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Intrahepatic regulation of antiviral T cell responses at initial stages of viral infection

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Abstract

It is generally accepted that the appropriate boost of early immune response will control viral replications and limit the immune-mediated pathology in viral hepatitis. However, poor immunity results in viral persistence, chronic inflammation and finally liver cirrhosis and carcinoma. As a peripheral non-lymphoid organ of immune surveillance, the liver continually encounters hundreds of molecules from the blood, including nutrients, toxins and pathogens. In this way, the liver maintains immune tolerance under healthy conditions, but responds quickly to the hepatotropic pathogens during the early stages of an infection. Although our knowledge of liver cell compositions and functions has been improved significantly in recent years, the intrahepatic immune regulation of antiviral T cells at the initial stage is complex and not well elucidated. Here, we summarize the role of liver cell subpopulations in regulating antiviral T cell response at the initial stages of viral infection. A better understanding of early hepatic immune regulation will pave the way for the development of novel therapies and vaccine design for human viral hepatitis.

Keywords

antiviral T cells; liver; viral hepatitis; immune regulation

Introduction

The liver is one of the first defense lines against pathogens in the external environment. This organ is continually exposed to various gut-derived molecules coming from the portal vein blood [1]. Although spleen and other lymphoid organs play an important role in host systemic immunity, the liver is necessary for resident T cell responses and is responsible for clearing hepatotropic pathogens such as hepatitis A, B and C viruses [2]. The antiviral T cell responses in the initial stages are critical for early viral control and disease outcomes. Insufficient responses result in viral persistence and chronic inflammation, while excessive

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cytotoxic T lymphocyte (CTL) responses cause immunopathogenesis. Therefore, it is necessary to elucidate the local T cell regulation in the liver to better understand how the liver orchestrates immune responses during viral infection [2].

Besides the metabolic roles in a healthy individual, hepatocytes can regulate T cell immunity by surface co-stimulatory molecules (e.g. CD80 and CD86) and cytokine/chemokine production (e.g. CXCL10 and IL-7) [3–5]. The liver resident cells, including liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), and hepatic stellate cells (HSCs) can function as antigen-presenting cells (APCs) to prime naïve T cells, although the effect is not potent as that of liver CD103⁺ dendritic cells (DCs) [6, 7]. Other liver resident and infiltrated lymphocytes, including natural killer (NK) cells, NKT cells, $\gamma\delta$ T cells and innate lymphoid cells (ILCs) can control viral replication and regulate T cell functions through producing cytokines and granules, such as IFN- γ , IL-17, granzyme B and perforin [8–11].

The characteristics of liver immune tolerance mediated by liver cells have been described in recent years. HSCs and KCs can express anti-inflammatory cytokines, such as IL-10 and TGF β , to inhibit T cell activation and proliferation [12–14]. The co-inhibitory molecules PD-L1 have been detected in several liver cell populations, including hepatocytes, HSCs, KCs and LSECs, contributing to the inhibition of effector T cell functions and T cell exhaustion [15–18]. HSCs and KCs are also reported to support Treg cell differentiation and cytokine production, leading to impaired liver T cell responses [19, 20]. Therefore, the liver is a double-edged sword and orchestrates the immunogenic response and immune tolerance during viral hepatitis.

In this review, we summarize the major functions of liver cells and their role in regulating intrahepatic T cell responses in viral hepatitis (Table 1). A better understanding of the mechanisms of antiviral T cell regulation in liver microenvironment may aid in developing more detail studies involving future therapeutic candidates and vaccine design for human subjects with viral hepatitis.

Hepatocytes

Hepatocytes have been implicated in the initiation of adaptive T cells responses through secreting cytokines/chemokines, presenting viral antigens, and modulating surface regulatory receptors. Early hepatitis C virus (HCV) infection induces human hepatocytes-derived CXCL10 to attract macrophages and lymphocytes into liver parenchyma [4, 5]. Cultured hepatoma cells sense HCV infection via TLR3 and produce CCL5 for effector T cell recruitment to the portal tracts [4, 21]. Hepatocytes, but not the immune cells are the major source of IL-7 [22], which is critical for immune cell survival, differentiation, effector cytokine production and cytotoxic activity [23, 24]. Hepatocytes also contribute to antiviral immunity by expressing innate immune cytokines, including type I and III interferons (IFNs) during HCV infection [25, 26]. In acute lymphocytic choriomeningitis virus (LCMV) infection, type I interferon (IFN-I) protects antiviral T cells by directly inhibiting regulatory T cell differentiation and NK cell cytotoxicity [27]. IFN-lambda-1 consistently suppresses IL-13 production, but elevates IFN- γ secretion in cultured human CD4 T cells [28]. These

findings indicate that hepatocyte-derived cytokines facilitate antiviral T cell responses in viral hepatitis.

Hepatocytes can be induced to express MHCII and present antigen to naïve CD4 T cells [29]. MHC II-expressing hepatocytes induced Th2 differentiation in viral infection, resulting in impaired IFN- γ production by virus-specific T cells, and prolonged viral persistence [30]. Additionally, although hepatocytes contact with and prime liver-resident and circulating naïve CD8 T cells [31], the ability of the antigen presentation by hepatocytes is not efficient [32]. Notably, hepatocytes are also capable of expressing B7 family co-stimulatory and co-inhibitory ligands. Expression of CD86/B7.2 on hepatocytes results in increased activation and cytokine production of CD4 T cells in HCV-transgenic mice [3]. B7-H1, named as Programmed death-ligand 1 (PD-L1), is also expressed on hepatocytes and involved in the inhibition of effector CD8 T cell activation and proliferation [16]. It is reported that IFN-I-induced IL-7 from hepatocytes downregulates PD-1 levels on CD8 T cells to allow optimal antiviral T cell responses [22], indicating the crucial role of IFN-I/IL-7/PD-1 axis in hepatocyte-mediated T cell regulation.

Hepatic stellate cells

HSCs are liver-resident antigen-presenting cells for activating NKT cell, CD4 and CD8 T cell responses both in vitro and in vivo [33]. There are several TLRs expressed on HSCs, including TLR2, TLR3, TLR4, TLR7 and TLR9 [34]. Quiescent HSCs express TLR3 and respond to viral nucleic acids, such as Poly I:C [35]. HSCs promote fibrotic gene expression in response to HCV core protein through TLR2 [36]. These findings suggest that HSCs may recognize the virus and be activated via TLR signaling pathway, with subsequent regulation of liver-resident T cell responses.

There is accumulating evidence that HSCs are an immunotolerance cell type and inhibit T cell responses in the liver through several ways. First, HSCs can secrete anti-inflammatory cytokine IL-10 and may inhibit effector T cell activation [12, 37]. In addition, TGF- β 1⁺ HSCs suppress T cells via a cell surface-bound latent TGF- β 1/Glycoprotein A repetitions predominant complex [14]. Secondly, activated HSCs express inhibitory B7 molecules, including B7-H1 and B7-H4. Human HSCs exhibit potent immunoregulatory activity via B7-H1-mediated induction of apoptosis in activated T cells [15]. Similarly, activated murine HSCs inhibit early LCMV-specific CD8 T cell activation through B7-H4 [38]. Moreover, HSCs veto naïve CD8 T cell activation by inhibiting IL-2R and IL-2 cytokine expression on T cells in a CD54- and cell contact-dependent way [39]. Finally, HSCs promote Treg cells and suppress Th17 differentiation [19]. Adoptive transfer of HSCs attenuates liver injury in ischemia reperfusion mouse model by enriching Treg cells in the liver [40].

The role of HSCs in regulating T cell responses is still controversial and not well understood. Most studies are performed by using the cell line or cultured HSCs in vitro. The primary HSCs of a 3 day-culture are professional APCs and have a strong ability to prime naïve T cells [33]. However, day 7-cultured HSCs significantly suppress T cell activation [38]. The different roles of HSCs may be attributed to their active status in culture. Freshly isolated HSCs gradually lose lipid drops, upregulate expression of smooth muscle actin and

differentiates into myofibroblast when cultured *in vitro*. It is assumed that the co-stimulatory and inhibitory molecules as well as cytokine production may be distinct in cultured HSCs during this activation process. Thus, further *in vivo* studies are needed to elucidate the detailed role of HSCs in the early stage of viral hepatitis.

Kupffer cells

KCs, the largest population of liver resident macrophages, are specialized to perform scavenger and phagocytic functions, and to release pro-inflammatory cytokines to evoke intrahepatic innate immune responses [41]. KCs can uptake the viral particles from circulation via scavenger and complement receptors, which may limit infection, but also lead to the rapid apoptosis [42, 43]. The ability to capture viral particles by KCs is important for controlling viral dissemination, since KC depletion leads to excessive CTL responses and severe liver injury [44]. In contrast to DCs, naïve KCs express significantly low levels of MHCII and co-stimulatory molecules [45]. However, KCs can cross-present antigens and promote CD8 T cell proliferation, although the primed CD8 T cells exhibit low activated phenotypes as evidenced by low level of surface CD44 and intracellular IFN- γ [46]. In addition, KCs in Poly (I:C)- treated mice express higher level of MHCII and prime stronger T cell responses than naïve KCs [45]. These findings demonstrated that KCs act as incompetent APCs in viral infection. Interestingly, KCs are necessary for antiviral CD8 T cell-triggered influenza-associated hepatitis, since KCs play a critical role in formation of hepatic foci [47].

In contrast to their incompetent APC function, KCs maintain tolerance in the liver [45]. KCs can be activated by viral antigens via TLR2, resulting in increased IL-10 production [13, 48]. Elevated IL-10 in the liver suppresses the antiviral T cell activation and induce T cell exhaustion [13, 20, 49]. Importantly, KCs contribute to liver Treg cell-derived IL-10 production [20], and HBV particles also induce TGF- β production by KCs and probably promote Treg cell differentiation [50]. Beside IL-10 and TGF- β -mediated liver immune tolerance, activated KCs inhibit liver T cell responses through upregulation of co-inhibitory molecules [18]. By delivering the lipidoid nanoparticles carrying PD-L1 siRNA to KCs in vivo, Dolina et al. demonstrated that silence of PD-L1 in KCs during Ad and murine cytomegalovirus (MCMV) infection resulted in enhanced hepatic CD8 T cell accumulation, effector cytokine production, and viral clearance [18]. It is also reported that PD-1 expression is associated with CD8 T cell exhaustion in acute HCV infection [51]. Coincidentally, HCV core protein triggers TLR2 pathway and upregulates PD-L1 expression on KCs [48], possibly contributing to the inhibition of T cell responses via PD-1/PD-L1 pathway. In addition, KCs promote Treg cell expansion and impair antiviral T cell responses by galectin-9 (Gal-9) and T cell immunoglobulin- and mucin-domain-containing molecule (Tim-3) signaling pathway [52, 53]. In a previous study, we reported that intrahepatic CD8 T cells have a high level of PD-1⁺Tim-3⁺ subsets in viral hepatitis [54], meaning to us that KCs may suppress T cell responses and maintain liver tolerance through Gal-9/Tim-3 pathway in the initial stage of viral infection.

Liver sinusoidal endothelial cells

LSECs contain fenestrations (pores in the hepatic sinusoid endothelium), which facilitate the transfer of molecules between blood and liver as well as contact of lymphocytes and hepatocytes [55]. Unlike DCs, LSECs express low level of MHCII and CD86, and are insufficient to activate naïve T cells [56]. However, LSECs can cross-present antigens released from Ad-infected hepatocytes and promote TNF- α production by effector CTLs, resulting in the clearance of infected hepatocytes [57]. Interestingly, by using HSC-restricted MHC-I mice, Katrin et al. revealed that HSCs transfer MHCI molecules to LSECs and support *in vivo* LSEC cross-presentation after hepatotropic viral infection [58]. Therefore, although LSECs are the weak APCs, they can promote CTL response through the way of cross-presentation in viral infection.

In addition to the cross-presentation function, LSECs induce liver tolerance by several ways. First, LSECs tune down the intrahepatic effector CTL responses via liver sinusoidal endothelial cell lectin (LSEctin), which is a member of C-type lectin receptor family [59]. LSEctin upregulation in the liver causes the inhibition of the antiviral activity of CTLs and delayed viral clearance [59]. Secondly, LSECs suppress DCs, making them incapable of priming CD8 T cells. Interaction of LSECs and DCs results in reduced co-stimulatory functions and DC-derived IL-12 production [60]. Additionally, although LSECs are capable of initiating T cell immunity, interaction with naïve CD8⁺ T cells leads to decreased expression of CD80 and CD86, but increased PD-L1 on LSECs, indicating that LSECs induce liver tolerance via PD-1/PD-L1 signaling pathway [17, 61]. Interestingly, LSECs cross-presentation at low antigen concentrations results in tolerance, while they promote effector T cell differentiation at high antigen concentrations [61]. Accordingly, we have the hypothesis that LSECs promote antiviral T cells in the initial stage of viral infection when the concentration of viral antigen is relative high. However, during the contracted stage of viral hepatitis when the concentration of viral antigen declines, LSECs suppress antiviral immunity and protect against the immune-mediated liver damage.

Dendritic cells

Naïve liver DC subsets are poor stimulators, express few co-stimulatory molecules necessary for T cell activation and keep the hepatic immune homeostasis [62]. However, liver DCs become immunogenic in response to hepatotropic viral infection and act as APCs to support CD8 T cell responses in the liver [7]. Liver-resident CD103⁺ DCs are potent APCs and strongly prime antiviral CD8 T cells *in situ* [7]. In addition, DC-derived IL-23 increases HBsAg-stimulated differentiation of naïve CD4 T cells into Th17 cells and exacerbates liver inflammation [63]. Myeloid DCs expressing CD80, CD83 and CD40, are enriched in the liver and capable of producing IFN- α and IL-12 in human viral hepatitis [64]. These findings suggest that liver DCs can function as APCs upon the stimulation of pathogens. Interestingly, DCs with high level of lipid are immunogenic and incapable of activating adaptive T cells, while DC with low level of lipid induce regulatory T cells and maintain hepatic tolerance [65]. Additionally, Human liver DCs show a BDCA-1⁺ phenotype and produce substantial amounts of IL-10, resulting in more generation of Treg cells and hepatic tolerance [66]. The pDCs, a unique subtype of liver DCs, are weak to stimulate T cell

activation; however, they can sense HCV-infected cells and rapidly produce large amount of IFN-I to inhibit viral infection [67, 68]. In addition, the pDC-derived IFN- α is important for the activation of NK cells, NKT cells and antigen-specific CD8 T cells [69].

NKT cells

NKT cells can be activated in both antigen-dependent and independent manners and promptly secrete both type 1 and type 2 cytokines such as IFN- γ and IL-4, allowing them to have functional plasticity of both pro-inflammatory and immune regulatory characteristics [70]. Baron et al. reported that non-classical NKT cells that are CD1d restricted but nonreactive to α -Galactosylceramide (α -GalCer), are activated in response to hepatocytes expressing hepatitis B viral antigens in acute HBV infection, leading to liver inflammation and injury [71]. Further study shows that blockade of an NKG2D–ligand interaction prevents the HBV- and CD1d-dependent, non-classical NKT cell-mediated acute hepatitis [72]. In another study, activation of classical NKT cells by α -GalCer upregulates IFN- γ /IFN- α/β levels in the liver of HBV-transgenic mice and inhibits HBV replication [73].

The role of NKT cells in regulating adaptive T cell responses is not clear. It is reported that acute HBV patients have more NKT cells and increased IFN- γ -producing T cells compared with healthy patients [74]. However, other studies reported that NKT cell numbers are negatively correlated with the frequency of HBcAg-specific CTLs in acute HBV patients [75]. Immunization of both HBsAg and α -GalCer induces Valpha14⁺ NKT cell activation, resulting in strong CTL responses and severe liver injury [76]. Moreover, this NKT cell-mediated CTL activation is dependent on IL-2 and CD40-CD40L interaction [76], suggesting that NKT cells may have the potential to promote antiviral T cell responses in the liver.

Notably, NKT cells regulate CTL responses differently according to the organs and invading pathogens. Zeissig S et al. infected mice with HBV-expressing adenoviral particles and found NKT cell activation and IFN- γ secretion in the liver, but not in the spleen as early as 1 day after infection [10]. Hepatic T cells in wild-type (WT) mice exhibit strong activation phenotypes in response to infection with Ad-HBV; however, CD1d-deficient mice have impaired T cell responses and delayed viral clearance [10]. In contrast, Diana et al. demonstrated that splenic invariant NKT (iNKT) cells rapidly increase IFN- γ production in LCMV infection. Elevated IFN- γ subsequently promotes IL-12 secretion by conventional DC, resulting in strong antiviral CD8 T cells [77]. However, they found that liver iNKT cells promotes IFN-I from pDC in OX40L-OX40 dependent pathway and controlled viral infection, resulting in mild CTL responses and low liver damage [77]. Thus, further studies are needed to understand the tissue-specific role of NKT cells in innate and adaptive immune responses.

NK cells

NK cells are the key cell population in early viral infection due to their role as the first defensive line via rapid secretion of large amounts of antiviral factors such as IFN- γ and

granules [11]. In healthy liver, NK cells have decreased cytotoxic activity but increased local expression of the immunosuppressive cytokine, IL-10 to maintain tolerance in the liver [78]. However, once the host is infected by hepatotropic virus, activated NK cells produce abundant IFN- γ that is responsible for the inhibition of viral replication and optimal priming of virus-specific T cells [79]. Cytotoxic ability is strongly increased in activated NK cells and play an important role in killing of infected hepatocytes, but also causes liver damage [80]. Thus, NK cells are indispensable for innate immune system and viral clearance. However, NK cells have been recently reported to have an immunoregulatory role in viral infection and inhibit the adaptive T cell response by lysing virus-specific T cells [81]. Blockage of NK cells leads to a stronger antiviral T cell response and efficient viral clearance in various organs [81]. Additionally, lysis of CD4 T cells by NK cells results in the loss of support for CD8 T cells and causes T cell exhaustion and viral persistence [81]. Although NK cells also directly kill CD8 T cells via NK cell cytotoxic receptor NKG2D and impair the CD8 T cell immunity, it may reduce the liver injury and improve the survival during the lethal CTL action [82]. These new insights of NK cell function expand our view on the role of this key cell type and suggest that the activated NK cells should appear at the right time and right place to benefit the host during an infection; though their relative importance may vary from virus to virus.

Innate lymphoid cells

ILCs are a heterogeneous group of innate immune cells that lack antigen specific receptors, but can produce various cytokines [83]. Based on the cytokine production and transcription factors, ILCs are divided into three groups. Group 1 ILCs are composed of NK cells and ILC1, which produce IFN- γ and are under the control of the T-bet transcription factor. Group 2 ILCs are induced by IL-25 or IL-33, expressing type 2 cytokines IL-5 and IL-13. GATA3 and ROR α are key transcription factors for ILC2 differentiation. Group 3 ILCs are enigmatic, including IL-22-producing NKp46⁺ cells, IL-17A/IL-22-producing CD4⁺ lymphoid tissue inducer-like cells and IL-17/22/IFN- γ -producing NKp46⁻ cells. ILC3 are mainly controlled by ROR γ t and AhR transcriptional factors [84]. ILCs preferentially located at barrier surfaces, such as intestinal tract, lung and skin, but are also found in lymphoid organs such as spleen and mesenteric lymph node [84].

The role of ILCs in the liver is not well understood. IFN- γ -producing ILC1 are found in the liver and their precursors are Eomes⁻ NK cells [85]. It is reported that ILC1 population is elevated in chronic HBV patients and correlated with liver damage, suggesting the pro-inflammatory role of ILC1 in viral hepatitis [86]. Although the role of ILC1 in early viral hepatitis is not clear, the cytokine IFN- γ produced by ILC1 should be involved in the inhibition of viral replication and the initiation of early antiviral immune response. It is conceivable that ILC2 induction and activation will polarize to type 2 immune responses and suppress inflammatory cytokines, leading to tissue wound healing in hepatitis [87, 88]. These findings indicate that ILC2 may play an anti-inflammatory role in viral hepatitis. In the early stage of viral hepatitis, IL-33 is released from the necrotic hepatocytes and induces ILC2 in the liver [89]. IL-33 treatment induces ILC2 in the liver and protects liver by increasing T cell activation and reducing tissue damage [90]; however, little is known about ILC2 in chronic viral hepatitis. The identity and role of hepatic ILC3 are a challenge due to

the few numbers of this population in the liver. Besides, there is no useful method to expand ILC3 both in *vivo* and in *vitro*. We demonstrated that viral infection increases IL-17⁺ ILC3 population in the liver. These cells express high level of IL-7R and ROR γ t transcription factor, and secrete the pro-inflammatory cytokine IL-17A and IL-17F [9]. It is possible that liver ILC3 would also express the anti-inflammatory cytokine IL-22 and protect against liver injury. Further studies are still needed to elucidate the exact role of IL-22⁺ ILC3 in regulating antiviral T cell responses in acute and chronic viral hepatitis.

$\gamma\delta$ T cells

The liver is a rich source of $\gamma\delta$ T cells, which execute the function of immunosurveillance and immunoregulation [91]. $\gamma\delta$ T cells can produce several kinds of cytokines, control the replication of pathogens and prime the adaptive immune responses. In Ad-induced mouse hepatitis model, $\gamma\delta$ T cells-produced IFN- γ promotes chemokines CXCL9 and CXCL10 in hepatocytes and recruits CXCR3⁺ CD8 T cells into the liver, leading to increased liver inflammation and tissue damage [92]. Consistently, $\gamma\delta$ T cell deficiency is liver protective in Ad-induced liver damage [92]. We found that $\gamma\delta$ T cells are the early source of IL-17, which induces DC maturation and enhances the early adaptive T cell response in Ad infection [93]. Although $\gamma\delta$ T cells play a pathogenic role in viral hepatitis, the mechanisms are distinct due to the different strains of virus. In a mouse hepatitis virus (MHV) model, $\gamma\delta$ T cells contribute to liver immunopathological damage via the TNF- α dependent pathway, but not mediated by IL-17 or IFN- γ [94]. In addition, $\gamma\delta$ T cells can be educated by damage-associated molecular patterns (DAMP) molecules at the beginning of viral infection and contribute to the activation of APCs [95]. DAMP molecule IL-33 promotes hepatic IFN- γ -producing $\gamma\delta$ T cells, but inhibits IL-17⁺ ones in early LCMV infection [95], probably contributing to DC activation and the following antiviral T cell responses.

Conclusion

The liver is an immunological organ with unique properties of immune tolerance that facilitate the viral escape from specific antiviral immunity. The elegant antiviral T cell responses are critical for viral clearance, while limiting the immune-mediated pathology. In contrast, dysregulation of liver antiviral immunity, such as T cell exhaustion, results in viral persistence, and finally leads to liver cirrhosis and carcinoma. Therefore, the hepatic regulation of T cell responses in the initial stages of viral infection is the key event and determiner for disease progression. Liver cells preferentially play a dual role according to the hepatic immune microenvironment. On one hand, they function as liver resident APCs and are capable of priming naïve T cells in the early stage of viral infection. On the other hand, they induce liver tolerance and inhibit effector T cell responses in the contraction phase by co-inhibitory signals, anti-inflammatory cytokine production and immune-suppressive cell induction. In the past twenty years, the understanding of liver immunology has rapidly increased. Several key cell populations have been identified and their roles in local hepatic environment have been investigated; however, further studies are still needed to determine the unique role of these liver cells in regulating antiviral immunity during viral hepatitis.

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Abbreviations

Ad	adenovirus
APCs	antigen-presenting cells
CTL	cytotoxic T lymphocyte
DAMP	damage associated molecule pattern
DCs	dendritic cells
Gal-9	galectin-9
$\gamma\delta$ T	gamma delta T
HSCs	hepatic stellate cells
iNKT	invariant NKT
IFNs	interferons
IFN-I	type I interferon
ILCs	innate lymphoid cells
KCs	kupffer cells
LCMV	lymphocytic choriomeningitis virus
LSECs	liver sinusoidal endothelial cells
LSEctin	liver sinusoidal endothelial cell lectin
MHV	mouse hepatitis virus
NK	natural killer
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
Tim-3	T cell immunoglobulin- and mucin-domain-containing molecule
TLRs	toll-like receptors
Treg	regulatory T
WT	wild-type

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Highlights

Liver resident cells play both antigen-presenting functions and immune-inhibitory effects to orchestrate liver immune response to viral infection.

Liver kupffer cells are weak antigen presenting cells and induce CD8 T cell exhaustion through IL-10 and PD/1PD-L1 pathway.

Type 2 and 3 innate lymphoid cells play the different roles in regulating antiviral T cell response in the liver.

Table 1

Regulation of antiviral T cell response by liver cells

Cell types	Reagent & Models	Working mechanism	Action on antiviral T cells	Ref
Hepatocytes	HCV patients	secrete CXCL10	attract T lymphocytes into the liver of human HCV patients	4, 5
		activate NF- κ B signals via TLR3, secrete chemokines (e.g. CCL5)	recruit liver effector T cells	21
	HCV and CD86-transgenic mouse	co-stimulatory molecule CD86	activate liver CD4 T cells	3
	Lymphocytic choriomeningitis virus (LCMV)	secrete IL-7 and downregulate Socs3	increase effector T cell function	24
		secrete IFN-I	inhibit Treg cells, protect antiviral T cells against NK cell regulation	27
		surface MHCII expression	induce Th2 differentiation, inhibit virus-specific T cell function, impair viral clearance	30
	Adenovirus (Ad)	increase PD-L1 by infection and IFN, function on T cells via PD-1/PD-L1	inhibit T cell proliferation and IFN- γ production	16, 22
HSCs	Vaccinia virus expressing LCMV gp33 epitope	upregulate PD-L1 express, IL-2 restores the PD-L1-mediated inhibition	inhibit cytokine production from T cells, suppress T cell activation and proliferation inhibit the T cell recall response	38
KCs	LCMV	control viral replication in hepatocytes	KCs depletion increase CD8 T cell-mediated injury	44
	Influenza virus	probably influence cell sequestration or actively promote deletion	increase liver virus-specific CD8 T cell numbers	47
	HBV-carrier mouse	HBV core antigen and TLR2 interaction, increase IL-10 production	induce CD8 T cell exhaustion	13
	Ad-OVA and MCMV-OVA	silence of PD-L1 in KCs by PD-L1 short-interfering RNA encapsulated in lipidoid nanoparticles	increase intrahepatic CD8 T cell accumulation increase IFN- γ and Granzyme B production promote CD8 T cell proliferation facilitate CD8 T memory cells in late stage	18
LSECs	Adenovirus	cross-presentation of antigen released from adenovirus-infected hepatocytes	cross-prime effector CTLs to release TNF and kill virus-infected hepatocytes through caspase activation	59
		HSCs transfer MHC-I molecules to LSECs for cross-presentation	increase antiviral CTLs, exacerbate CTL-mediated hepatitis	58
		express LSECtin	inhibit intrahepatic effector CTLs, delay viral clearance	59
	Acute HBV infection	express LSECtin	reduce HBV-specific IFN- γ + cells, delay the viral clearance in blood and hepatocytes	59
DCs	Ad-OVA and MCMV-OVA	Liver resident CD103 ⁺ DCs as major APCs in response to hepatotropic viral infection	induce antigen-specific CD8 T cell response in situ	7
	HBV patients	IL-23 production by HBV surface and core antigen stimulation	indispensable for HBV surface Ag-stimulated Th17 differentiation in the liver	63
	Adenovirus	TLR-9 ligand-stimulated liver pDCs secrete high level of IFN- α	activate antigen-specific CD8 T cells	69

Cell types	Reagent & Models	Working mechanism	Action on antiviral T cells	Ref
NKT cells	Ad-HBV	ER-associated transfer of lipids onto CD1d leads to NKT cell activation	critical for liver T cell activation and IFN- γ production	10
	LCMV	induce IFN- α from pDC in an OX40L-OX40 dependent pathway	mild liver CTL response and limited liver injury	77
NK cells	LCMV	lysis of CD4 T cells, kill CD8 T cells via NKG2D	inhibit antiviral T cell response in various organs, improve survival in lethal CTL action	81, 82
	Adenovirus	NK cell-derived IFN- γ	required for optimal priming of CTL responses	80
ILC2	Adenovirus	Produce type 2 cytokines	inhibit TNF- α from T cells	90
ILC3	Adenovirus	Produce IL-17A and IL-17F	increase liver T cell response and injury	9
$\gamma\delta$ T cells	Adenovirus	Produce CXCL9 and CXCL10	recruit CXCR3 ⁺ CD8 T cells into the liver	92
		Produce IL-17A	enhance intrahepatic adaptive T cell response	93