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Review

Role of the intestinal microbiome in liver disease

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ABSTRACT

The liver integrates metabolic outcomes with nutrient intake while preventing harmful signals derived from the gut to spread throughout the body. Direct blood influx from the gastrointestinal tract through the portal vein makes the liver a critical firewall equipped with a broad array of immune cells and innate immune receptors that recognize microbial-derived products, microorganisms, toxins and food antigens that have breached the intestinal barrier. An overwhelming amount of evidence obtained in the last decade indicates that the intestinal microbiota is a key component of a wide variety of physiological processes, and alterations in the delicate balance that represents the intestinal bacterial communities are now considered important determinants of metabolic syndrome and immunopathologies. Moreover, it is now evident that the interaction between the innate immune system and the intestinal microbiota during obesity or autoimmunity promotes chronic liver disease progression and therefore it might lead to novel and individualized therapeutic approaches. In this review, we discuss a growing body of evidence that highlights the central relationship between the immune system, the microbiome, and chronic liver disease initiation and progression.

1. Introduction

The multiple physiological processes that are dependent on the reciprocal interaction between the liver and the gastrointestinal tract highlight the critical functional relationship between these organs. The portal vein, which conducts venous blood from the intestines and the spleen, provides ~75% of the blood supply to the liver (1000–1200 mL/min). Therefore, the liver is constantly exposed to multiple noxious and beneficial products or microorganisms derived from the small and large intestines [1].

In recent years, it has been widely demonstrated that the intestinal microbiota have critical functions in multiple aspects of mammalian physiology including regulation of body weight and related metabolic homeostasis, instruction of the immune system, and regulation of epithelial cell responses that are essential to maintain mutualism [2,3]. The human gastrointestinal tract hosts 10–100 trillion bacteria containing approximately 500–1500 different bacterial species [4]. The intestinal microflora significantly differs among species and individuals. Host genotype, age, health status, diet and exposure to antibiotics are critical parameters that regulate the configuration of the intestinal microflora [5,6]; moreover, disturbances in the ecosystem of bacterial communities within the gastrointestinal tract can initiate serious metabolic and inflammatory pathologies.

The liver's strategic location confers it with the important role of translating physiological and pathological processes within the gastrointestinal tract into metabolic and immunologic outcomes. Therefore, it is becoming increasingly clear that the intestinal microbiota is a central component of hepatic pathophysiology. Here, we review recent evidence that highlights the influence of the gut microbiota on chronic hepatic diseases, with a special emphasis on how the interactions between the innate immune system and the microbiota determine the progression of liver disease.

2. Interactions between the intestinal microbiota and the innate immune system in the context of liver diseases

A large array of pattern-recognition receptors (PRRs) of the innate immune system mediates the fine interaction between the host and its intestinal microflora [7]. Although originally these receptors were mainly regarded for their role in recognizing invading pathogenic microorganisms and priming adaptive immune

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responses, it is now clear that PRRs and their downstream signaling cascades are essential for the recognition of the commensal microflora. The interaction between commensal microorganisms and the host PRRs under homeostatic conditions is necessary to locally contain the microbiota and maintain mutualism [8]; and disruption of multiple innate immune signaling pathways has been associated with a wide array of aberrant pathological processes including abnormal development of the intestinal immune system, altered intestinal epithelial homeostasis and severe intestinal injury [9].

The expression of innate immune receptors has been reported in multiple hepatic (hematopoietic and non-hematopoietic) cells such as biliary epithelial cells, sinusoidal endothelial cells, hepatic stellate cells, Kupffer cells and hepatocytes [10–14]. Innate PRRs expression in the liver provides an additional surveillance system recognizing microbial-derived products that are originated in the gastrointestinal tract. Therefore, the liver has to maintain a delicate balance between its ability to keep tolerance toward translocated microbial-derived products or food antigens and its ability to promote immune responses against persistent or harmful microbial stimulus that result from intestinal breach and are indicative of systemic microbial spread. In the sections below, we will describe and discuss how the interactions between hepatic PRRs with microorganisms contribute to the pathogenesis of chronic of liver disease.

2.1. Toll-like receptors

The first class of PRRs identified was the Toll-like receptors, or TLRs. TLRs recognize a variety of microbial ligands, including bacterial and fungal cell wall components as well as nucleic acids [15]. Multiple cells in the liver express significant levels of multiple TLRs and have long been recognized to be critical determinants in the pathogenesis of chronic liver diseases. Specifically, TLR2, TLR3, and TLR4 are highly expressed in Kupffer cells and respond to endotoxin stimulation leading to the rapid production of TNF-α, IL-6, and IFN-γ. Furthermore, the expression of TLRs has been found on biliary epithelial cells, hepatic stellate cells, hepatocytes and liver sinusoidal endothelial cells [1] (Fig. 1).

The signaling pathway activated through TLR4-MyD88-NF-kB has been found to be fundamental to the pathophysiological processes that drive multiple liver diseases such as viral hepatitis, hepatocellular carcinoma, fatty liver disease, cirrhosis and fibrosis. Activation of TLR4 in Kupffer cells has been shown to promote alcoholic liver disease [16]. In addition, hepatic TLR4 expression is increased in animal models of non-alcoholic steatohepatitis (NASH) [17], Primary Sclerosing Cholangitis (PSC) [18], and Primary biliary cirrhosis (PBC) [14]. Moreover, TLR4-deficient mice fed a high-fat diet have decreased levels of hepatic steatosis [19]. Interestingly, genetic data from humans identified a polymorphism in the gene encoding TLR4, which attenuates the signaling downstream of the receptor in response to LPS stimulation, and has been associated with a decreased risk to developing cirrhosis [20,21].

TLR9-dependent activation of IRF-7 to induce the expression of type I interferons (IFNs), has also been associated with enhanced severity of inflammatory liver disease. Interestingly, type I IFNs were recently described to protect from TLR9-associated liver damage, an effect mediated by the endogenous IL-1 receptor antagonist [22]. A protective role for type I IFNs in a TLR4-driven model of alcoholic liver disease has also been recently reported [23].

The critical role of TLRs in chronic liver disease suggests that increased microbial translocation across the gastrointestinal tract and hepatic recognition of microbial products is an important component of liver pathology (Fig. 1); however, direct evidence to support this hypothesis has been lacking until recently. Seki et al. demonstrated that the microbiota is an important component for the development of hepatic fibrosis since deficiency in TLR4 signaling and antibiotic treatment reduced hepatic fibrosis after bile duct ligation. The underlying mechanism driving fibrosis

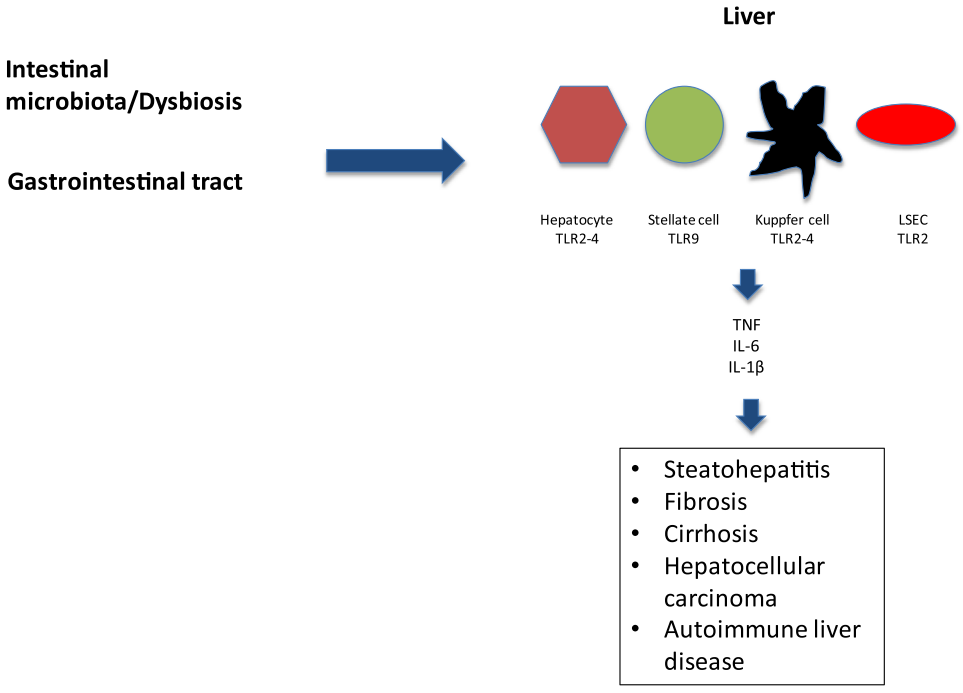

Fig. 1. Pattern recognition receptors expressed in multiple hepatic cells regulate the pathogenesis liver disease. NLRP6 regulates the intestinal microbial ecology. Dysbiosis and intestinal inflammation are associated with increased permeability and influx of PAMPs into the portal circulation. In the liver, TLR activation in multiple liver cells leads to chronic inflammation and disease progression.