Review

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Immune outcomes in the liver: Is CD8 T cell fate determined by the environment?

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Summary

The liver is known for its tolerogenic properties. This unique characteristic is associated with persistent infection of the liver by the hepatitis B and C viruses. Improper activation of cellular adaptive immune responses within the liver and immune exhaustion over time both contribute to ineffective cytotoxic T cell responses to liver-expressed antigens in animal models, and likely play a role in incomplete clearance of chronic hepatitis virus infections in humans. However, under some conditions, functional immune responses can be elicited against hepatic antigens, resulting in control of hepatotropic infections. In order to develop improved therapeutics in immune-mediated chronic liver diseases, including viral hepatitis, it is essential to understand how intrahepatic immunity is regulated. This review focuses on CD8 T cell immunity directed towards foreign antigens expressed in the liver, and explores how the liver environment dictates the outcome of intrahepatic CD8 T cell responses. Potential strategies to rescue unresponsive CD8 T cells in the liver are also discussed.

Keywords: Cytotoxic T cells; Tolerance; Immunity; Viral hepatitis; Antigen load; CD8 T cell exhaustion; CD4 T cell help.

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Abbreviations: APCs, antigen-presenting cells; CTLs, cytotoxic CD8 T cells; DCs, dendritic cells; HBV, hepatitis B virus; HCV, hepatitis C virus; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LCMV, lymphocytic choriomeningitis virus; LNs, lymph nodes; LSECs, liver sinusoidal endothelial cells; MHC-I, major histocompatibility complex class I; PD-1, programmed death 1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; rAAV, recombinant adeno-associated virus; TCR, T cell receptor; TLR, toll-like receptor.

Introduction

The liver is the target organ of the hepatitis B and C viruses (HBV, HCV), which are associated with the development of chronic liver disease. It is estimated that over 500 million people worldwide are persistently infected with HBV or HCV, representing a major global health problem of considerable human and financial costs. However, HBV and HCV infections are not always persistent: more than 90% of HBV infection in adults and 20% of HCV infections result in viral control or clearance. The reasons why the same viruses persist in some individuals but are cleared in others, and why other hepatotropic viruses, such as hepatitis A, are more effectively eliminated remain unclear. It is likely that these two divergent outcomes are related to the paradoxical immunological properties of the liver itself.

Although effective immune response can be elicited within the liver, under some circumstances the liver induces a state of immune unresponsiveness known as tolerance. This phenomenon underpins the spontaneous acceptance of allogeneic liver transplants observed in several animal models (reviewed in [1]). Injection of antigens via the portal route resulting in direct delivery to the liver [2], and targeting gene expression to the liver [3], both often lead to tolerance. While this intriguing tolerogenic property of the liver has long been known, the mechanisms underlying this phenomenon are not yet completely understood. It is tempting to speculate that some pathogens exploit this tolerogenic property to persist within the liver.

The hallmark of an efficient immune response is the generation of effector cells that eliminate infected cells and/or secrete cytokines that suppress pathogen replication or recruit other arms of the immune response to promote pathogen clearance. CD8 T cells are critical for pathogen clearance, as after activation, they acquire the ability to kill infected cells and secrete cytokines which have direct anti-microbial properties (reviewed in [4]). In the liver, functional cytotoxic CD8 T cells (CTLs) are essential for the resolution of acute HBV [5] and HCV [6] infections. Consistent with this, virus-specific CD8 T cells isolated from patients chronically infected with HBV or HCV have impaired function. This failure to generate a productive anti-viral response results in persistent viral replication that promotes chronic liver disease [7–10]. Therefore, the induction of a functional CD8 T cell

response against hepatic antigens is associated with better clinical outcomes. In this review, we first discuss the mechanism of T cell activation and the signals required for generating an optimal CD8 T cell response, then the factors that might lead to loss of CD8 T cell responses to liver-expressed antigen and thus promote chronic hepatotropic infections.

Key points

- Some individuals develop persistent HBV or HCV infection, while others clear these viruses. The mechanisms underlying these divergent outcomes remain unclear.
- Intrahepatic CD8 T cell activation generally results in tolerance. This outcome occurs in the presence of a high intrahepatic antigen load, and in the absence of inflammatory signals within the liver.
- CD8 T cells specific for liver-expressed antigen that have undergone initial effective activation in secondary lymphoid organs become functionally impaired by continuous exposure to high antigen load within the liver, leading to T cell exhaustion. As a result, antigen-expressing liver cells cannot be cleared.
- Unresponsive CD8 T cells can potentially be revived by blocking signals involved in T cell exhaustion. External stimulants, such as help from CD4 T cells, may also promote CD8 T cell functionality. These strategies represent potential therapeutic interventions for immune-mediated chronic liver diseases.

The multiple signals required for effective CD8 T cell priming

CD8 T cells recognize, via their T cell receptor (TCR), short peptides presented on major histocompatibility complex class I molecules (MHC-I) displayed on the surface of antigen-presenting cells (APCs) (Fig. 1A) [11,12]. Although MHC-I is expressed on most cell types, it is generally accepted that naïve CD8 T cells are activated by professional APCs, mostly dendritic cells (DCs), in secondary lymphoid organs, including the spleen and lymph nodes (LNs). MHC-I molecules expressed by DCs can associate with peptides derived from either antigens synthesized endogenously within infected cells (e.g. viral proteins), or from exogenous antigens captured by the APCs. These two pathways for MHC-I presentation are called direct and cross presentation respectively (Fig. 1B and C; reviewed in [13]). Direct presentation occurs in most cell types. In contrast, cross presentation is largely restricted to some DC subsets [14] and is particularly essential for eliciting CD8 T cell responses against pathogens that do not infect DCs.

During an infection, naïve CD8 T cells are recruited to lymphoid tissues, undergo activation, proliferate, and acquire cytolytic effector function. This productive CD8 T cell activation leading to effector function is known as "priming".

CD8 T cell priming requires at least three separate yet integrated signals (Fig. 1A). Signal 1 is provided by the binding of the TCR to the MHC-I/peptide complex (reviewed in [15]). The strength of this interaction, or TCR affinity, determines the

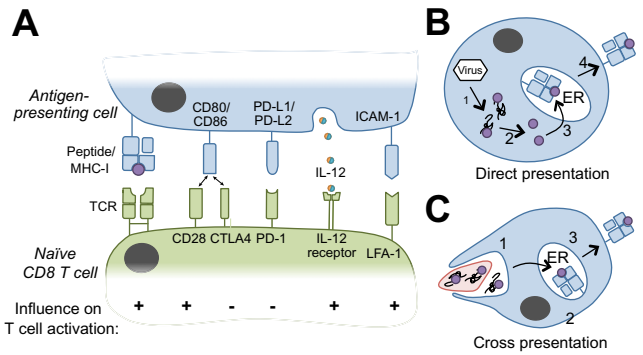

Fig. 1. Signals for inducing a functional CD8 T cell response. (A) Naïve CD8 T cells receive various signals from APCs during primary T cell activation. The first essential signal for activation is from the interaction between the TCR on T cells and the peptide/MHC-I complex expressed on APCs. The second essential signal is generated from ligation of co-stimulatory receptors (e.g. CD28) on T cells to their ligands e.g. CD80/CD86) displayed on APCs. Other signals may also influence the outcome of T cell activation. These include interactions between co-inhibitory molecules expressed by T cells with their ligands expressed by APCs (e.g. interaction between PD-1/PD-L1 and/or between CTLA4 and CD80/CD86), which suppress T cell priming. In contrast, the release of pro-inflammatory cytokines, such as IL-12, by APCs enhances T cell activation. Adhesion molecules (e.g. ICAM-1) on APCs also promote interaction between T cells and APCs, enhancing TCR signal transduction. (B and C) Direct and cross presentation to generate peptides for antigen presentation on MHC-I. (B) In direct presentation, antigens are expressed endogenously within the APCs (1). Antigens are processed into short peptides (2) which are complexed with MHC-I inside the endoplasmic reticulum (ER) (3). The peptide/MHC-I complexes are transported to the cell surface for antigen presentation to CD8 T cells (4). (C) During cross presentation, antigens are acquired exogenously, from either antigen-carrying donor cells or the extracellular space (1). These captured antigens are processed and bind to MHC-I (2) for antigen presentation (3).

intensity of signal 1 and the quality of CD8 T cell immunity induced [16,17]. Signal 2 is required to sustain signal 1 and is typically provided by a range of co-stimulatory molecules (reviewed in [18]). CD80 and CD86 are generally induced on DCs during infection or inflammation [19] and bind to CD28 expressed by T cells. To modulate the signal provided by the TCR and co-stimulatory molecules, APCs also express co-inhibitory molecules able to downregulate T cell activation (reviewed in [20]). For instance, the binding of the T cell co-inhibitory receptor programmed death 1 (PD-1) to its ligands, programmed death ligand-1 (PD-L1) or -2 (PD-L2), inhibits T cell activation [21–23]. Likewise, cytotoxic T lymphocyte antigen 4 (CTLA-4) is another receptor for CD80 and CD86, that in contrast to CD28, acts as a negative regulator of the T cell signaling pathway (reviewed in [24]). To sustain productive priming, extra signals are required. Inflammatory cytokines, such as interleukin (IL)-12 and type I interferon, provide an additional stimulation to CD8 T cells (also known as signal 3) that promotes their proliferation, survival and effector function [25–28].

The outcome of T cell priming thus results from the integrated signal provided by TCR, co-stimulatory and co-inhibitory molecules, as well as inflammatory cytokines.

Sustained interactions between CD8 T cells and APCs also require adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) [29]. In addition to consolidating T cell/DC association, the binding of ICAM-1 to LFA-1 expressed by T cell also provides additional stimulatory signals [30]. Furthermore, conventional CD4 T cells can provide help to elicit optimal CD8 T cell responses via activation of antigen-presenting DCs to