Gastroenterology 2014;146:1193–1207

Hepatic Immune Regulation and Its Involvement in Viral Hepatitis Infection

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The liver has unique immune regulatory functions that promote the induction of tolerance rather than responses to antigens encountered locally. These functions are mediated by local expression of coinhibitory receptors and immunosuppressive mediators that help prevent overwhelming tissue damage. Over the years, we have gained more insight into the local regulatory cues that determine the functional complexity of immune responses regulated locally in the liver. Both the unique hepatic microenvironment and the particular liver sinusoidal cell populations, in addition to hepatocytes, actively modulate immune responses locally in the liver and thereby determine the outcome of hepatic immune responses. This is of high biological and clinical relevance in hepatitis B virus and hepatitis C virus infections, which can cause acute and persistent infections associated with chronic inflammation in humans that eventually progress to cirrhosis and hepatocellular carcinoma. Here, we review current knowledge about the balance between immunity and tolerance in the liver and how this may affect our understanding of the determinants of hepatitis B virus and hepatitis C virus clearance, persistence, and virus-induced liver disease.

Keywords: Persistent Viral Infection; Immune Exhaustion; Co-Inhibitory Molecules; T-cell Immunity.

Different cell types contribute to the elimination of viral infections in the liver. There is consensus that virus-specific $CD8^+$ T cells most likely play a prominent role because they are able to clear the virus by noncytolytic and cytolytic effector functions as soon as viral antigens are presented by infected hepatocytes via major histocompatibility complex (MHC) class I alleles. The dominant role of virus-specific $CD8^+$ T cells is further supported by experimental depletion studies of $CD8^+$ T cells that delay the clearance of hepatotropic viruses in chimpanzees.[1,2] Help from $CD4^+$ T cells, however, is needed to prime and maintain vigorous and protective $CD8^+$ T-cell responses. The mechanism contributing to virus-specific $CD8^+$ T-cell failure and thus persistence of hepatotropic infections is still poorly understood. Multiple mechanisms most likely contribute to this virus-specific T-cell failure, such as emergence of viral escape mutations, T-cell exhaustion mediated by inhibitory receptors, lack of $CD4^+$ T-cell help, or direct suppression by cytokines or regulatory T cells (Tregs). In recent years, there has been a stronger focus on cells of the innate immune response, such as natural killer (NK) cells, which account for the majority of innate immune cells in the liver or nonconventional T cells. Clearly, the complex host-virus interactions taking place in a virus-infected liver can only be fully understood if the liver microenvironment and all different specialized key immune cell populations are considered in this context. Here, we summarize current knowledge about the different cell populations that mediate hepatic immune regulation and thus affect immunity to viral hepatitis infection.

Hepatic Microanatomy and Functions

The liver fulfills key functions in metabolism for proteins, carbohydrates, and lipids and for elimination of toxic waste products via bile. These functions are facilitated by the hepatic (micro)anatomy. Delivery of blood from the gastrointestinal tract, enriched in nutrients and bacterial degradation products, via the portal vein and arterial blood supply fuel large amounts of blood continuously to the liver. The extensive liver sinusoidal meshwork increases the overall vessel diameter in the liver, leading to a slow blood flow that allows interaction of circulating immune cells with liver-resident cell populations or myeloid cells located in the hepatic sinusoids.

The metabolic function of the liver is primarily seen as a feature of liver parenchymal cells (ie, hepatocytes). This is supported by liver-resident cell populations such as liver sinusoidal endothelial cells (LSECs) and Kupffer cells, the hepatic macrophage population, that have scavenger cell functions. These scavenger cell populations are instrumental in uptake of bloodborne molecules and transcytosis

Abbreviations used in this paper: **Bim, BCL-2 interacting mediator of cell death; HBV, hepatitis B virus; HCV, hepatitis C virus; IFN, interferon; IL, interleukin; iMATE, intrahepatic myeloid cell aggregates associated with T-cell expansion; LSEC, liver sinusoidal endothelial cell; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed death 1; TGF, transforming growth factor; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor–related apoptosis-inducing ligand; Treg, regulatory T cell.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2013.12.036

to hepatocytes, which may also facilitate liver targeting of hepatotropic viruses.[3,4]

Figure 1 is a schematic view of the microarchitecture of the liver sinusoidal network, where hepatocytes are separated from blood passing through the sinusoids by stellate cells, LSECs, and Kupffer cells. Interestingly, LSECs and lymphatic endothelial cells share several features such as non-diaphragmed fenestrae; lack of a basement membrane; common surface markers such as vascular endothelial growth factor receptor 3, mannose receptor, and Liver/lymph node-specific intercellular adhesion molecule-3-grabbing integrin (L-SIGN); and functional properties such as antigen presentation.[5–7] The hepatic sinusoids are the main place where bloodborne immune cells first interact with liver cell populations, directly exert their antimicrobial effector function, or transmigrate into the liver parenchyma.[8]

The Balance Between Immunity and Tolerance in the Liver

Most pathogens are successfully cleared in the liver, and even those pathogens establishing infection can eventually be eliminated by the immune response.[8,9] Over the years, we have gained more insight into the local regulatory cues that determine the functional complexity of immune responses regulated locally in the liver.[7,10,11] Both the unique hepatic microenvironment and certain liver sinusoidal cell populations in addition to hepatocytes actively modulate immune responses locally in the liver and thereby determine the outcome of hepatic immune responses.

The Liver Microenvironment

Because of its anatomic location, the liver is exposed to nutrient-rich blood entering the liver via the portal vein, which also contains bacterial degradation products that gain access to the systemic circulation from the gut lumen.[12] The presence of pathogen-associated microbial patterns is therefore a physiological situation that obviously does not lead to overt organ damage as a consequence of innate immune activation and inflammation. Numerous immune regulatory mediators, such as pathogen-associated microbial pattern–induced release of interleukin (IL)-10 by Kupffer cells or transforming growth factor (TGF)-β from stellate cells, and development of local refractoriness

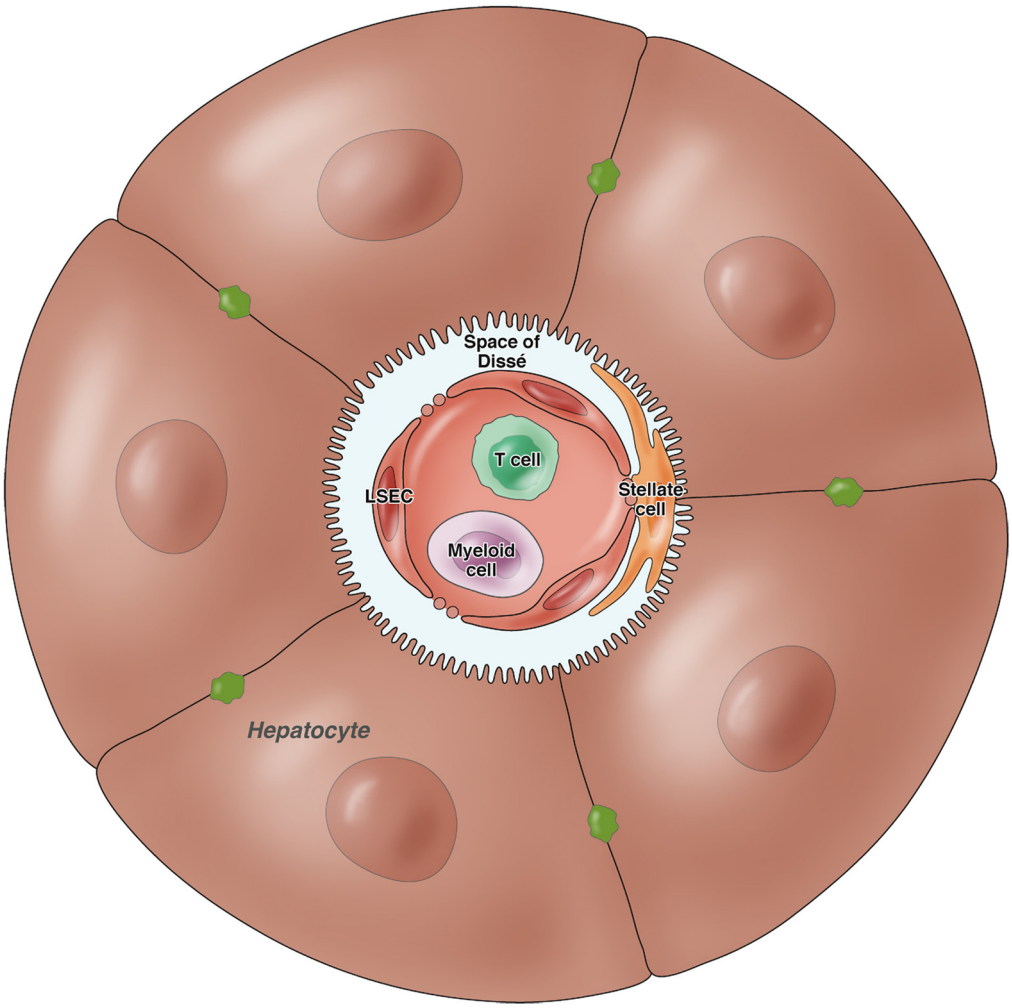

Figure 1. Schematic view of the microarchitecture of the hepatic sinusoid. Hepatocytes are separated from blood passing through the sinusoids by stellate cells, LSECs, and Kupffer cells.