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Immune function of nonparenchymal liver cells

X.K. Xing[1], H.Y. Wu[2], H.G. Feng[1] and Z.Q. Yuan[1]

[1]Department of Life Science and Technology, Xinxiang Medical University, Xinxiang, China
[2]Department of Forensic Biology, Xinxiang, China

Corresponding author: X.K. Xing
E-mail: biyingxiao@163.com

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ABSTRACT. The liver is the human body largest digestive and metabolic organ, and a very important immune organ. This paper discusses the location and morphology of hepatic sinusoidal endothelial cells, dendritic cells, hepatic stellate cells, and Kupffer cells in the liver and their role in regulating immune functions. Therefore, here we provide a preliminary understanding of the immune regulatory function of liver cells, and information on the occurrence and treatment of liver diseases.

Key words: Dendritic cell; Hepatic sinusoidal endothelial cell; Hepatic stellate cell; Immune; Kupffer cell

INTRODUCTION

The liver is the human body largest digestive and metabolic organ, in addition to being a very important immune organ. The liver has a unique dual blood supply, with 20% of the blood coming from the hepatic artery and 80% from the portal vein, which is rich in bacterial products, environmental toxins, and food antigens. The liver is the site of convergence of antigens from the gastrointestinal tract and innate immune system. The liver's anatomical location and functional characteristics make it one of the most vulnerable organs in the human body. Therefore, the liver should have a perfect defensive immune system to ensure its normal operation and unaltered physiological function of innate immune system.

The liver is the site for the production of cytokines, complement components, and acute reactive proteins. The defensive immune system of the liver comprises a very complex cell population. The liver comprises parenchymal and non-parenchymal cells, which account for 80 and 20% of the total liver cells, respectively. The non-parenchymal cells mainly include liver sinusoidal endothelial cells (LSECs), dendritic cells (DCs), hepatic stellate cells (HSCs), and Kupffer cells (KCs) (Mohar et al., 2015). These cells have different structural functions and sources of differentiation, and they regulate the local and systemic immune function. The natural immune system of the liver regulates inflammation by balancing the production of pro-inflammatory and anti-inflammatory cytokines. As an important natural immune organ, the liver plays an important role in preventing tumor transformation and liver injury, defending against microbial invasion, and repair.

LSECs

Blood from the portal vein and the hepatic artery confluences into the liver sinus. The hepatic sinusoidal capillary wall has large gaps between endothelial cells. The slow blood flow in the hepatic sinus is beneficial because the antigens from the gastrointestinal tract and the immune system can pass through smoothly and are in full contact with the immune components of the liver that can effectively regulate the immune response.

LSEC is a microvascular cell that is attached to the inner surface of the hepatic sinus, which separates the blood cells from the liver and the hepatic cells preventing their direct contact. LSECs account for 70% of the total nonparenchymal liver cells. The phenotype and function of LSECs is very different from that of common capillary endothelial cells. Under physiological conditions, an LSEC has many fenestrae, ranging from less than 100 nm to more than 1 to 2 μm. LSECs lining the liver sinus form a structure that lacks a basement membrane; therefore, blood cells and plasma components can diffuse into the Disse space, enabling material exchange and immune responses.

LSEC is different from other vascular endothelial cells, which function as inflammatory mediators. LSEC has an active antigen presenting function under physiological conditions and immune response efficiency and antigen presentation is similar to that of a DC. Under physiological conditions, LSECs constitutively express a series of surface molecules required for antigen presentation, such as major histocompatibility complex (MHC) class I and II molecules, cluster of differentiation (CD)54, CDl06, and co-stimulatory molecules such as CD80, CD86, and CD40 (Racanelli and Rehermann, 2006). Additionally, LSECs express CDl02, CD31, CD 209L, Toll-like receptor (TLR)-4, CDl4, CD32, CD36, CD4, CDllC, CD95, CD95L, tumor necrosis factor (TNF) (ligand) superfamily member 10 (TNFSF10), TNF, etc. Antigen presentation by LSECs is mainly

affected by the constituents of the liver internal environment such as endotoxins, prostaglandin E2, interleukin (IL)-10, liver cells, and portal blood flow components (Limmer and Knolle, 2001). LSECs express lower levels of co-stimulatory molecules than DCs, which are relatively immature and highly express co-stimulatory molecules upon maturation, thereby triggering an immune response. Therefore, LSEC is a cell population that promotes immune tolerance (Elvevold et al., 2008).

Additionally, LSECs can also capture T cells and induce their apoptosis in the liver, which is characteristic of other antigen-presenting cells (APC). The liver is referred to as a graveyard of T cells, which sufficiently implicates the liver ability to capture and destroy living T cells, especially the activated T cells. In the late phase of an immune response, a large number of activated T cells were not dispersed throughout the immune system, but were confined to the liver and apoptotic. LSEC is the main cell involved in this process because of the following two reasons. First, LSECs are aptly located to have good contact with the circulating lymphocytes, and they constitutively express CD54, CDl06, and other adhesion molecules. Therefore, LSECs do not need to be activated to interact with the corresponding adhesion molecules on the T cell surface, thus, confining it to the liver. Second, LSECs have the potential to destroy T cells because they constitutively express death receptors such as CD95L, TNFSF10, and membrane binding TNF-α. Therefore, the apoptosis of T cells may be caused by its interaction with LSEC.

DCs

DCs were discovered in 1973 by the Canadian scholar, Steinman. They are the most powerful APCs, and named for the maturity of the many dendritic or pseudopodia-like protrusions. DCs are mostly distributed in the periphery of the portal vein, and some in the liver parenchyma (Bosma et al., 2006). DCs can be classified into myeloid DCs (MDC, CD8a-CD11b+) and lymphoid DCs (LDC, CD8a+CD11b-) based on their source and surface markers (Geissmann et al., 2010). Various subtypes of DCs have different molecular phenotypes and secrete different cytokines to induce Th0 cells to differentiate into Thl or Th2 cells, and regulate between the two kinds of immune responses. MDC is stimulated to secrete IL-12, which induces Th0 to differentiate into Th1, and induces a Th1 cell and cytotoxic T cell-mediated immune response by secreting interferon (IFN)-α and IL-2. LDC mainly induces Th0 to differentiate into Th2, through IL-4, and induces a Th2 cell-mediated immune response by secreting IL-10. Furthermore, LDC can secrete a large amount of class I IFN upon stimulation by an external antigen, which directly inhibits the replication of the virus, and activates natural killer (NK), B, T, and MD cells, to induce and enhance the antiviral immune response.

Most DCs in the human body are immature, express MHC molecules, and secrete IL-10. However, they do not express CD58, CD54, CD86, etc., which are required to activate T cells. Compared with bone marrow derived- and spleen DCs, liver DCs do not express co-stimulatory molecules and have a weakened ability to activate naïve allogeneic T cells (Pillarisetty et al., 2004). However, immature dendritic cells have a strong ability to capture and present antigens. DCs capture antigens and travel through the lymphatic vessels to the secondary lymphoid tissue, and spontaneously mature during this process. Subsequently they present antigens to T cells, and activate a T cell-mediated immune response. Therefore, DCs are an important bridge between the initial and the acquired immune response. Mature DCs highly express MHC molecules, co-stimulatory molecules (CD40, CD80, and CD86), and adhesion molecules (CD50 and CD54) on their membrane surface. Among these, the MHC molecule and initial recognition of the T cell

surface antigen receptor generate the first activation signal, the co-stimulatory molecules involved in DCs and T cells provide the second activation signal. Rat liver-DC gradually matures from the central portal vein, and travels through the Disse space in the hepatic sinus into the hepatic lymphatic system (Sato et al., 1998).

In healthy livers, DCs are undifferentiated. Their immature state is because of the special liver microenvironment. Hepatic nonparenchymal cells can secrete IL-10 and TGF-β; other liver cells can also secrete IL-10 (Lee et al., 2005). IL-10 and TGF-β inhibit hepatic DC maturation and its ability to stimulate T cells, which is associated with the liver transplantation tolerance (Khanna et al., 2000). Liver DCs may induce host activation of T cells by apoptosis ligand/receptor pathway to induce liver transplantation tolerance (Qian et al., 1997).

HSCs

HSCs are also known as fat storage cells, Ito cells, sinus cells, and vitamin A storage cells. They are nonparenchymal cells and account for 5-15% of the total number of liver cells. HSCs are located in the space between liver cells and LSECs (Disse space) (Ford et al., 2015). HSCs are in contact with their adjacent hepatocytes, hepatic sinusoidal endothelial cells, and nerve terminals through the self-synapse. Morphologically, HSCs are typically small, stationary, and have lipid droplets (like a retinoid substance) in their cytoplasm. Upon stimulation by pathogenic factors, HSCs are activated and their cell phenotype changes, becoming large and flat. They lose their ability to store lipid particles, become capable of secreting high amounts of extracellular matrix, and secrete many pro-inflammatory and pro-fibrosis cytokines, and can transform into muscle fiber mother cells (He et al., 2015). This is the basis of liver fibrosis.

HSCs can express many kinds of molecules involved in antigen presentation:human leukocyte antigen (HLA I and HLA II), which participate in protein antigen presentation; cluster of differentiation (CDIb and CDIc), which participate in lipid antigen presentation; co-stimulatory molecules (CD40 and CD80), which are required for efficient T cell activation; CD68, which is an intracellular protein that is responsible for translocating the antigen to the lysosome (Viñas et al., 2003).

HSCs can express co-stimulatory factors (CD40, CD80, and CD86), which are involved in antigen presentation, related to T cell activation and the CD28 expressing T cell regulation. HSCs can express TLR-2, which mainly identifies the peptides on the surface of gram positive bacteria; TLR-4, which mainly identifies the lipopolysaccharides that compose the cell wall of gram negative bacteria; and TLR-9, which can identify bacteria with non-methylated DNA through a specific signal transduction pathway-mediated cell immunity. Activated HSCs can also express co-stimulatory molecules such as CD40, which can bind the CD40-L on the T cell surface, and promote the production of IL-8 and monocyte chemotaxis protein-l. Additionally, activated HSCs can release the complement factor C4, and express the C5a and the Fc receptors.

HSC storage of vitamin A and secretion of TGF-β can induce the production of CD4+CD25+Foxp3+ Treg cells (Strober, 2008). Inactivated HSCs do not express CD274. After exposure to IFN-7 or activated T cells, activated HSCs expressed inhibitory cytokines (CD274, IL-6, IL-10, TGF-β), and promoted the early apoptosis of T cells (Yu et al., 2004). IL-10 is a negative immune regulation factor, which can inhibit the antigen presenting function of macrophages. Activated HSCs can express the IL-10 receptor, secrete IL-10, and simultaneously inhibit its activation through a negative feedback loop (Mathurin et al., 2002).

KC

KCs are macrophages that reside in the hepatic sinus. It is the largest natural macrophage population in the human body, accounting for 80-90% of the total number of natural macrophages and 20% of the liver nonparenchymal cells (Duarte et al., 2015). They are mainly located in the portal vein, which is an important part of the cellular immunity machinery of the human body. KCs are large in size and irregularly shaped, with their perikarya protruding into the gap cavity or completely free in the sinus cavity. Their filopodia are attached to the surface of the endothelial cells, inserted into the endothelial gap, or extended into the Disse space through the fenestrae, and are thereby interleaved with hepatocyte microvilli. The structure of KCs lays a foundation for the mutual coordination and influence of liver cells and other cell functions. Kupffer cells not only carry out non-specific phagocytosis and clearance of bacteria and foreign bodies such as antigenic substance in the bloodstream, but also play roles in specific immune response, anti-tumor immunity, detoxification of endotoxin, anti-infection, regulating microcirculation, and metabolism.

The KC surface has many functional receptors and proteins that are related to immune response, such as immunoglobulin G (IgG) Fc receptors (including CD64, CD32, and CDl6), complement receptor (including the complement receptor L, complement receptor 3, and complement receptor 4), mannose receptor, I region-associated antigen, and other surface molecules (such as CDl3, CDl5, and CD68). *In vivo*, Kupffer cells are generally in the resting state. Upon stimulation by pathogens or cytokines, they can be activated and have an enhanced function. They synthesize and secrete TNF-α, IL-l, IL-6, oxygen free radicals, peanut arachidonic acid, and various bioactive substances involved in the body inflammatory response (Heymann et al., 2015). KCs express MHC class II antigens, which can present foreign antigens to the reactive T cells, and thus confer tolerance (Sano et al., 1987). Therefore, the effective uptake of an antigen into the liver is essential to the formation mechanism of portal vein tolerance.

Recent studies have found that the KC is involved in acute rejection after liver transplantation. Th17, a new subtype of CD4+ T cells, is produced by the differentiation of CD4+ T cells, after liver transplantation. Th17 then induces acute rejection. The differentiation of Th17 was regulated by IL-6 and TGF-β, which are both secreted by KCs. KCs can secrete high concentrations of IL-6 and TGF-β after liver transplantation (Xie et al., 2010).

KC can enhance the process of immune tolerance in liver transplantation. Before transplantation, pre-treatment with KCs can inhibit the alanine aminotransferase enzyme, increase the levels of aspartate amino transferase, and decrease TNF-α and IL-1 expression levels, consequently preventing the apoptosis of liver cells, and enhance the immune tolerance of liver transplantation. The expression level of indoleamine 2,3-dioxygenase is closely related toad can be used as an indicator to evaluate immune tolerance. After orthotopic liver transplantation, inhibiting histone deacetylase 11 can increase the expression of IL-10 in KCs, inducing immune tolerance. Therefore, KCs can be used therapeutically to induce immune tolerance (Chen and Qi, 2012; Lian et al., 2012; Luan et al., 2012).

CONCLUSION

Therefore, the liver plays a very important role in immune regulation. Altogether, the function of liver immune cells and the secretion various factors, provide a wide range of local and systemic regulations for the liver's immune response, thereby preventing the occurrence

and development of many diseases. Although many mechanisms have been elucidated, the liver function as an immune organ is indisputable. This review provides new direction to researching liver and systemic diseases in the future.

Conflicts of interest

The authors declare no conflict of interest.

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