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Review article

Immunity, tolerance and autoimmunity in the liver: A comprehensive review

Derek G. Doherty*

Division of Immunology, School of Medicine, Trinity College Dublin, Ireland

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ABSTRACT

The hepatic immune system is constantly exposed to a massive load of harmless dietary and commensal antigens, to which it must remain tolerant. Immune tolerance in the liver is mediated by a number of specialized antigen-presenting cells, including dendritic cells, Kupffer cells, liver sinusoidal endothelial cells and hepatic stellate cells. These cells are capable of presenting antigens to T cells leading to T cell apoptosis, anergy, or differentiation into regulatory T cells. However, the hepatic immune system must also be able to respond to pathogens and tumours and therefore must be equipped with mechanisms to override immune tolerance. The liver is a site of accumulation of a number of innate lymphocyte populations, including natural killer cells, $CD56^{+}$ T cells, natural killer T cells, γδ T cells, and mucosal-associated invariant T cells. Innate lymphocytes recognize conserved metabolites derived from microorganisms and host cells and respond by killing target cells or promoting the differentiation and/or activation of other cells of the immune system. Innate lymphocytes can promote the maturation of antigen-presenting cells from their precursors and thereby contribute to the generation of immunogenic T cell responses. These cells may be responsible for overriding hepatic immune tolerance to autoantigens, resulting in the induction and maintenance of autoreactive T cells that mediate liver injury causing autoimmune liver disease. Some innate lymphocyte populations can also directly mediate liver injury by killing hepatocytes or bile duct cells in murine models of hepatitis, whilst other populations may protect against liver disease. It is likely that innate lymphocyte populations can promote or protect against autoimmune liver disease in humans and that these cells can be targeted therapeutically. Here I review the cellular mechanisms by which hepatic antigen-presenting cells and innate lymphocytes control the balance between immunity, tolerance and autoimmunity in the liver.

Abbreviations: AIH, autoimmune hepatitis; ALD, autoimmune liver disease; APC, antigen-presenting cell; CTLA-4, cytotoxic T cell antigen-4; DC, dendritic cell; α-GC, α-galactosylceramide; mDC, myeloid dendritic cells; EAE, experimental autoimmune encephalomyelitis; FasL, Fas ligand; FoxP3, forkhead box P3; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HMB-PP, (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate; HSC, hepatic stellate cell; IDO, indoleamine 2,3-dioxygenase; iNKT, invariant natural killer T cell; KC, Kupffer cell; KIR, killer immunoglobulin-like receptor; IFN-γ, interferon-γ; IL, interleukin; LSEC, liver sinusoidal endothelial cell; MAIT, mucosal-associated invariant T cell; MDSC, myeloid-derived suppressor cell; MIC, MHC class I polypeptide-related protein; MHC, major histocompatibility complex; MR1, MHC class I-like molecule-1; MS, multiple sclerosis; NK, natural killer cell; NKT, natural killer T cell; NLR, nucleotide-binding oligomerization domain-like receptor; NOD, non-obese diabetic mouse; PBC, primary biliary cirrhosis; PD-L1, programmed death ligand-1; PGE2, prostaglandin E2; PSC, primary sclerosing cholangitis; RLR, retinoic acid inducible gene 1-like receptor; SLE, systemic lupus erythematosus; TCR, T cell receptor; TGF-β, transforming growth factor-β; Th, T helper; TNF-α, tumour necrosis factor-α; TLR, toll-like ligand; TRAIL, TNF-related apoptosis-inducing ligand; Treg, regulatory T cell.

* Division of Immunology, School of Medicine, Trinity College Dublin, Institute of Molecular Medicine, St. James's Hospital, Dublin 8, Ireland.
E-mail address: derek.doherty@tcd.ie.

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Contents

1. Immunity and tolerance in the liver

The human liver receives approximately 1.5 L of blood every minute, from the gastrointestinal tract via the portal vein, and from the systemic circulation via the hepatic artery. This blood supply carries a massive antigenic load of harmless dietary and commensal products, to which the hepatic immune system must remain tolerant. At the same time, the hepatic immune system needs to be able to respond to a variety of blood-borne viruses, bacteria and parasites in addition to metastatic cells that frequently home from other body locations to the liver. The need for tight immune regulation, or tolerance, in the liver is provided for by an abundance of immunosuppressive cells, cytokines and ligands in the liver, that ensure that pathogen products (such as bacterial lipopolysaccharide) and antigens that are encountered in the liver generally do not stimulate immune responses [1–3]. This predominantly tolerogenic role of the hepatic immune system was first shown in 1969 by Calne and co-workers [4] who found that porcine liver allografts that were mismatched for major histocompatibility complex (MHC) antigens were frequently accepted in the absence of immunosuppression. Subsequent studies confirmed this phenomenon in other species and found that recipients of liver allografts are more likely to accept non-liver allografts from the same donor than from a third individual [5]. The liver tolerance effect may facilitate persistent infection by pathogens, such as hepatitis B and C viruses (HBV and HCV) and *Plasmodium falciparum*, and may support the establishment of metastatic tumours in the liver. However, immune tolerance in the liver can be efficiently broken, resulting in robust hepatic immunity against pathogens and sometimes immune-mediated liver damage. Immune tolerance to self-antigens in the liver can also breakdown, leading to autoimmune liver disease (ALD). Three distinct but overlapping ALDs of humans are identified as autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC).

2. Autoimmune liver disease

AIH, PSC and PBC share common pathways of immune-mediated liver injury, involving the hepatic recruitment of $CD4^+$ and $CD8^+$ T lymphocytes and plasma cells which recognise and destroy liver cells with the subsequent development of liver fibrosis, which can progress to cirrhosis and liver failure. The pathogeneses of these ALDs are described in many excellent reviews [6–12] and will not be discussed in detail here. Although the three diseases exhibit similarities in their pathogenesis, they differ in their patterns of liver injury. AIH is characterised by an inflammatory cell infiltrate, mainly composed of cytotoxic T cells and plasma cells, around the portal tracts which invades and causes progressive destruction of the liver parenchyma, termed interface hepatitis. In contrast, the large intra- and extra-hepatic bile ducts are targeted in PSC leading to biliary tree obliteration resulting in biliary cirrhosis and portal hypertension. In PBC, the small bile ducts are damaged leading to portal tract destruction and biliary cirrhosis.

The three types of ALD can also be distinguished by their autoantibody profiles. AIH can be divided into two clinically-distinct diseases according to the presence of either antinuclear antibodies and anti-smooth muscle antibodies, which characterise type 1 AIH (AIH-1), or anti-liver/kidney microsomal type 1 antibodies and anti-liver cytosol antibodies which are found in patients with type 2 AIH (AIH-2). In contrast, PBC patients typically have high levels of antimitochondrial antibodies, while PSC patients can have perinuclear anti-neutrophil cytoplasmic antibodies. The aetiologies of AIH, PSC and PBC are not well-understood but appear to involve a combination of genetic and environmental factors, with the strongest genetic susceptibility factors being the inheritance of allotypes of the MHC class II proteins, which present antigenic peptides to $CD4^+$ T cells. The MHC class II allotypes DR3, DR4 and DR52a, all of which share a common amino acid sequence motif in their antigen-binding domains, are overrepresented in patients with AIH-1 [13], whereas DR7 predisposes to AIH-2 [14], DR8 confers susceptibility to PBC [15], and DR52a is overrepresented in PSC [16].

3. Immune dysregulation in autoimmune liver disease

ALD is characterised by hepatic infiltrates of $CD4^+$ and $CD8^+$ T cells, which display cytotoxicity against liver or biliary cells and

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