Clinics and Research in Hepatology and Gastroenterology (2016) xxx, xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

SEMINAR

# Liver immunology: How to reconcile tolerance with autoimmunity

**Charlotte R. Grant** [1], **Rodrigo Liberal** [*,1]

*Institute of Liver Studies, King's College London School of Medicine at King's College Hospital, Denmark Hill, London SE5 9RS, United Kingdom*

**Summary** There are several examples of liver tolerance: the relative ease by which liver allografts are accepted and the exploitation of the hepatic microenvironment by the malarial parasite and hepatotrophic viruses are notable examples. The vasculature of the liver supports a unique population of antigen presenting cells specialised to maintain immunological tolerance despite continuous exposure to gut-derived antigens. Liver sinusoidal endothelial cells and Kupffer cells appear to be key to the maintenance of immune tolerance, by promoting T cell anergy or deletion and the generation of regulatory cell subsets. Despite this, there are three liver diseases with likely autoimmune involvement: primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis. How can we reconcile this with the inherent tolerogenicity of the liver? Genetic studies have uncovered several associations with genes involved in the activation of the innate and adaptive immune systems. There is also evidence pointing to pathogenic and xenobiotic triggers of autoimmune liver disease. Coupled to this, impaired immunoregulatory mechanisms potentially play a permissive role, allowing the autoimmune response to proceed.


*Abbreviations:* PPR, pattern recognition receptor; HBV, hepatitis B virus; HCV, hepatitis C virus; TLR, toll-like receptor; IFN, interferon; LSEC, liver sinusoidal endothelial cell; APC, antigen presenting cell; MHC, major histocompatibility complex; PDL-1, program death ligand-1; PD-1, program death-1; LPS, lipopolysaccharide; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; AMA, anti-mithocondrial antibodies; PDC, pyruvate dehydrogenase complex; IBD, inflammatory bowel disease; UC, ulcerative colitis; AILD, autoimmune liver disease; ANA, anti-nuclear antibodies; SMA, smooth muscle antibodies; anti-LKM-1, anti-liver kidney microsomal type-1; anti-LC-1, anti-liver cytosol type-1; GWAS, genome-wide association study; STAT, signal transducer and activator of transcription; IRF, interferon regulatory factor; Treg, regulatory T cell.

* Corresponding author.
*E-mail address:* rodrigo.liberal@kcl.ac.uk (R. Liberal).
[1] Contributed equally.

http://dx.doi.org/10.1016/j.clinre.2016.06.003
2210-7401/

Please cite this article in press as: Grant CR, Liberal R. Liver immunology: How to reconcile tolerance with autoimmunity. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.06.003

## Introduction

The liver is a tolerogenic organ, as testified by several striking examples. In healthy experimental pigs [1], mice [2] and rats [3] liver allografts have been accepted long-term, relative to other organs, without the need for immunosuppression [4]. In humans, the successful temporary withdrawal of immunosuppression after liver transplantation has long been appreciated in patients requiring drug tapering for clinical reasons [5]. Moreover, in several clinical trials, immunosuppression has been prospectively withdrawn in approximately 20% of patients, who have been labelled 'operationally' tolerant [6].

Secondly, the liver is home to clinically relevant pathogens, including the sporozoite life-cycle stage of the malarial parasite, the world's most deadly human pathogen, accounting for up to 1.24 million deaths annually [7]. *Plasmodium* spp. utilise immune avoidance mechanisms in order to infect hepatocytes and achieve persistence. After being injected into the skin by an infected mosquito, sporozoites migrate quickly in the circulation to the liver sinusoids to avoid phagocytic clearance, where they target Kupffer cells or endothelial cells in order to cross the sinusoidal barrier and gain access to the hepatocytes [8—11]. Sporozoites then remain undetected by pattern recognition receptors (PRRs) in non-acidified parasitophorous vacuoles where they replicate and develop into merozoites, before entering erythrocytes [10,12].

Chronic hepatitis B (HBV) and hepatitis C (HCV) affect approximately 350 million and 170 million people, respectively [13]. HCV and HBV proteins modulate the host innate immune response by, for example, limiting recognition by toll-like receptors (TLRs) [14,15] and dampening anti-viral type-1 interferon (IFN) signalling [16—21]. The HCV virus core protein also directly impairs CD4 and CD8 T cell function [22]. HCV and HBV elude humoral and cellular immunity by continually selecting escape variants [23,24], and HCV can also evade the neutralising antibody response by direct cell—cell 'crawling' [25].

These, and other, examples of hepatotropic pathogen immune avoidance should be considered in the context of host-intrinsic mechanisms that also contribute to the subversion of immunity and the establishment of persistence within the liver (reviewed in [13]). Host-intrinsic mechanisms are best explained by taking into consideration the vasculature of the liver, which supports a unique population of innate immune system cells, specialised in maintaining tolerance despite continuous exposure to gut-derived antigens.

## Vasculature of the liver

The liver receives blood from two sources: the hepatic artery and the portal vein, both of which enter via the porta hepatis before branching to perfuse each liver lobe. By far, the main contributor is the portal vein, accounting for approximately 80% of hepatic blood supply. Terminal branches of each vessel distribute blood to the hepatic sinusoids; these low-pressure, slow-flowing channels supply blood to the repetitive functional units of the liver, the hepatocytes, enabling them to perform their metabolic functions and to degrade toxic blood constituents. The hepatic sinusoids are lined with liver sinusoidal endothelial cells (LSECS), which facilitate the passage of blood plasma into the space of Dissé by virtue of their fenestrae or 'sieve plates' and lack of continuous basement membrane [26]. The space of Dissé promotes the exchange of molecules between the blood and hepatocytes while providing a passage for plasma to feed into the lymphatic vessels.

Because the liver is constantly exposed to blood-borne pathogens and the toxic/antigenic products of digestion, it is home to several populations of specialised antigen presenting cells (APCs), including the aforementioned LSECs as well as Kupffer cells and dendritic cells (DCs). These populations provide a critical first line of defence against pathogen invasion and also help clear the blood of unwanted antigenic/toxic material by endocytosis. However, the predominantly innocuous food-derived material contained within the blood necessitates the induction of immunological unresponsiveness, or tolerance. Under steady-state conditions, liver APCs limit the induction of an adaptive immune response, preventing effector cell proliferation and skewing differentiation to favour the generation of regulatory cell subsets [27] (Fig. 1).

## Liver sinusoidal endothelial cells

LSECs line the hepatic sinusoids, sampling their contents for processing and presentation to CD8 and CD4 effector T cells in the context of class I or class II major histocompatibility (MHC) molecules, respectively. Like professional APCs, LSECs can present exogenous antigen via MHC class I to CD8 T cells, a process known as cross-presentation [28,29]. The interaction between LSECs and CD8 T cells results in lower expression of the co-stimulatory molecules, CD80 and CD86, and increased expression of the co-inhibitory molecule programmed death ligand-1 (PDL-1) by LSECs. CD8 T cell expression of programmed death-1 (PD-1) also increases as a result of this interaction, therefore enabling co-inhibition to exceed co-stimulation [30]. The induction of CD8 T cell tolerance by LSECs requires low concentrations of antigen, similar to those found in the liver in the absence of infection. At higher antigen concentrations, CD8 T cell IL2 production acts in an autocrine manner to override co-inhibition, allowing LSECs to induce CD8 T cell differentiation [29]. It is well known that the liver can impart its tolerogenic effect systemically; intraportal administration of donor antigens lengthens graft survival in the skin [31], kidney, heart [32] and intestine [33] transplantation settings. How the liver participates in the induction of systemic immune tolerance is not fully understood, however, in one study, the presentation of soluble antigen by LSECs in vivo led to systemic antigen-specific immune tolerance [34,35]. The predominant mechanisms by which this was achieved were proposed to be clonal deletion and the induction of anergy [34,35].

Naïve CD4 T cells primed by LSECs produce the anti-inflammatory cytokines IL10 and IL4 [36]. LSECs also suppress the expansion of IFN$\gamma$-producing Th1 cells [37]. Moreover, in an MHC class II chimeric mouse model, in which professional APCs were devoid of MHC class II expression, CD4 T cells primed by LSECs lacked pro-inflammatory cytokine production, had in vitro regulatory ability and were

Please cite this article in press as: Grant CR, Liberal R. Liver immunology: How to reconcile tolerance with autoimmunity. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.06.003