host when administered in adequate amounts" (Food and Agriculture Organization of the United Nations and World Health Organization, 2002; Neish, 2009). Prebiotics are indigestible carbohydrates such as inulin, galactooligosaccharides and fructooligosaccharides that stimulate the growth and activity of beneficial bacteria within the intestinal microflora. The human gastrointestinal (GI) tract is colonized by 500–1500 different species and subspecies of bacteria. The gut microbiota comprises predominantly Gram-positive Firmicutes (60–80%) and Gram-negative Bacteroidetes (20–40%). The predominant genuses are *Lactobacillus* and *Bifidobacterium* (Backhed, 2012; Berg, 1996; Tap et al., 2009), while species of bacteria differ significantly between host species and individuals and can vary according to host genotype, age, health status, diet, and previous exposure to antibiotics (Henao-Mejia, Elinav, Thaiss, Licona-Limon, & Flavell, 2013). The main functions of these bacteria are to maintain a microbial barrier against established and potential pathogens; to regulate the immune response, motility, perfusion, and permeability of the intestinal wall; and to produce vitamins (Lata, Jurankova, Kopacova, & Vitek, 2011). Their presence along the GI tract is influenced by several factors, including diet, intraluminal pH, bacterial adhesion, mucin secretion, and bacterial antagonism. Changes in any of these factors can affect the environment that supports the gut microbiota, thus altering the number of microorganisms available to maintain intestinal homeostasis and lead to excessive energy production and calorie extraction, with negative effects on metabolism and obesity that can lead to liver disease (Neish, 2009; Visvanathan et al., 2007).

2. Roles of the microbiota in the liver immune system

The liver is constantly exposed to multiple noxious and beneficial products and microorganisms derived from blood flow (1000–1200 ml/min) via the portal vein, which carries blood out of the spleen and intestines (Henao-Mejia et al., 2013). This blood flow creates a constant interaction between the host and its intestinal microflora, and this interaction is closely regulated to prevent activation of the immune system against the host. Interactions between the host and its intestinal microflora are mediated by a group of pattern-recognition receptors (Carvalho, Aitken, Vijay-Kumar, & Gewirtz, 2012). These receptors and their downstream signaling cascades are essential for the proper recognition of commensal microorganisms, and their interaction is necessary for maintaining mutualism and preventing hyperactivation of the immune system. The expression of innate immune receptors has been observed in multiple sites, such as biliary epithelial cells (BECs), hepatocytes, hepatic stellate cells, sinusoidal endothelial cells and Kupffer cells (Hosel et al., 2012; Visvanathan et al., 2007; Wang et al., 2005, 2009; Yokoyama et al., 2006). Toll-like receptors (TLRs), a type of pattern-recognition receptors, have recently been recognized as key components of the liver's immune system and participate in the progression of liver diseases.

Thirteen TLRs have been identified in mammals, where TLR2, TLR4, and TLR9 are the most studied TLRs linked to the development of liver disease. These TLRs launch an immune response that begins with a signaling cascade resulting in the activation of genes with proinflammatory activity, such as interleukin (IL) 6, IL-8, IL-12 and tumor necrosis factor-α (TNF-α) (Aderem & Ulevitch, 2000).

Under pathological conditions, the composition of the gut microbiota and intestinal permeability are altered and there is a breakdown in TLR tolerance against endogenous ligands, resulting in repeated inflammation and contribution to the appearance of chronic liver diseases. The intestinal barrier is disrupted under stressful situations such as pathogen–enterocyte interaction, drugs, inflammation, and hypoxia. Disruption of this barrier provides the opportunity for previously excluded antigens and endotoxins to enter the enterocytes and systemic circulation. This situation has been described as a "leaky gut" and the resulting phenomenon as metabolic endotoxemia (Sharma, Garg, & Aggarwal, 2013). TLR4 expressed in Kupffer cells is activated by the lipopolysaccharide (LPS)-binding protein CD14 complex which initiates an inflammatory cascade that involves mitogen and stress activated protein kinases, p38, interferon regulatory factor 3, Jun-N-terminal kinase, and the nuclear factor kappa β (NF-κB) (Ruiz