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Review

The intestinal microbiota and microenvironment in liver☆,☆☆

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ABSTRACT

The intestinal microbiome plays a significant role in the development of autoimmune diseases, in particular, inflammatory bowel diseases. But the interplay between the intestinal tract and the liver may explain the increased association with autoimmune liver diseases and inflammatory bowel diseases. The gut–liver axis involves multiple inflammatory cell types and cytokines, chemokines and other molecules which lead to the destruction of normal liver architecture. Triggers for the initiation of these events are unclear, but appear to include multiple environmental factors, including pathogenic or even commensal microbial agents. The variation in the gut microbiome has been cited as a major factor in the pathogenesis of autoimmune liver disease and even other autoimmune diseases. The unique positioning of the liver at the juncture of the peripheral circulation and the portal circulation augments the interaction between naïve T cells and other hepatic cells and leads to the disruption in the development of tolerance to commensal bacteria and other environmental agents. Finally, the innate immune system and in particular toll-like receptors play a significant role in the pathogenesis of autoimmune liver disease.

Contents

1. Introduction

The liver and the gastrointestinal tract are intimately connected in the context of metabolic activity and immune responses, primarily resulting from their close anatomical and physiological relationship [1]. The liver has a dual blood supply. A quarter of the blood supply is derived from the systemic circulation which reaches the liver through the hepatic artery. The other three quarters are gut derived nutrient-rich blood that enters the liver through the portal vein. The term "gut–liver axis" has been coined to reflect the immunological phenomenon linking the two in health and disease [2].

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Microbes exist in the gut environment and play a significant role in digestion, and are a part of the mucosal immune system that helps shape our ability to distinguish safe and danger signals [3,4]. Since the liver receives blood from both systemic circulation and the intestines, microbes in the intestines may also affect the immune environment in the liver. Portal venous blood returning from the intestines contains the products of digestion, along with antigens and microbial products that originate from the bacteria in the small and large intestines [5]. The exposure of liver cells to antigens, and to microbial products derived from the intestinal bacteria, results in a distinctive local immune environment that modulates immune tolerance in the liver [6–8].

To establish this tolerogenic environment, hepatic immune cells including Kupffer cells, natural killer cells, dendritic cells and lymphocytes, together with other nonparenchymal cells including endothelial cells and stellate cells orchestrate a controlled and organized response to these potentially highly inflammatory factors from the intestines [9,10]. However, this tolerance is quite metastable and can be reversed by the right combination of signals, resulting in active local immunity [5]. For example, changes in the composition of the microbiome or alterations in gut permeability can promote translocation of microbes into the portal circulation that delivers blood directly to the liver [2]. These gut-derived microbial components represent danger signals for the host cells in liver, activate the inflammatory cascade in immune cells and modulate the function of liver parenchymal cells [9].

There is a growing body of evidence showing that the intestinal microbiome possesses critical functions in liver physiology and metabolic homeostasis [11]. Gut-derived bacterial products aggravate hepatic fibrosis [12,13], whereas, gut sterilization helps prevent hepatic fibrosis after bile-duct ligation [12]. Moreover, disruption of the intestinal mucosal barrier facilitates bacterial translocation and promotes the progression of liver fibrosis [13]. Prior studies also suggested that the gut microbiota may affect the progression of non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) [14,15]. This dysbiosis in the digestive tract results in the exacerbation of hepatic steatosis and obesity [16].

The relationship between intestinal homeostasis and autoimmune liver diseases is summarized in this review by discussing the potential involvement of intestinal homeostasis in the pathogenesis of autoimmune liver diseases [17–19], the understanding of which will ultimately steer the development of novel clinical treatments.

2. Gut microbiota participates in the initiation and maintenance of autoimmune liver diseases by modulating the innate immune system

As the first line of defense against pathogens, the innate immune system mediates interactions between the hosts and their intestinal microflora [20]. Pattern recognition receptors widely expressed on innate immune cells and parenchymal cell are essential for the recognition and clearance of commensal and pathogenic microflora [21]. The conflict between the innate immune system and gut microflora is not only necessary to repel the invasion of pathogenic microorganisms, but also critical to maintain a balanced immune response that is reflected in good overall health [22,23]. Evidence has been shown that the dysbiosis of innate immunity in the gastrointestinal tract is one of the most important factors in the initiation and perpetuation of autoimmune liver injury [24]. The gut microflora thereby plays a significant role in the pathogenesis of autoimmune liver diseases.

2.1. Biliary innate immunity

Bile ducts are a significant component of liver architecture, as biliary epithelial cells (BECs) maintain contact with pathogen associated molecular patterns (PAMPs) originating from intestinal microflora derived from bile [25]. As part of the lining of the bile duct, BECs act as a barrier and express a series of molecules associated with immune recognition and response, including toll-like receptors (TLRs), histocompatibility complex (MHC) antigens, adhesion molecules and co-stimulatory molecules [26]. BECs thus play a role in both the innate and adaptive immune systems. This distinct characteristic of BECs facilitates their role in the defense against microbial infection, but also renders such cells uniquely susceptible to autoimmune disorders such as PBC and PSC (Fig. 1A) [27–31].

Biliary epithelial cell antibodies (BEC-Abs), which have been found to be present in high frequency in the bile ducts of patients with PSC, up-regulate expression of TLR4 and TLR9 as well as MyD88 on cultured BECs [32]. TLR-expressing BECs, when further stimulated with lipopolysaccharide and CpG DNA, produce proinflammatory cytokines and chemokines including interleukin-1β, interleukin-8, interferon-γ, tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor, and transforming growth factor-β (Fig. 1A) [32,33]. Upregulation of TLRs as a result of binding of PSC BEC-Abs demonstrated that BEC-Ab may be a critical regulator of cholangitis in PSC. Specifically, binding of lipopolysaccharide and CpG DNA to their respective TLRs induces BECs to produce pro-inflammatory cytokines and chemokines, leading to the further recruitment of inflammatory cells and resulting in cholangitis in PSC. This indicates that environmental factors are essential triggers that can initiate inflammation in the livers of patients with PSC [32]. Interestingly, PSC often coexists with ulcerative colitis [34], suggesting that alteration of the gut microbiome may also play a role in inflammatory bowel disease. Furthermore, accentuated responses of both TLR4 and TLR9 have been reported in the intestinal epithelium of patients with ulcerative colitis [35,36]. These observations suggest that stimulators of TLRs from the digestive tract in PSC patients with ulcerative colitis may play a role in the pathogenesis of PSC.

Based on evidence, we can surmise that gut microbes render BECs active participants and mediators of their own destruction in PSC (Fig. 1A). On the one hand, microbial pathogens from the gut can possibly circulate to bile ducts in the liver and activate an inflammatory response via TLR activation. On other hand, the adaptive immune response mediated by BEC-Ab may facilitate the innate immune responses by induction of functional TLRs on the bile duct epithelium of PSC patients. Thus, both the innate and adaptive immune responses cooperate to establish a pro-inflammatory loop, resulting in an enhanced or sustained inflammatory signaling in BECs, leading to the autoimmune injury found in BECs in PSC patients.

Bacterial products have also been implicated in the pathogenesis of bile duct diseases other than PSC [37]. Several bacterial products have been detected in liver tissue from patients with PBC, suggesting an association with the development of PBC [38,39]. Similar to PSC, TLR4 was found to be expressed at high levels on BECs in PBC patients. This aberrant expression of TLR4 was also observed in periportal hepatocytes of PBC livers and extended to interlobular hepatocytes in advanced stages of PBC [40]. The deviant distribution of TLR4 in the livers of PBC patients suggests the involvement of bacterial pathogens and TLR4 in different stages of PBC.

2.2. Innate immune cells

Liver innate immune cells are essential effector cells that undergo various forms of activation in response to stimuli, including microbial signals originating from the gut. Many autoimmune disorders have been linked to dysfunctional innate immune cells responding against commensal microflora. Such aberrant immune responses partially contribute to the pathogenesis of PBC.

The innate immune cells of patients with PBC demonstrate higher reactivity than controls (Fig. 1B). For example, the frequency and absolute number of blood and liver natural killer (NK) cells in patients with PBC, as well as their cytotoxic activity and perforin expression, are increased [41,42]. Moreover, monocyte-derived macrophages (MDMϕ) in patients with PBC polarize most likely to M1, and they exhibit strong