Review

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Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance

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Summary

The term cirrhosis-associated immune dysfunction refers to the main syndromic abnormalities of immune function, immunodeficiency and systemic inflammation that are present in cirrhosis. The course of advanced cirrhosis, regardless of its aetiology, is complicated by cirrhosis-associated immune dysfunction and this constitutes the pathophysiological hallmark of an increased susceptibility to bacterial infection, distinctive of the disease. Cirrhosis impairs the homeostatic role of the liver in the systemic immune response. Damage to the reticulo-endothelial system compromises the immune surveillance function of the organ and the reduced hepatic synthesis of proteins, involved in innate immunity and pattern recognition, hinders the bactericidal ability of phagocytic cells. Systemic inflammation, in form of activated circulating immune cells and increased serum levels of pro-inflammatory cytokines, is the result of persistent episodic activation of circulating immune cells from damage-associated molecular patterns, released from necrotic liver cells and, as cirrhosis progresses, from pathogen-associated molecular patterns, released from the leaky gut. Cirrhosis-associated immune dysfunction phenotypes switch from predominantly "pro-inflammatory" to predominantly "immunodeficient" in patients with stable ascitic cirrhosis and in patients with severely decompensated cirrhosis and extra-hepatic organ failure (e.g. acute-on-chronic liver failure), respectively. These cirrhosis-associated immune dysfunction phenotypes represent the extremes of a spectrum of reversible dynamic events that take place during the course of cirrhosis. Systemic inflammation can affect the functions of tissue somatic cells and modify the clinical manifestation of cirrhosis. The best characterized example is the contribution of systemic inflammation to the haemodynamic derangement of cirrhosis, which correlates negatively with prognosis.

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Abbreviations: CAID, cirrhosis-associated immune dysfunction; IL, interleukin; NK, natural killer; PRR, pattern recognition receptor; LPS, lipopolysaccharide; LBP, lipopolysaccharide binding protein; TLR, toll-like receptor; NLR, NOD-like receptor; Th cell, T helper cell; Tc cell, cytotoxic T cell; PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; GALT, gut-associated lymphoid tissue; MLN, mesenteric lymph node.

Introduction

The immune system plays a dual role in the pathogenesis of cirrhosis such that, besides the role of immune-mediated inflammatory mechanisms, cirrhosis itself also leads to immune system dysfunction. The immune system mediates hepatocyte damage due to alcohol, virus infection or autoimmunity, driving fibrogenesis through hepatic stellate cell activation. In addition, cirrhosis leads to impairment of the immune system with an inability to protect the host from bacterial infection and dysregulated immune cell activation.

This paper reviews the myriad of dynamic detrimental effects that cirrhosis has on the immune system that we have designated cirrhosis-associated immune dysfunction (CAID). This concept includes two main syndromic alterations: (i) immunodeficiency, due to an impaired response to pathogens at different levels of the immune system, and (ii) systemic inflammation, as a consequence of persistent and inadequate stimulation of cells of the immune system (Fig. 1). CAID should be considered a complication of cirrhosis of any aetiology. It accounts for many distinctive features of cirrhosis such as a predisposition to bacterial infection and a poor response to vaccination [1–3]. It may also play an important role in endothelial activation and the haemodynamic disturbance of cirrhosis and contributes to other clinical manifestations, such as asthenia.

Contribution of the liver to the systemic homeostasis of the immune system

The liver regulates homeostasis of the immune system through two mechanisms. First, it plays a role in immune surveillance, defending against blood-borne pathogens via its double blood

Key Points

- Cirrhosis-associated immune dysfunction refers to both immunodeficiency and systemic inflammation that occur in cirrhosis
- Immunodeficiency in cirrhosis results from damage to the local immune surveillance function of the liver, reduced synthesis of pattern recognition receptors, and damage at the systemic level of immune response cell function
- Systemic inflammation accompanies immunodeficiency and is attributed to persistent immune cell stimulation as well as to PAMPs and DAMPs from a leaky gut and a damaged liver, respectively. Inflammation is reflected by an increased production of pro-inflammatory cytokines, their enhanced serum levels, and the upregulated expression of cell activation markers
- The cirrhosis-associated immune dysfunction phenotypes represent the extremes of a spectrum of reversible dynamic events that take place during the course of cirrhosis. Under constant PAMPs challenge, the immune response pattern in cirrhosis switches from a predominantly "pro-inflammatory" phenotype in patients with "stable" decompensated cirrhosis to a predominantly "immunodeficient" one in patients with severely decompensated cirrhosis and extra-hepatic organ failure (e.g. ACLF)
- Systemic inflammation can affect the function of tissue somatic cells and modify the clinical expression of cirrhosis. The best example is the contribution of systemic inflammation to the haemodynamic derangement of cirrhosis, which correlates negatively with prognosis

supply, thereby avoiding the systemic spread of microbial and dietary antigens arriving from the gut [4]. This function of the liver is offset by the local immune tolerance to non-pathogenic exogenous material [5]. The second mechanism, used by the liver to drive homeostasis of the immune system, is the synthesis of soluble molecules that are essential for an effective immune response [6].

Immune surveillance: Role of the liver

The liver exerts its antimicrobial surveillance function through different populations of resident antigen presenting cells and lymphocytes. These are organized in a manner specifically designed to maximize screening for both systemic and gut-derived pathogens. The liver antigen presenting cells include Kupffer and sinusoidal endothelial cells, which comprise the reticulo-endothelial system of the liver, and dendritic cells. Kupffer cells reside within the sinusoidal vascular space and represent the largest group of fixed macrophages in the body, and sinusoidal endothelial cells form a sieve-like, fenestrated endothelium. Unlike macrophage populations of other organs, Kupffer cells occur on the intraluminal side of the vasculature and can capture bacteria under flow conditions. Kupffer cells are specialized at eliminating insoluble waste by phagocytosis through a variety of receptors. As such, Kupffer cells are endowed with unique complement receptors that can bind avidly to complement component 3b (C3b) under shear conditions [7]. Sinusoidal endothelial cells are responsible for the elimination of soluble macromolecules and colloidal waste by endocytosis. Kupffer and sinusoidal endothelial cells are also antigen presenting cells, constitutively expressing MHC class I and II and co-stimulatory receptors in addition to molecules that promote antigen uptake, including mannose and scavenger receptors [8,9]. Despite Kupffer cells being critical for microbial capture, their role in microbial killing seems to be dependent on the nature of the pathogen and on the recruitment of additional immune cells to the liver [10]. The liver also contains several populations of dendritic cells, which characteristically have a reduced capacity to drive the activation of T cells, in part due to both, their "immature" development status, and to the local cytokine milieu of the liver, including high interleukin (IL)-10 and low IL-12 levels [11].

Additionally, the liver contains populations of both resident and transiting T and B lymphocytes scattered throughout the parenchyma and the portal tracts that are important in the defensive adaptive immune response. Further, the liver is enriched in natural killer (NK) cells and unconventional lymphocytes (natural killer T and $\gamma\delta$ T cells), which have roles in innate immune responses of the liver.

Besides conferring strong local innate immunity, the liver is a major site of induction of local and systemic adaptive immune responses, mediated by T lymphocytes, playing a critical role in the homeostatic regulation of the immune system. The delicate balance between immunity and tolerance, observed in the liver, is driven by several mechanisms. In the specific antigen challenging micro-environment of the liver, tolerance is maintained through: (i) the direct access of naive CD8+ T cells to antigen presenting cells in the absence of CD4+ T cell activation [12], (ii) the constitutively low abundance of MHC expression by liver-resident cells [13], and (iii) high IL-10 production by Kupffer and sinusoidal endothelial cells [14]. All these mechanisms promote the non-activation and/or apoptosis of CD4+ T lymphocytes. Further, the expression of adhesion molecules facilitates the sequestering of circulating activated T cells, particularly CD8+ T cells, by the liver endothelium [4].

Relevance of the liver in the systemic immune response

The liver, primarily through its hepatocytes, is a major source of proteins involved in innate and adaptive immune responses, including complement components and many secreted pattern-recognition receptors (PRRs) [15]. Complement proteins play roles in the regulation and effector stage of the immune response, and their activation gives rise to a wide range of opsonic, inflammatory and cytotoxic activities. The liver is also the main source of soluble PRRs (e.g. C reactive protein, lipopolysaccharide [LPS]-binding protein [LBP], peptidoglycan-recognition protein, soluble CD14), which activate complement, induce opsonization and regulate immune cell function [16,17]. The liver also produces other acute phase proteins, such as hepcidin, fibrinogen and proteinase inhibitors, which participate in the innate immune response and in controlling tissue damage and repair during inflammation. Hepatocytes synthesize and secrete most of these proteins in response to different pro-inflammatory cytokines (e.g. TNFα, IL-6), generated in the course of a systemic inflammatory responses.