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Review

Insights into Virus-Induced Immune Mediated Liver Pathology

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Key Words
Liver • Chronic viral infection • $CD8^+$ T cells • Liver pathology

Abstract
In the context of chronic viral infections, the hepatic microenvironment dictates the outcome of the disease by influencing propagation of virus and regulation of cytotoxic $CD8^+$ T cell response. Nevertheless, such regulation could be beneficial as it resolves the disease or could be detrimental as it causes liver pathological consequences. Liver pathology is a hallmark of chronic viral infection in both human and murine models. Such models show viral infection of hepatocytes and subsequent direct hepatic damage. Other compelling studies showed that liver injury was a consequence of overshooting $CD8^+$ T cells response in experimental mice, so-called immune-mediated liver pathology. This review highlights the viral-induced immune mediated aspects of liver pathology based on the lymphocytic choriomeningitis virus (LCMV) and Hepatitis virus settings.

Introduction

The liver is a unique solid organ in mammals with many endocrine, metabolic, and secretory functions [1, 2]. Under certain circumstances, the liver can be a paramount hub for T cell activation and is deemed as an immune synapse skewed toward tolerance [3]. The liver cell populations are dissected into two types of cells: parenchymal and non-parenchymal. Parenchymal cells comprise hepatocytes and represent 60–70 % of total liver cells, or 90 % of the total liver mass. The remaining non-parenchymal fraction is responsible for the tolerogenic properties of the liver and is diverse and encompasses cholangiocytes (epithelial cells lining the bile ducts), liver sinusoidal epithelial cells (LSEC), Kupffer cells and hepatic stellate cells (HSC), which is fat-storing cells also known as Ito cells, and intrahepatic immune cells [4-7].

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The liver harbors a wide range of innate and adaptive immune cells. Innate immune cells are scattered in the parenchyma and portal tracts and are composed of Kupffer cells and lymphocytes that constitute around 20% and 25% of the non-hepatocyte populations, respectively. Liver-resident lymphocytes include B cells, conventional T cells, unconventional T cells (NKT and TCR γδ T cells), NK cells, eosinophils, neutrophils, and resident hepatic DC as professional APC along with Kupffer cells [6, 8, 9].

Strategically located in the abdominal cavity and exposed to blood circulation, the liver is vulnerable to microbial and metabolic insults culminating in liver injury. In murine models, liver pathology could be mirrored by signs of illness such as; cachexia, ataxia, hunched posture, ruffled fur, and a moribund state. Furthermore, the liver might be diffused with necrotic spots, that appear as white or hemorrhagic areas [10]. Quantitatively, the liver dysfunction can be monitored by analyzing liver enzymes levels as functional readout of liver pathology such as; alanine aminotransferase (ALT), a liver enzyme indicating the site of liver damage [11, 12], aspartate aminotransferase (AST), which is less specific than ALT [13], lactate dehydrogenase (LDH), and glutamate dehydrogenase (GDH), a mitochondrial hepatic enzyme [13].

Infection with hepatotropic viruses can result in serious damage to hepatocytes [14]. Injury to liver tissue can be induced by the virus itself if the virus is cytolytic, causing direct harm to the hepatocytes and pathogen-driven liver injury. Immune activation within the liver can also damage the liver. The virus-induced hepatocyte damage is virus and species specific and therefore difficult to model in animal experiments. In contrast, some hepatocyte-toxic immune mechanisms are comparable between humans and mice. Therefore, the identification of virus-induced immunopathology in mice might be applicable in human virus-induced hepatitis.

The immune mediated liver pathology after virus infection could be limited or overt depending on many factors such as; genetic predisposition factors, the age of the host upon infection, the dose and route of infection [15]. Furthermore, the balance between the immunity and immunopathology is further determined by the levels of proinflammatory and anti-inflammatory factors [16]. The state in which the proinflammatory factors outpace the anti-inflammatory, viral clearance ,and tissue damage ensued [15].

In this review we discuss immune-mediated mechanisms, that were recently described in the context of liver pathology induced during LCMV and Hepatitis virus infections as well as the roles of different immune cells and intrinsic factors (Table 1 and Fig. 1).

Table 1. The cellular and soluble factors that provoke or curb the virus-induced immune mediated liver pathology

Immune function	Factors exacerbate immune-mediated liver pathology	Factors ameliorate immune-mediated liver pathology
Adaptive immune cells	• $CD8^+$ T cells • $CD4^+$ T cells	• B cells
$CD8^+$ T cell- intrinsic factors	• IRF4 • BATF • IL-10	• CEACAM1 • Perforin
Regulatory NK cells	• FcεRIγ	• Qa-1b • Progranulin • IL-10 • PD-L1
Innate immune cells	• Kupffer cells via inflammatory mediators	• Kuppfer cells via apoptotic cells uptake • CD169+ macrophages via PD-1 • Dendritic cell- derived IL-10
Liver specific factors	• Hypercholesterolemia • platelet-derived vasoactive serotonin	• FXR • IL-7 • IL-22 • IL-6

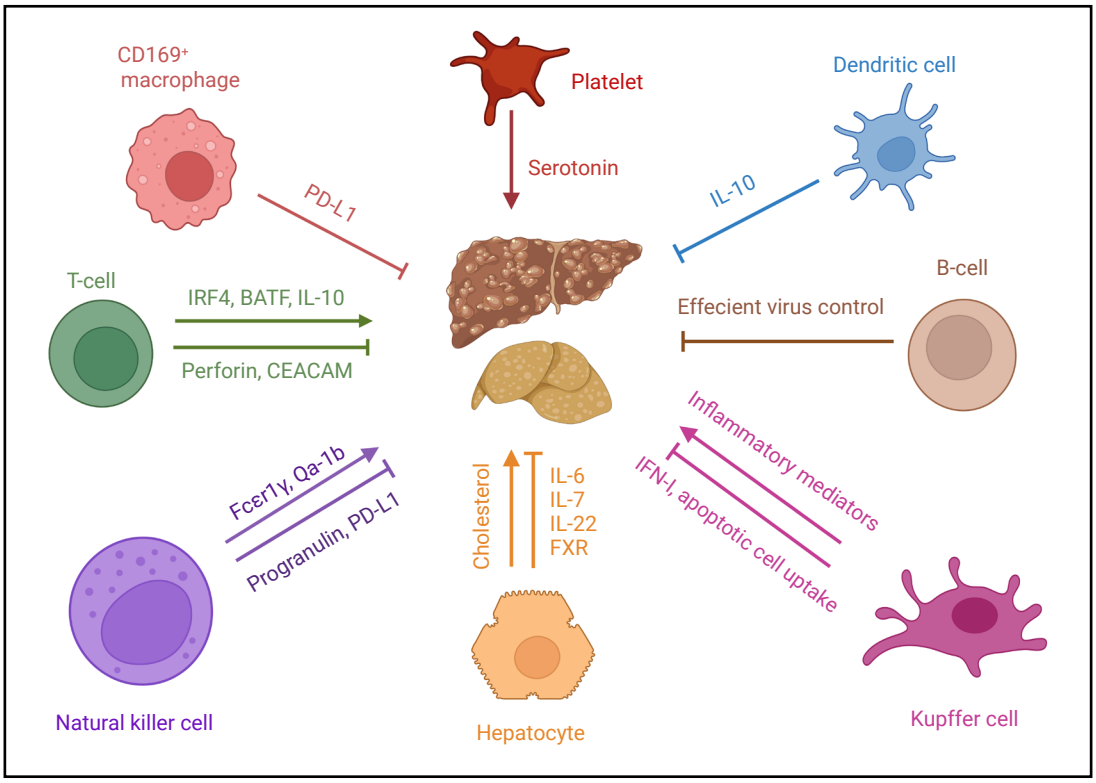

Fig. 1. The key factors modulating virus induced immune-mediated liver injury (→ = exacerbate liver injury; ⊣ = ameliorate liver injury). Created with BioRender.com.

Hepatitis virus and immune-mediated liver pathology

Hepatitis A virus (HAV), hepatitis B virus (HBV) or hepatitis C virus (HCV) are the leading causes of Viral hepatitis worldwide. Hepatitis virus infection culminates in liver injury, which is mirrored by increased serum levels of liver enzymes and fulminant liver damage. Recurrent liver injury contributes to cirrhosis and hepatocellular carcinoma. Acute HCV infection is often subclinical, whereas acute HAV or HBV infection tends to result in symptomatic hepatitis in adults. It is commonly believed that, liver damage is not directly caused by the hepatitis virus load but rather is mediated by immune cells and their products (immune-mediated) [17, 18].

The role of CD4⁺ T cells

$CD4^+$ T cells have remarkable role in potentiating liver injury during Hepatitis virus infections. One study conducted in adults chimpanzees after infection with hepatitis B virus (HBV), a noncytopathic DNA virus that causes acute and chronic hepatitis and hepatocellular carcinoma [19], showed that high and low HBV inoculum resulted in vigorous $CD4^+$ T cells response and accompanying liver immunopathology, and this detrimental effect of robust $CD4^+$ T cells is reversed upon $CD4^+$ T cell depletion before virus administration, resulting in precluded T-cell priming, persistent infection with minimal immunopathology [20].

In the context of chronic HBV infections in HBVTg mouse model, TH17-derived IL-22 activates IL-22R1-expressing Hepatic stellate cell (HSCs) and stimulates HSC to produce high levels of chemokines, such as CXCL10 and CCL20, which selectively provoke Th17 cell migration into the inflammatory liver. Subsequently, the increased intra-hepatic Th17 cell responses produce more IL-22 and simultaneously recruit more inflammatory cells into the liver. Thus, increased IL-22 worsens chronic liver inflammation and fibrosis by promoting Th17 cell recruitment *in vitro* and *in vivo* [21, 22].

T helper 1 (Th1) and cytotoxic T cell responses are known to contribute to immunopathology in certain infections, including the progression to cirrhosis in a proportion of cases of chronic HCV infections [23]. Hepatitis C virus (HCV)-specific Th17, liver injury-provoking immune cells, can be induced *in vitro* and regulated by transforming growth factor-β [24]. Similarly, HCV stimulates nuclear factor kappa B- dependent production of thymic stromal lymphopoietin (TSLP). TSLP released by HCV-Infected cells activates DCs and produce factors crucial for Th17 differentiation [25].

During acute HAV infection, the immune-mediated host injury can be modulated by FOXP3+ T regulatory (Treg) cells. The suppressive activity and the number of Treg cells subsets and are inversely correlated with the degree of liver injury. Further, reduced inhibitory activity of the Treg cell population results in severe liver injury during acute HAV infection. Mechanistically, the reduction of Treg numbers during acute HAV infection is due to FAS-mediated apoptosis [26].

Moreover, the suppressive function of Treg cells can be directly inhibited by the binding of HAV particles to Treg cells through the immunoregulatory receptor TIM1 [27]. Moreover, $CD4^+$ T cell responses seem to have a key role in resolving HAV, whereas the role of $CD8^+$ T cells is debating. In addition to $CD8^+$ T cells, which contribute to both virus clearance and liver injury during hepatitis virus infection, $CD4^+$ T cells have a substantial role in liver injury.

The role of $CD8^+$ T cells

In addition to $CD4^+$ T cells, $CD8^+$ T cells have a substantial role in liver injury. Virus-specific $CD8^+$ T cells can contribute to both virus control and liver injury in hepatitis virus infection [18].

In humans infected with HBV, studying the pathogenesis of HBV was restricted to circulating compartments rather than intrahepatic environments. This obstacle was resolved by establishing transgenic mouse model of HBV infection in which HBV-encoded antigens are expressed at the hepatocyte surface in a form recognizable by major histocompatibility complex (MHC) class I-restricted, in which liver damage occurs after transfer of virus-specific $CD8^+$ T cells [28].

The adoptive transfer of HBV-specific $CD8^+$ T cells into liver-specific HBV-transgenic mice causes acute necrotic liver injury, which mimic acute viral hepatitis in humans [17, 29]. In this model, HBV-specific $CD8^+$ T cells directly induce the apoptosis of proximal hepatocytes. Liver injury is exaggerated by antigen-nonspecific mononuclear cells, which are recruited to the liver by the HBV-specific $CD8^+$ T cells via the production of CXCL9 and CXCL10 [29].

Furthermore, during the acute phase of Hepatitis C virus (HCV), the liver damage was associated with $CD8^+$ T cells infiltration [30]. As aforementioned, T cells have a paramount role in mediating liver damage as demonstrated by increase in serum ALT levels during acute HAV, HBV and HCV infections. For example, in chimpanzees infected with HCV, upsurge the delayed HCV-specific $CD8^+$ T cells and their recruitment to the hepatic tissue coincide with elevated serum ALT levels, as well as virus clearance [31]. In contrast to the cytotoxic activity of $CD8^+$ T cells, IFNγ, a non-cytolytic antiviral cytokine, is induced by $CD8^+$ T cells cells and can eliminate viruses without severe injury to the liver [17].

The role of Kupffer cells

It is well documented that, Kupffer cells are key contributors in liver injury in the settings of hepatitis B virus (HBV) or hepatitis C virus (HCV) pathogenesis [32, 33] by either promoting the intrahepatic accumulation of pathogenic T cells and/or production of inflammatory mediators that are directly toxic for the hepatocyte [34-36].

Dissimilarly, another study showed that, the Kupffer cells hamper the severity of $CD8^+$ T cells mediated liver injury in HBV replication-competent transgenic mice by removing apoptotic hepatocytes that are killed by effector $CD8^+$ T cells in a scavenger receptor-dependent manner. Kupffer cell depletion exacerbates liver immunopathology in models of acute viral hepatitis. Failure to remove the apoptotic hepatocytes results in making them necrotic and release high-mobility group box 1 (HMGB-1) protein, inducing neutrophils infiltration [37].

The role of IL-10

IL-10 is regarded as an anti-inflammatory cytokine that modulates the extent of host immunity to infection by exerting suppressive effects on different cell types including $CD8^+$ T cells and promoting liver immunopathology [38-42]. Upon hepatocellular antigen encounter, HBV-specific $CD8^+$ T cells release IL-10 that protects it from apoptosis via enhancing their responsiveness to IL-2 and prevent the $CD8^+$ T cells from dying and subsequently promoting acute liver pathology, this finding is corroborated by the use of mouse models of HBV pathogenesis which revealed that the IL-10 produced by effector $CD8^+$ T cells promoted their own intrahepatic survival and thus supported, rather than suppressed liver immunopathology [43]. The progressive liver injury observed in chronic HCV may be related to an upregulation cell-mediated responses that apart from their antiviral effects may also lead to nonspecific macrophage tissue damage. In more details, the progressive liver injury seen in chronic HCV is associated with the upregulation of intrahepatic Th1-like cytokines and the downregulation of IL-10, a Th2-like cytokine. These results suggest a role for delayed-type hypersensitivity immune reactions in HCV related liver injury [44].

LCMV and immune-mediated liver pathology

LCMV, a member of *Arenaviridae* family, is a well-established mouse model for acute and chronic virus infections, and it has enabled the identification of many immunological principles that were eventually validated in human infections. LCMV is one of the most widely used infection models for the study of virus-host immunity interactions. With the use of LCMV as a model pathogen, T cell exhaustion and the key role of immune pathology in disease have emerged.

The role of $CD8^+$ T cells

LCMV is a noncytolytic virus, and any immunopathology, disease or eventual death seen in this model is usually mediated by T cells [45]. The virus-infected hepatocytes are recognised by $CD8^+$ T cells killing which results in fulminant immunopathology and liver damage [46]. T cell-driven liver immunopathology in the context of LCMV infections was reported in different experimental models. Zinkernagel *et al.* firstly reported that LCMV-WE-induced hepatitis in mice is an immunopathologically mediated disease caused by T cell-mediated destruction of infected liver cells [47]. Upon establishment of a chronic infection, virus-specific $CD8^+$ T cells can lose their function, a process known as T cell exhaustion. It is known that the T cell exhaustion is essential to prevent severe immunopathology [48]. Regulation of $CD8^+$ T cell-mediated immunopathology has to be seen in the balancing context of virus control. In a setting of high early virus load and upregulation of exhaustive signals, virus will persist. However, a reduction in $CD8^+$ T cell exhaustion might accelerate liver immunopathology. In a contrasting setting of acute virus infection, where $CD8^+$ T cells are only partially exhausted and can still control the virus, immunopathology will be limited [49]. Therefore, minimizing virus propagation in the liver can be a very effective method to limit LCMV-induced immunopathology.

The destruction of hepatocytes depends at least partially on perforin. In fact, perforin-mediated cytotoxicity is vital to eradicate LCMV infection [50]. This is observed during acute infection with LCMV, which cannot be controlled in perforin-deficient mice [51]. In addition to the importance of perforin in cytotoxicity, it was also established that perforin downmodulates $CD8^+$ T cell responses. This regulatory function of perforin arises from the observation that perforin-deficient mice have vigorous $CD8^+$ T cell expansion. The liver of perforin-deficient animals shows T-cell infiltrates in the liver and the clusters of $CD8^+$ T cells around the foci of LCMV-infected cells. This excessive accumulation of activated $CD8^+$ T cells resulted in immune-mediated damage in persistently infected *perf*$^{-/-}$ mice [52].

Furthermore, other immune cells such as B cells have a prime role in preventing in T cell- mediated Immunopathology. For instance, a recent report showed that B cell deficiency exacerbates $CD8^+$ T cell-mediated immunopathology after infection with the LCMV strain Docile as noticed by rapid and fatal $CD8^+$ T cell-mediated immunopathological disease in B cells-devoid animals. $B^{-/-}$ mice rapidly develop a fatal $CD8^+$ T cell-mediated immunopathological disease after LCMV Docile infection due to concurrent presence of functional LCMV-specific $CD8^+$ T cells and target cells expressing LCMV antigens, enhancing anti-LCMV immunity in $B^{-/-}$ mice decreases target cell structures for $CD8^+$ T cells and thereby prevents LCMV-induced immunopathology [53].

The role of $CD8^+$ T cells - intrinsic modulators

Other than direct cytotoxicity against infected cells, $CD8^+$ T cells have intrinsic factors that sustain their effector functions such as; interferon regulatory factor 4 (IRF4), binding partner B-cell-activating transcription factor (BATF) and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1). It was speculated that genetic deletion of IRF4 and its cooperating binding partner BATF in $CD8^+$ T cells resulted in suboptimal $CD8^+$ T-based defences after infection with the lymphocytic choriomeningitis virus, ensuing in inferior immunopathology, and promotion of viral persistence [54]. Intrinsic expression of IRF4 in $CD8^+$ T cells was essential for optimal expansion [54]. Another factor that contributed to activation of virus specific $CD8^+$ T cells is CEACAM1 [55]. CEACAM1 is fundamental for recruiting lymphocyte-specific protein kinase (Lck) into the T cell receptor complex to form an efficient immunological synapse. Therefore, intrinsic lack of CEACAM1 limited expansion of LCMV-specific $CD8^+$ T cells. In line with this, treatment with an anti-CEACAM1 antibody enhanced proliferation of virus-specific $CD8^+$ T cells and enhanced virus control [55].

The role of Kupffer cells

Kupffer cells have a prominent role in controlling LCMV. Minutes after infection, they capture LCMV particles and prevent their propagation in interferon (IFN)-I dependent manner. This mechanism of "capture and famish" is essential for fast control of virus and prevention of a severe immunopathology. Absence of Kupffer cells even in the presence of IFN-I results in disseminated virus propagation, infection of hepatocytes and subsequent $CD8^+$ T cell mediated killing of hepatocytes [56].

The role of $CD169^+$ macrophages

In addition to initiating antiviral immune activation, $CD169^+$ macrophages also produce cytokines early after infection and thereby shape the antiviral immune response during chronic virus infection. IFN-I, which can be produced in $CD169^+$ macrophages early after infection, upregulates PD-L1 within liver resident macrophages. Thus, CD169+ macrophages regulate PD-L1 expression, an important inhibitor for $CD8^+$ T cells, via type I interferon and thereby prevent severe immunopathology after LCMV infection [57]. Depletion of $CD169^+$ macrophages in CD169-DTR mice makes them highly susceptible to chronic virus infection [57]. CD169-DTR mice have limited immune activation in the early phase of infection and a limited induction of inhibitory signals during persistence of the infection, which results in prolonged immunopathology. Mechanistically, limited upregulation of PD-L1 led to the absence of a PD-1/PD-L1 interaction. As a result, CD169-DTR mice developed a fatal $CD8^+$ T cell mediated immunopathology during chronic viral infection [58].

The role of NK cells

Natural killer and natural killer T cells may also contribute to liver pathology [59-61]. Lang *et al.* showed that, existence of NK cells promotes immunopathology, as they temper $CD8^+$ T cells immunity, ensuing in viral persistence and virus-induced hepatitis, and this effect was not due to direct effect of NK cells on virus load or IFN signalling, but rather via $CD8^+$ T cells [62].

NK cell-driven regulation of $CD8^+$ T cells response has an impressive impact on chronicity of diseases [63]. Antibody-dependent NK cell depletion during the establishment of chronic LCMV infection, has variable impact ranging from beneficial to detrimental on the outcome of disease including immunopathology. For instance, using high dose inoculum, NK cell depletion result in superior T cell immunity and contributing to speed virus control with accelerated immunopathology [49]. There is a growing body of evidence to indicate that NK cells are modulators of T cell immunity. NK cells can positively or negatively affect T cells depending on the cytokine milieu that is determined by the nature of pathogenic insult and its tropism [63, 64]. One compelling study showed that, NK cell protects the host from immunopathology, since the host lacking NCR1, a novel NK cell activating marker, exhibited superior $CD8^+$ T cells and ensuing exacerbated immunopathology in the settings of chronic viral infections [65].

Similarly, a unique population of NK cells enriched in the murine liver, and charactreized by $CD49a^+CD49b^-$ and they so called liver-resident NK (LrNK) cells [66, 67], was found to temper the antiviral T cells in the course of acute infection and dampen the $CD8^+$ T cells-associated liver pathology, and this inhibitory effect of LrNK cells was abrogated by blocking the PD-L1 [68].

Very recently, we have found that robust antiviral T cell response is correlated with efficient virus clearance from the circulation and solid lymphoid and nonlymphoid organs and subsequent ameliorated virus-driven immunopathology, and the strong T cells response was due to the absence of Fc-receptor common gamma chain (FcεRIγ) subunit in NK cells which limited their regulatory function. FcεRIγ expression was essential for NCR1 signaling. Therefore, absence of FcεRIγ resulted in limited regulatory function of NK cells, enhanced $CD8^+$ T-cell expansion and fast control of the virus [69, 70]. By the same token, NK cells have a delicate role in shaping the anti-viral T cells immunity via featured equilibrium, affecting the outcomes of disease. A recent study showed that the LCMV-induced immunopathology is exacerbated in absence of Qa-1b, inhibitory ligands on T and B cells for NKG2A on NK cells, due to suboptimal T cell response that is negatively modulated by NK cells in LCMV settings [71]. In another series of experiments, activated virus-specific T cells were shown to be downregulated during an intermediate dose LCMV infection due to activity of NK cells, resulting in overt viral replication and subsequent immunopathology. In this setting, the amount of viral antigen is not enough to establish T cell exhaustion, thereby leading to a status in which efficient T cells are encountered with massive numbers of infected cells, ensuing in fatal immunopathology. Ablation of NK cells in this setting leads to an increased T cell response which is able to faster control the infection, and hence preventing liver pathological consequences [49].

As an evolving strategy for the $CD8^+$ T cells to escape from NK cells mediated killing and subsequent virus-driven liver pathology, after infection with the LCMV, progranulin levels increased, a phenomenon dependent on the presence of macrophages and type I IFN signaling, progranulin elevation can reduce NK cell cytotoxicity, and thereby enhancing the antiviral T cell response, improved virus control and amelioration of liver injury [72].

The role of Platelets

In recent years the importance of platelets during antiviral immune response became clear. Platelet depletion lowers intrahepatic accumulation of virus-specific $CD8^+$ T cells and resulted in accelerated organ damage [73]. Mechanistically, circulating effector $CD8^+$ T cells interact with platelets within the liver sinusoids. Upon detachment from platelets, effector $CD8^+$ T cells migrate within the sinusoids [74]. Beside this contribution of platelets to the antiviral immune response, platelets release serotonin upon activation in the liver [75]. Release of serotonin correlates with severely reduced sinusoidal microcirculation. Sinusoidal microcirculatory failure correlated with viral-induced hepatocyte damage and delayed infiltration of activated virus-specific $CD8^+$ T cells [75].

The role of Liver-specific factors

Many cytokines have non-redundant roles in modulating the immune hemostasis, clearing the virus and abrogating the organ pathology and subsequently offering a therapeutic promise. During infection with LCMV, IL-10 strongly influences anti-viral $CD8^+$ T cell responses and immunopathology [76, 77]. During persistent LCMV infection, IL-10 can potentiate virus dissemination and sustain T cell exhaustion [76]. Dendritic cell- derived IL-10 has been proven to specifically downregulate T-cell responses and fail to preclude viral dissemination and limit the immunopathology [76]. In line with these findings, IL-10 prevented organ failure in a model of virus infection in heart transplanted mice. In fact, IL-10 deficient mice transplanted with LCMV loaded heart died early after transplantation. Loss of IL-10 in recipients showed a systemic immune response with immunopathology indicating that absence of IL-10 prevents T cell exhaustion and subsequent exacerbated liver immunopathology [78].

IL-7 is a cytokine which promotes T cell growth. Long-term memory T cells express the IL-7 receptor [79, 80]. Accelerated IL-7 can be useful for control of infection with LCMV [81]. In a chronic LCMV infection, therapeutic application of IL-7 correlated with accelerated production of IL-6 and IL-22 [81]. Both cytokines are cytoprotective and have been identified to protect hepatocytes from T cell-mediated pathology and/or hepatotoxicity [82-84].

Another type of liver-intrinsic factors is Farnesoid X receptor (FXR). It is a unique receptor for synthesized bile acids in the liver. In addition to important role of bile acids as surfactant in solubilizing lipids and promoting the absorption of lipids in the gastrointestinal tract, they act as inflammagens [85]. By using FXR-deficient mice, Honke *et al.* showed that FXR expression in hepatocytes is very crucial for sensing free BAs during LCMV infection which are released from hepatocytes in a $CD8^+$ T cell-dependent manner. Activation of FXR led to upregulation of IFN-I expression. Additionally, FXR dampens the hyperproduction of BAs, thereby avoiding their toxic effect on monocyte proliferation and infiltration into the liver. This infiltration was essential in helping Kupffer cells to control viral infection. The absence of FXR reduces IFN-I production and the proliferation and patrolling of immune cells in the liver and leads to higher viral replication and, consequently, to severe viral-induced liver damage and $CD8^+$ T cell exhaustion during LCMV Infection [86].

Moreover, hypercholesterolemia has been acknowledged to be associated with LCMV-induced immunopathology as the high cholesterol levels represses the anti-viral $CD8^+$ T cells response [87]. It is likely that metabolic distress due to hypercholesterolemia may cause macrophage alterations and may inhibit Ag presentation leading to impaired stimulation of specific T cells. Moreover, hypercholesterolemia may alter the microenvironment between antigen presenting cells and T cells leading to preferential Th2 differentiation and may thereby impair generation of efficient antiviral CTL responses. In naive and activated T cells, membrane-protein interactions and TCR signaling critically depend on the integrity of cholesterol-containing lipid rafts, which are changes in the functionality of membrane domains containing glycosphingolipids and cholesterol. It is therefore possible that the observed reduced T cell reactivity in hypercholesterolemic mice is at least in part due to impaired TCR-associated signaling pathways [88-91].

Concluding Remarks

It is obviously apparent that the liver is not only a vital organ for biological functions, but also emerged as key immune organ, as it is a hub for immunological reactions by virtue of immune cells it harbors. The etiology of the liver damage is guided by the nature of the pathogen and its tropism, which instruct the early cytokine environment that further defines innate and adaptive immune responses, ensuing in liver pathology due to overshooting T cell response (immune-mediated) or due to direct virus attack (virus-induced). Thus, several factors influence liver immunopathology during virus infection. Elucidation of

the immunological basis for pathological consequences of hepatic invaders may yield immunotherapeutic and antiviral strategies to treat chronic infections and minimize the risk of its life-threatening sequelae.

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Conceptualization, T.A.H; resources, T.A.H.; writing—original draft preparation, T.A.H.; writing—review and editing, T.A.H., F.A. and H.B.. All authors have read and agreed to the published version of the manuscript.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Gordillo M, Evans T, Gouon-Evans V: Orchestrating liver development. Development 2015;142:2094-2108.
2 Gruppuso PA, Sanders JA: Regulation of liver development: implications for liver biology across the lifespan. J Mol Endocrinol 2016;56:R115-125.
3 Crispe IN: The liver as a lymphoid organ. Annu Rev Immunol 2009;27:147-163.
4 Alpini G, Phillips JO, Vroman B, LaRusso NF: Recent advances in the isolation of liver cells. Hepatology 1994;20:494-514.
5 Damm G, Pfeiffer E, Burkhardt B, Vermehren J, Nussler AK, Weiss TS: Human parenchymal and non-parenchymal liver cell isolation, culture and characterization. Hepatol Int 2013;7:951-958.
6 Racanelli V, Rehermann B: The liver as an immunological organ. Hepatology 2006;43:S54-62.
7 Tiegs G, Lohse AW: Immune tolerance: what is unique about the liver. J Autoimmun 2010;34:1-6.
8 Gao B, Jeong WI, Tian Z: Liver: An organ with predominant innate immunity. Hepatology 2008;47:729-736.
9 Freitas-Lopes MA, Mafra K, David BA, Carvalho-Gontijo R, Menezes GB: Differential Location and Distribution of Hepatic Immune Cells. Cells 2017;6:48.
10 Roth E, Pircher H: IFN-gamma promotes Fas ligand- and perforin-mediated liver cell destruction by cytotoxic CD8 T cells. J Immunol 2004;172:1588-1594.
11 Merrick BA, Bruno ME, Madenspacher JH, Wetmore BA, Foley J, Pieper R, Zhao M, Makusky AJ, McGrath AM, Zhou JX, Taylor J, Tomer KB: Alterations in the rat serum proteome during liver injury from acetaminophen exposure. J Pharmacol Exp Ther 2006;318:792-802.
12 Carakostas MC, Gossett KA, Church GE, Cleghorn BL: Evaluating toxin-induced hepatic injury in rats by laboratory results and discriminant analysis. Vet Pathol 1986;23:264-269.
13 Giannini EG, Testa R, Savarino V: Liver enzyme alteration: a guide for clinicians. CMAJ 2005;172:367-379.
14 Kiyasu PK, Caldwell SH: Diagnosis and treatment of the major hepatotropic viruses. Am J Med Sci 1993;306:248-261.
15 Rouse BT, Sehrawat S: Immunity and immunopathology to viruses: what decides the outcome? Nat Rev Immunol 2010;10:514-526.
16 Cicchese JM, Evans S, Hult C, Joslyn LR, Wessler T, Millar JA, Marino S, Cilfone NA, Mattila JT, Linderman JJ, Kirschner DE: Dynamic balance of pro- and anti-inflammatory signals controls disease and limits pathology. Immunol Rev 2018;285:147-167.
17 Guidotti LG, Chisari FV: Immunobiology and pathogenesis of viral hepatitis. Annu Rev Pathol 2006;1:23-61.
18 Shin EC, Sung PS, Park SH: Immune responses and immunopathology in acute and chronic viral hepatitis. Nat Rev Immunol 2016;16:509-523.
19 Chisari FV, Ferrari C: Hepatitis B virus immunopathogenesis. Annu Rev Immunol 1995;13:29-60.
20 Asabe S, Wieland SF, Chattopadhyay PK, Roederer M, Engle RE, Purcell RH, Chisari FV: The size of the viral inoculum contributes to the outcome of hepatitis B virus infection. J Virol 2009;83:9652-9662.

21 Zhao J, Zhang Z, Luan Y, Zou Z, Sun Y, Li Y, Jin L, Zhou C, Fu J, Gao B, Fu Y, Wang FS: Pathological functions of interleukin-22 in chronic liver inflammation and fibrosis with hepatitis B virus infection by promoting T helper 17 cell recruitment. Hepatology 2014;59:1331-1342.
22 Sun HQ, Zhang JY, Zhang H, Zou ZS, Wang FS, Jia JH: Increased Th17 cells contribute to disease progression in patients with HBV-associated liver cirrhosis. J Viral Hepat 2012;19:396-403.
23 Brady MT, MacDonald AJ, Rowan AG, Mills KH: Hepatitis C virus non-structural protein 4 suppresses Th1 responses by stimulating IL-10 production from monocytes. Eur J Immunol 2003;33:3448-3457.
24 Chang Q, Wang YK, Zhao Q, Wang CZ, Hu YZ, Wu BY: Th17 cells are increased with severity of liver inflammation in patients with chronic hepatitis C. J Gastroenterol Hepatol 2012;27:273-278.
25 Lee HC, Sung SS, Krueger PD, Jo YA, Rosen HR, Ziegler SF, Hahn YS: Hepatitis C virus promotes T-helper (Th)17 responses through thymic stromal lymphopoietin production by infected hepatocytes. Hepatology 2013;57:1314-1324.
26 Choi YS, Lee J, Lee HW, Chang DY, Sung PS, Jung MK, Park JY, Kim JK, Lee JI, Park H, Cheong JY, Suh KS, Kim HJ, Lee JS, Kim KA, Shin EC: Liver injury in acute hepatitis A is associated with decreased frequency of regulatory T cells caused by Fas-mediated apoptosis. Gut 2015;64:1303-1313.
27 Manangeeswaran M, Jacques J, Tami C, Konduru K, Amharref N, Perrella O, Casasnovas JM, Umetsu DT, Dekruyff RH, Freeman GJ, Perrella A, Kaplan GG: Binding of hepatitis A virus to its cellular receptor 1 inhibits T-regulatory cell functions in humans. Gastroenterology 2012;142:1516-1525 e1513.
28 Moriyama T, Guilhot S, Klopchin K, Moss B, Pinkert CA, Palmiter RD, Brinster RL, Kanagawa O, Chisari FV: Immunobiology and pathogenesis of hepatocellular injury in hepatitis B virus transgenic mice. Science 1990;248:361-364.
29 Iannacone M, Sitia G, Ruggeri ZM, Guidotti LG: HBV pathogenesis in animal models: recent advances on the role of platelets. J Hepatol 2007;46:719-726.
30 Rehermann B: Hepatitis C virus versus innate and adaptive immune responses: a tale of coevolution and coexistence. J Clin Invest 2009;119:1745-1754.
31 Shin EC, Park SH, Demino M, Nascimbeni M, Mihalik K, Major M, Veerapu NS, Heller T, Feinstone SM, Rice CM, Rehermann B: Delayed induction, not impaired recruitment, of specific CD8(+) T cells causes the late onset of acute hepatitis C. Gastroenterology 2011;141:686-695, 695.e1.
32 Heydtmann M: Macrophages in hepatitis B and hepatitis C virus infections. J Virol 2009;83:2796-2802.
33 Wu Z, Han M, Chen T, Yan W, Ning Q: Acute liver failure: mechanisms of immune-mediated liver injury. Liver Int 2010;30:782-794.
34 Kolios G, Valatas V, Kouroumalis E: Role of Kupffer cells in the pathogenesis of liver disease. World J Gastroenterol 2006;12:7413-7420.
35 Roberts RA, Ganey PE, Ju C, Kamendulis LM, Rusyn I, Klaunig JE: Role of the Kupffer cell in mediating hepatic toxicity and carcinogenesis. Toxicol Sci 2007;96:2-15.
36 Canbay A, Feldstein AE, Higuchi H, Werneburg N, Grambihler A, Bronk SF, Gores GJ: Kupffer cell engulfment of apoptotic bodies stimulates death ligand and cytokine expression. Hepatology 2003;38:1188-1198.
37 Sitia G, Iannacone M, Aiolfi R, Isogawa M, van Rooijen N, Scozzesi C, Bianchi ME, von Andrian UH, Chisari FV, Guidotti LG: Kupffer cells hasten resolution of liver immunopathology in mouse models of viral hepatitis. PLoS Pathog 2011;7:e1002061.
38 Saraiva M, O'Garra A: The regulation of IL-10 production by immune cells. Nat Rev Immunol 2010;10:170-181.
39 Gazzinelli RT, Wysocka M, Hieny S, Scharton-Kersten T, Cheever A, Kuhn R, Muller W, Trinchieri G, Sher A: In the absence of endogenous IL-10, mice acutely infected with Toxoplasma gondii succumb to a lethal immune response dependent on CD4+ T cells and accompanied by overproduction of IL-12, IFN-gamma and TNF-alpha. J Immunol 1996;157:798-805.
40 Couper KN, Blount DG, Riley EM: IL-10: the master regulator of immunity to infection. J Immunol 2008;180:5771-5777.
41 Wilson EB, Brooks DG: The role of IL-10 in regulating immunity to persistent viral infections. Curr Top Microbiol Immunol 2011;350:39-65.
42 Groux H, Bigler M, de Vries JE, Roncarolo MG: Inhibitory and stimulatory effects of IL-10 on human CD8+ T cells. J Immunol 1998;160:3188-3193.

43 Fioravanti J, Di Lucia P, Magini D, Moalli F, Boni C, Benechet AP, Fumagalli V, Inverso D, Vecchi A, Fiocchi A, Wieland S, Purcell R, Ferrari C, Chisari FV, Guidotti LG, Iannacone M: Effector CD8(+) T cell-derived interleukin-10 enhances acute liver immunopathology. J Hepatol 2017;67:543-548.
44 Napoli J, Bishop GA, McGuinness PH, Painter DM, McCaughan GW: Progressive liver injury in chronic hepatitis C infection correlates with increased intrahepatic expression of Th1-associated cytokines. Hepatology 1996;24:759-765.
45 Asano MS, Ahmed R: Immune conflicts in lymphocytic choriomeningitis virus. Springer Semin Immunopathol 1995;17:247-259.
46 Maini MK, Boni C, Lee CK, Larrubia JR, Reignat S, Ogg GS, King AS, Herberg J, Gilson R, Alisa A, Williams R, Vergani D, Naoumov NV, Ferrari C, Bertoletti A: The role of virus-specific CD8(+) cells in liver damage and viral control during persistent hepatitis B virus infection. J Exp Med 2000;191:1269-1280.
47 Zinkernagel RM, Haenseler E, Leist T, Cerny A, Hengartner H, Althage A: T cell-mediated hepatitis in mice infected with lymphocytic choriomeningitis virus. Liver cell destruction by H-2 class I-restricted virus-specific cytotoxic T cells as a physiological correlate of the 51Cr-release assay? J Exp Med 1986;164:1075-1092.
48 Yi JS, Cox MA, Zajac AJ: T-cell exhaustion: characteristics, causes and conversion. Immunology 2010;129:474-481.
49 Waggoner SN, Cornberg M, Selin LK, Welsh RM: Natural killer cells act as rheostats modulating antiviral T cells. Nature 2011;481:394-398.
50 Badovinac VP, Hamilton SE, Harty JT: Viral infection results in massive CD8+ T cell expansion and mortality in vaccinated perforin-deficient mice. Immunity 2003;18:463-474.
51 Kagi D, Ledermann B, Burki K, Seiler P, Odermatt B, Olsen KJ, Podack ER, Zinkernagel RM, Hengartner H: Cytotoxicity mediated by T cells and natural killer cells is greatly impaired in perforin-deficient mice. Nature 1994;369:31-37.
52 Matloubian M, Suresh M, Glass A, Galvan M, Chow K, Whitmire JK, Walsh CM, Clark WR, Ahmed R: A role for perforin in downregulating T-cell responses during chronic viral infection. J Virol 1999;73:2527-2536.
53 Straub T, Pircher H: Enhancing immunity prevents virus-induced T-cell-mediated immunopathology in B cell-deficient mice. Eur J Immunol 2019;49:782-789.
54 Grusdat M, McIlwain DR, Xu HC, Pozdeev VI, Knievel J, Crome SQ, Robert-Tissot C, Dress RJ, Pandyra AA, Speiser DE, Lang E, Maney SK, Elford AR, Hamilton SR, Scheu S, Pfeffer K, Bode J, Mittrucker HW, Lohoff M, Huber M, et al.: IRF4 and BATF are critical for CD8(+) T-cell function following infection with LCMV. Cell Death Differ 2014;21:1050-1060.
55 Khairnar V, Duhan V, Patil AM, Zhou F, Bhat H, Thoens C, Sharma P, Adomati T, Friendrich SK, Bezgovsek J, Dreesen JD, Wennemuth G, Westendorf AM, Zelinskyy G, Dittmer U, Hardt C, Timm J, Gothert JR, Lang PA, Singer BB, et al.: CEACAM1 promotes CD8(+) T cell responses and improves control of a chronic viral infection. Nat Commun 2018;9:2561.
56 Lang PA, Recher M, Honke N, Scheu S, Borkens S, Gailus N, Krings C, Meryk A, Kulawik A, Cervantes-Barragan L, Van Rooijen N, Kalinke U, Ludewig B, Hengartner H, Harris N, Haussinger D, Ohashi PS, Zinkernagel RM, Lang KS: Tissue macrophages suppress viral replication and prevent severe immunopathology in an interferon-I-dependent manner in mice. Hepatology 2010;52:25-32.
57 Shaabani N, Duhan V, Khairnar V, Gassa A, Ferrer-Tur R, Haussinger D, Recher M, Zelinskyy G, Liu J, Dittmer U, Trilling M, Scheu S, Hardt C, Lang PA, Honke N, Lang KS: CD169(+) macrophages regulate PD-L1 expression via type I interferon and thereby prevent severe immunopathology after LCMV infection. Cell Death Dis 2016;7:e2446.
58 Frebel H, Nindl V, Schuepbach RA, Braunschweiler T, Richter K, Vogel J, Wagner CA, Loffing-Cueni D, Kurrer M, Ludewig B, Oxenius A: Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. J Exp Med 2012;209:2485-2499.
59 Adams DH, Ju C, Ramaiah SK, Uetrecht J, Jaeschke H: Mechanisms of immune-mediated liver injury. Toxicol Sci 2010;115:307-321.
60 Swain MG: Hepatic NKT cells: friend or foe? Clin Sci (Lond) 2008;114:457-466.
61 Muhlen KA, Schumann J, Wittke F, Stenger S, Van Rooijen N, Van Kaer L, Tiegs G: NK cells, but not NKT cells, are involved in Pseudomonas aeruginosa exotoxin A-induced hepatotoxicity in mice. J Immunol 2004;172:3034-3041.

62 Lang PA, Lang KS, Xu HC, Grusdat M, Parish IA, Recher M, Elford AR, Dhanji S, Shaabani N, Tran CW, Dissanayake D, Rahbar R, Ghazarian M, Brustle A, Fine J, Chen P, Weaver CT, Klose C, Diefenbach A, Haussinger D, et al.: Natural killer cell activation enhances immune pathology and promotes chronic infection by limiting CD8+ T-cell immunity. Proc Natl Acad Sci U S A 2012;109:1210-1215.
63 Crouse J, Xu HC, Lang PA, Oxenius A: NK cells regulating T cell responses: mechanisms and outcome. Trends Immunol 2015;36:49-58.
64 Pallmer K, Oxenius A: Recognition and Regulation of T Cells by NK Cells. Front Immunol 2016;7:251.
65 Pallmer K, Barnstorf I, Baumann NS, Borsa M, Jonjic S, Oxenius A: NK cells negatively regulate CD8 T cells via natural cytotoxicity receptor (NCR) 1 during LCMV infection. PLoS Pathog 2019;15:e1007725.
66 Peng H, Jiang X, Chen Y, Sojka DK, Wei H, Gao X, Sun R, Yokoyama WM, Tian Z: Liver-resident NK cells confer adaptive immunity in skin-contact inflammation. J Clin Invest 2013;123:1444-1456.
67 Sojka DK, Plougastel-Douglas B, Yang L, Pak-Wittel MA, Artyomov MN, Ivanova Y, Zhong C, Chase JM, Rothman PB, Yu J, Riley JK, Zhu J, Tian Z, Yokoyama WM: Tissue-resident natural killer (NK) cells are cell lineages distinct from thymic and conventional splenic NK cells. Elife 2014;3:e01659.
68 Zhou J, Peng H, Li K, Qu K, Wang B, Wu Y, Ye L, Dong Z, Wei H, Sun R, Tian Z: Liver-Resident NK Cells Control Antiviral Activity of Hepatic T Cells via the PD-1-PD-L1 Axis. Immunity 2019;50:403-417 e404.
69 Hamdan TA, Lang PA, Lang KS: The Diverse Functions of the Ubiquitous Fcgamma Receptors and Their Unique Constituent, FcRgamma Subunit. Pathogens 2020;9:140.
70 Duhan V, Hamdan TA, Xu HC, Shinde P, Bhat H, Li F, Al-Matary Y, Haussinger D, Bezgovsek J, Friedrich SK, Hardt C, Lang PA, Lang KS: NK cell-intrinsic FcepsilonRIgamma limits CD8+ T-cell expansion and thereby turns an acute into a chronic viral infection. PLoS Pathog 2019;15:e1007797.
71 Xu HC, Huang J, Pandyra AA, Lang E, Zhuang Y, Thons C, Timm J, Haussinger D, Colonna M, Cantor H, Lang KS, Lang PA: Lymphocytes Negatively Regulate NK Cell Activity via Qa-1b following Viral Infection. Cell Rep 2017;21:2528-2540.
72 Huang A, Shinde PV, Huang J, Senff T, Xu HC, Margotta C, Haussinger D, Willnow TE, Zhang J, Pandyra AA, Timm J, Weggen S, Lang KS, Lang PA: Progranulin prevents regulatory NK cell cytotoxicity against antiviral T cells. JCI Insight 2019;4:e129856.
73 Iannacone M, Sitia G, Isogawa M, Marchese P, Castro MG, Lowenstein PR, Chisari FV, Ruggeri ZM, Guidotti LG: Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nat Med 2005;11:1167-1169.
74 Benechet AP, Iannacone M: Determinants of hepatic effector CD8(+) T cell dynamics. J Hepatol 2017;66:228-233.
75 Lang PA, Contaldo C, Georgiev P, El-Badry AM, Recher M, Kurrer M, Cervantes-Barragan L, Ludewig B, Calzascia T, Bolinger B, Merkler D, Odermatt B, Bader M, Graf R, Clavien PA, Hegazy AN, Lohning M, Harris NL, Ohashi PS, Hengartner H, et al.: Aggravation of viral hepatitis by platelet-derived serotonin. Nat Med 2008;14:756-761.
76 Brooks DG, Trifilo MJ, Edelmann KH, Teyton L, McGavern DB, Oldstone MB: Interleukin-10 determines viral clearance or persistence *in vivo*. Nat Med 2006;12:1301-1309.
77 Ejrnaes M, Filippi CM, Martinic MM, Ling EM, Togher LM, Crotty S, von Herrath MG: Resolution of a chronic viral infection after interleukin-10 receptor blockade. J Exp Med 2006;203:2461-2472.
78 Gassa A, Jian F, Kalkavan H, Duhan V, Honke N, Shaabani N, Friedrich SK, Dolff S, Wahlers T, Kribben A, Hardt C, Lang PA, Witzke O, Lang KS: IL-10 Induces T Cell Exhaustion During Transplantation of Virus Infected Hearts. Cell Physiol Biochem 2016;38:1171-1181.
79 Kaech SM, Tan JT, Wherry EJ, Konieczny BT, Surh CD, Ahmed R: Selective expression of the interleukin 7 receptor identifies effector CD8 T cells that give rise to long-lived memory cells. Nat Immunol 2003;4:1191-1198.
80 Chazen GD, Pereira GM, LeGros G, Gillis S, Shevach EM: Interleukin 7 is a T-cell growth factor. Proc Natl Acad Sci U S A 1989;86:5923-5927.
81 Pellegrini M, Calzascia T, Toe JG, Preston SP, Lin AE, Elford AR, Shahinian A, Lang PA, Lang KS, Morre M, Assouline B, Lahl K, Sparwasser T, Tedder TF, Paik JH, DePinho RA, Basta S, Ohashi PS, Mak TW: IL-7 engages multiple mechanisms to overcome chronic viral infection and limit organ pathology. Cell 2011;144:601-613.
82 Radaeva S, Sun R, Pan HN, Hong F, Gao B: Interleukin 22 (IL-22) plays a protective role in T cell-mediated murine hepatitis: IL-22 is a survival factor for hepatocytes via STAT3 activation. Hepatology 2004;39:1332-1342.

83 Zenewicz LA, Yancopoulos GD, Valenzuela DM, Murphy AJ, Karow M, Flavell RA: Interleukin-22 but not interleukin-17 provides protection to hepatocytes during acute liver inflammation. Immunity 2007;27:647-659.
84 Klein C, Wustefeld T, Assmus U, Roskams T, Rose-John S, Muller M, Manns MP, Ernst M, Trautwein C: The IL-6-gp130-STAT3 pathway in hepatocytes triggers liver protection in T cell-mediated liver injury. J Clin Invest 2005;115:860-869.
85 Allen K, Jaeschke H, Copple BL: Bile acids induce inflammatory genes in hepatocytes: a novel mechanism of inflammation during obstructive cholestasis. Am J Pathol 2011;178:175-186.
86 Honke N, Shaabani N, Hardt C, Krings C, Haussinger D, Lang PA, Lang KS, Keitel V: Farnesoid X Receptor in Mice Prevents Severe Liver Immunopathology During Lymphocytic Choriomeningitis Virus Infection. Cell Physiol Biochem 2017;41:323-338.
87 Ludewig B, Jaggi M, Dumrese T, Brduscha-Riem K, Odermatt B, Hengartner H, Zinkernagel RM: Hypercholesterolemia exacerbates virus-induced immunopathologic liver disease via suppression of antiviral cytotoxic T cell responses. J Immunol 2001;166:3369-3376.
88 Zhou X, Paulsson G, Stemme S, Hansson GK: Hypercholesterolemia is associated with a T helper (Th) 1/Th2 switch of the autoimmune response in atherosclerotic apo E-knockout mice. J Clin Invest 1998;101:1717-1725.
89 Seiler P, Aichele P, Odermatt B, Hengartner H, Zinkernagel RM, Schwendener RA: Crucial role of marginal zone macrophages and marginal zone metallophils in the clearance of lymphocytic choriomeningitis virus infection. Eur J Immunol 1997;27:2626-2633.
90 Simons K, Ikonen E: Functional rafts in cell membranes. Nature 1997;387:569-572.
91 Janes PW, Ley SC, Magee AI, Kabouridis PS: The role of lipid rafts in T cell antigen receptor (TCR) signalling. Semin Immunol 2000;12:23-34.