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REVIEW

γδ T cells in liver diseases

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Abstract **γδ T cells display unique developmental, distributional, and functional patterns and can rapidly respond to various insults and contribute to diverse diseases. Different subtypes of γδ T cells are produced in the thymus prior to their migration to peripheral tissues. γδ T cells are enriched in the liver and exhibit liver-specific features. Accumulating evidence reveals that γδ T cells play important roles in liver infection, non-alcoholic fatty liver disease, autoimmune hepatitis, liver fibrosis and cirrhosis, and liver cancer and regeneration. In this study, we review the properties of hepatic γδ T cells and summarize the roles of γδ T cells in liver diseases. We believe that determining the properties and functions of γδ T cells in liver diseases enhances our understanding of the pathogenesis of liver diseases and is useful for the design of novel γδ T cell-based therapeutic regimens for liver diseases.**

Keywords γδT cells; liver infection; non-alcoholic fatty liver disease; autoimmune hepatitis; liver fibrosis and cirrhosis; liver cancer; liver regeneration

Introduction

γδ T cells belong to a unique innate lymphocyte subset. Research on the differentiation, distribution, function, and application of γδ T cells has achieved considerable progress since the discovery of the γδ T-cell lineage approximately 30 years ago. T cells develop from multipotent progenitor CD4–CD8-double-negative (DN) thymocytes in the thymus and undergo four stages (DN1, $CD44^+CD25^-$; DN2, $CD44^+CD25^+$; DN3, $CD44^-CD25^+$; and DN4, $CD44^-CD25^-$) [1]. T-cell receptor (TCR) rearrangement begins at the DN2–DN3 stages, and γδ TCRs or preTCRs are expressed at the DN3–DN4 stages [2]. Cell differentiation into αβ or γδ T-cell lineages is determined at the DN3 stage [3]. γδ T cells can produce at least two distinct subsets, namely, interferon (IFN)-γ- and interleukin (IL)-17-producing γδ T cells. The segregation of γδ T-cell functional subsets can be distinguished by cell surface markers. CD27 segregates γδ T cells into IL-17-producing $CD27^-$ γδ T cells, and IFN-γ-producing $CD27^+$ γδ T cells [4]. $CCR6^+$ γδ T cells exclusively produce IL-17A, whereas $NK1.1^+$ γδ T cells readily produce IFN-γ [5]. Increasing evidence suggests that the functional polarization of γδ T cells is developmentally programmed in the thymus rather than in localized peripheral tissues [6]. Therefore, TCR signals play an essential role, beyond lineage commitment, in the functional polarization of γδ T cells. In contrast to conventional adaptive T cells, which recognize peptide antigens presented by antigen-presenting cells in a MHC-dependent manner, γδ T cells can recognize nonpeptide antigens and stress-induced ligands [7]. Moreover, γδ T cells are preferentially located in peripheral mucosal tissues [8] and play a protective role in pathogen clearance, tumor surveillance, and tissue repair and a deleterious role in autoimmunity, allergy, and carcinogenesis through cytokine secretion and/or cytotoxicity [9]. Thus, γδ T cells contribute not only to immune balance and tissue homeostasis but also to immune disorders and tissue pathogenesis. In fact, the effector functions of γδ T cells are determined by developmental polarization, tissue localization, and environment cues. Growing evidence reveals that γδ T cells in the liver respond to liver-targeted insults and modulate the development of liver diseases [10,11]. As such, this review focuses on the roles of γδ T cells in liver diseases (Fig. 1).

Although the liver is recognized as an important organ in

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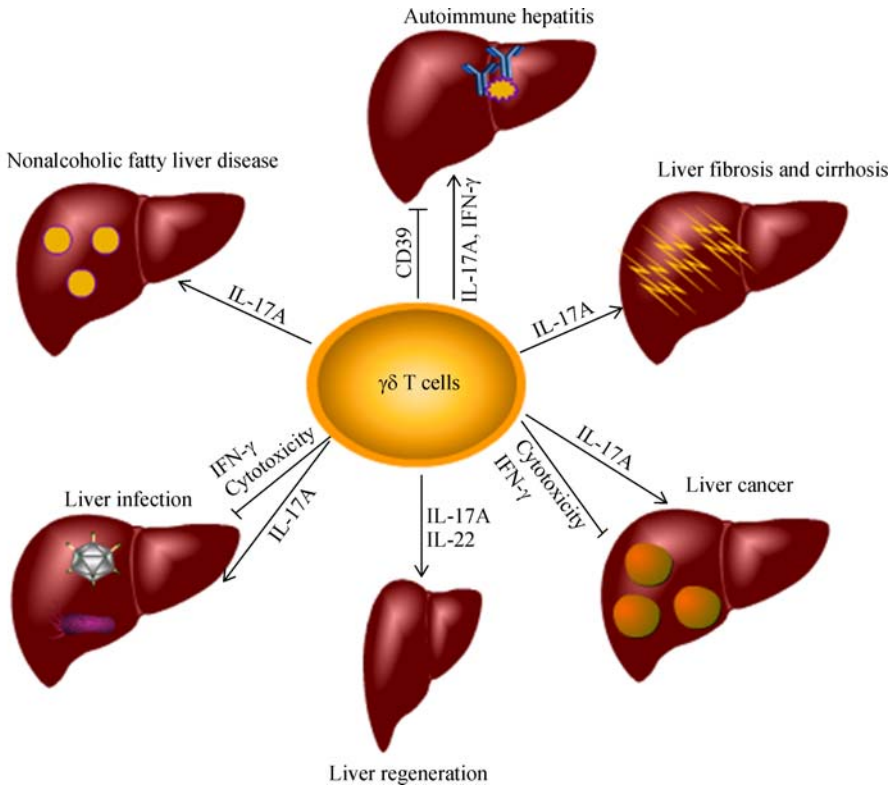

Fig. 1 γδ T cells in liver diseases. The effector functions of hepatic γδ T cells are context-dependent, although IL-17A-producing γδ T cells predominantly localize in the liver. On the one hand, hepatic IL-17A-producing γδ T cells not only play pathogen-promoting roles in infection-induced liver injury, non-alcoholic fatty liver disease, autoimmune hepatitis, liver fibrosis/cirrhosis, and liver cancer but also promote liver regeneration (shown as →). On the other hand, hepatic IFN-γ-producing γδ T cells play protective roles in liver infection and liver cancer (shown as ⊣) and also mediate autoimmune hepatitis (shown as →). In addition, hepatic γδ T cells suppress the inflammatory response by expressing inhibitory molecules (such as CD39, shown as ⊣).

the defense against blood-borne infections, liver injury can also be triggered by drugs, toxins, pathogen infections, over-eating, and genetic disorders [12]. Moreover, persistent liver damage is likely to induce the progression of mild chronic liver disease to liver fibrosis, liver cirrhosis, liver cancer, and liver failure [13]. The liver displays tissue-specific features that need to be emphasized in this study because prior knowledge of these features enhances the understanding of the induction, development, and end stage of liver disease. First, the liver is a barrier organ that segregates the digestive tract from the rest of the body. It possesses a special blood circulation system, wherein 80% of blood supply from the portal vein is rich in bacterial products, environment toxins, and food-derived antigens that are purified by the liver from the intestines; meanwhile, the remaining blood from the hepatic artery provides nutrients and oxygen [14,15]. Second, the liver is an immune-tolerant organ. Liver tolerance is manifested by immune hyporesponsiveness in the context of allogeneic liver transplants and liver infections and is maintained and modified by diverse intrahepatic cells, including immune cells and non-immune cells [16,17]. Third, the liver is an organ with predominant innate immunity. It is enriched with Kupffer cells, natural killer cells, natural killer T (NKT) cells, and γδ T cells [18–22]. These liver features reflect the close relationship among its anatomical location, immune status, immune components, functions, and liver disease. In this study, we highlight advances in the understanding of the properties and roles of hepatic γδ T cells in liver diseases and discuss the potential of γδ T cells as therapeutic targets in treating liver diseases.

Hepatic γδ T cells

γδ T cells constitute approximately 2%–10% of the total T cells in the peripheral blood, whereas hepatic γδ T cells account for 3%–5% of the total liver lymphocytes and 15%–25% of the total number of liver T cells [18]. In terms of phenotype, hepatic γδ T cells exhibit mixed Vγ chains (including Vγ1, Vγ4, and Vγ6 in mice and Vδ1 and Vδ3 in humans) [23]. Hepatic γδ T cells in the murine liver contain a high fraction of $V\gamma4^{+}$ cells with enhanced functional activation; meanwhile, hepatic γδ T cells in the human liver are more mature than their counterparts in peripheral blood [24]. Recently, our group carefully analyzed hepatic γδ T cells [25]. Hepatic γδ T cells are highly localized to the

liver and rarely transported. Hepatic γδ T cells also display active and mature phenotype characterized by high frequency of $CD44^{high}CD62L^{low}$γδ T cells in the liver. In terms of function, IL-17A-producing γδ T cells increase in number and become predominant in the liver with age, accompanied by a decrease in IFN-γ-producing γδ T cells. Therefore, hepatic γδ T cells exhibit a unique phenotype and composition. Commensal microbes in the gut maintain the homeostasis of hepatic IL-17A-producing γδ T cells in a lipid antigen/CD1d-dependent manner; this phenomenon may explain the steady increase in hepatic IL-17A-producing γδ T cells with age [25]. Accumulating evidence suggests that hepatic γδ T cells play important roles in maintaining hepatic physiological homeostasis and modulating hepatic pathological progression. Thus, we review the roles of hepatic γδ T cells in diverse liver diseases.

γδ T cells in liver infection

Viral hepatitis is an inflammatory liver disease induced mainly by hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. In HBV infection, approximately 5% of infected individuals develop chronic hepatitis B (CHB), whereas the remaining 95% of adult patients achieve resolution of hepatitis B infection [26,27]. Clinical studies show that the frequencies of peripheral and hepatic Vδ2 T cells decrease with disease progression, from tolerance to activation [28]. In addition, the ability of Vδ2 T cells with an activated memory phenotype to produce IFN-γ and induce cytotoxicity is impaired in CHB patients, although it can be enhanced by IFN-α treatment [29]. Therefore, γδ T cells in CHB patients protect the host against HBV infection. Nonetheless, γδ T cells mediate liver injury and contribute to HBV-associated acute-on-chronic liver failure [30]. Hepatic IL-17A-producing γδ T cells also induce $CD8^+$ T cell exhaustion by recruiting myeloid-derived suppressor cells (MDSC) in the HBV-induced immunotolerance mouse model [31]. Similar conclusions concerning patients with chronic HBV infection still require further clinical studies. As suggested by the aforementioned observations, distinct γδ T subsets produce unique effects as disease progress after HBV infection.

In contrast to HBV infection, HCV infection induces chronic hepatitis at a high rate [32]. Vδ2 T cells exhibit an activated phenotype and enhanced cytotoxicity in HCV-infected patients. Moreover, hepatic Vδ2 T cells display more cytotoxic functions than peripheral Vδ2 T cells [33]. However, the elevated hepatic γδ T cells exhibit strong cytotoxicity against hepatocytes and mediate liver injury in HCV-infected patients [34]. Vδ2 T cells also exhibit a markedly impaired capacity to produce IFN-γ, the key molecule in combating HCV infection, although the activation of Vδ2 T cells by nonpeptide antigens can inhibit HCV replication through IFN-γ release [35]. In HBV- and HCV-infected individuals, γδ T cells display different functions. This condition may result in different outcomes.

In addition to viral infection, γδ T cells also participate in other hepatotropic pathogen infections. For instance, hepatic γδ T cells remarkably expand and protect the liver against *Trypanosoma cruzi* infection by producing IFN-γ [36]. Hepatic γδ T cells limit inflammation induced by *Listeria monocytogenes* infection and necrotic liver lesions by killing chemokine-producing macrophages in a Fas ligand (FasL)-dependent manner [37]. Hepatic γδ T cells contribute to granulomatous inflammatory and hepatic lesions by producing IL-17A in mice infected with *Schistosoma japonicum* [38]. Thus, improved therapeutic strategies based on γδ T cells for liver infections should be explored to enhance the antipathogenic potential while attenuating the risk of tissue damage.

γδ T cells in non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of chronic liver disorders ranging from simple steatosis to non-alcoholic steatohepatitis and cirrhosis [39]. IL-17 accelerates NAFLD progression by recruiting neutrophils and inducing reactive oxygen species [40]. Thus, IL-17A neutralization efficiently attenuates high-fat diet-induced NAFLD [41]. Hepatic γδ T cells are major providers of IL-17A in HFD/HFHCD-induced NAFLD [25]. IL-17A-producing γδ T cells are elevated in mouse livers with NAFLD. γδ T cell deficiency protected mice from NAFLD, characterized by reduced steatohepatitis and liver damage. The adoptive transfer of hepatic γδ T cells into HFHCD-fed mice accelerates NAFLD. Similar to the findings in mice, IL-17A-producing $CD161^+$ γδ T cells are enriched in the livers of patients with NAFLD [10]. Therefore, IL-17A-producing γδ T cells are a major regulating factor in NAFLD progression. However, the mechanism of γδ T cell subset activation requires further exploration. Therefore, blocking or deleting IL-17A-producing γδ T cells may be a feasible therapeutic regimen for NAFLD treatment.

γδ T cells in autoimmune liver diseases

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) are the three major autoimmune liver diseases (ALDs). AIH is an inflammation of the liver and characterized by periportal hepatitis, hypergammaglobulinemia, and the presence of serum autoantibodies [42]. PBC is a chronic cholestatic liver disease characterized by the destruction of small intrahepatic bile ducts and the presence of antimitochondrial antibodies [43]. PSC is the hepatobiliary

manifestation of inflammatory bowel disease, characterized by chronic inflammation and bile duct fibrosis [44]. The percentages and absolute numbers of γδ T cells are elevated in the peripheral blood and in the portal areas of patients with AIH, PSC, or PBC [45,46]. Meanwhile, γδ T cells in the peripheral blood of patients with ALD are activated [47]. γδ T cells in patients with AIH produce more IFN-γ and granzyme B, contributing to liver damage [48]. In addition, γδ T cell-derived IL-17A mediates hepatocyte damage in Jα18 knockout (KO) mice with AIH [49]. The roles of IL-17A in autoimmune liver diseases have been reviewed [50], suggesting therapeutic potential for ALD treatment by targeting the IL-17 signaling pathway. Nonetheless, γδ T cells can produce suppressor cytokines to prevent hepatitis induced by autoreactive T cells [51]. Moreover, in ConA-induced NKT cell-mediated ALD, IL-17A-producing $V\gamma4^+$ γδ T cells protect mice from liver damage by inhibiting the pathogenic effect of NKT cells [52]. Therefore, distinct subsets of γδ T cells may exist simultaneously during ALD progression. Furthermore, the roles of specific γδ T cell subsets in ALD are context dependent. Thus, the modulation of γδ T cells may be a useful strategy in treating ALD.

γδ T cells in liver fibrosis and cirrhosis

Chronic inflammation promotes liver fibrosis and subsequently leads to cirrhosis, which is characterized by the excessive accumulation of extracellular matrix production by hepatic stellate cells (HSCs) [13]. CCL20 is strongly upregulated upon chronic liver injury in mice and in human patients with cirrhosis, which results in the recruitment of IL-17-producing γδ T cells to the liver in a CCR6-dependent manner to restore hepatic fibrosis by promoting HSC apoptosis in a FasL-dependent manner [53]. However, HSC-derived CCL20 induced by exosomes recruiting IL-17A-producing $CCR6^+$ γδ T cells to exacerbate liver fibrosis was reported [54]. IL-17A stimulates α-smooth muscle actin, tumor growth factor (TGF)-β, IL-6, and collagen expression in HSCs in liver fibrosis [55,56]. In fact, the contradictory roles of γδ T cells in liver fibrosis are a result of different mechanisms. The cytotoxicity against HSCs induces γδ T cells to play a protective role, whereas IL-17A confers γδ T cells to exhibit a deleterious role.

γδ T cells in liver cancer

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths and shows a poor five-year survival rate [57]. γδ T cells can efficiently kill liver tumor cell lines *in vitro* [4]. Nonetheless, infiltration by γδ T cells and associated IFN-γ secretion and cytotoxicity in HCC tumor tissues are significantly compromised compared with paired peritumoral tissues, which is partially mediated by Treg cells in a TGF-β- and IL-10-dependent manner [58]. However, the levels of peritumoral γδ T cells are negatively correlated with tumor size and incidence of recurrence in HCC [59]. This phenomenon indicates that peritumoral γδ T cells can still exert an antitumor effect in patients with HCC. Therefore, enhancing the infiltration and function of γδ T cells in HCC tumor tissues is a promising immunotherapy for HCC. However, IL-17A-producing Vγ4 γδ T cells in HCC recruit MDSCs, resulting in the suppression of the $CD8^+$T-cell response and the promotion of tumor growth [60]. Moreover, HCC formation following the introduction of Hepa1–6 cells is suppressed in γδ TCR KO mice [61]. The antitumor ability of γδ T cells cannot be surpassed. Human Vγ9Vδ2 T cells display a strong cytotoxic activity against HCC [62,63], and CD226 promotes Vγ9Vδ2 T-cell-mediated death of human HCC cells [64]. Zoledronate increases HCC cell sensitivity to Vγ9Vδ2 T lymphocyte-mediated killing [65]. Although the roles of different subsets of γδ T cells are extensively explored in HCC, the potential immunotherapies based on γδ T cells require further investigation.

γδ T cells in liver regeneration

Regeneration is a unique feature of the liver compared with other organs and is important for rescuing liver function after hepatic resection or in acute and chronic liver disease. Multiple cytokines, including IL-6, IL-22, and TNF-α, act to promote liver regeneration [66]. Recently, liver regeneration is significantly impaired in IL-17A KO mice compared with the wild-type mice following partial hepatectomy [24,67]. Hepatic γδ T cells increase within the first three hours but return to baseline six hours after partial hepatectomy. Hepatocyte proliferation is markedly impaired in $TCR\delta^{-/-}$ mice and is accompanied by low levels of IL-17A and IL-22. Mechanistically, hepatic γδ T cells induce a proregenerative phenotype in inflammatory hepatic cells through IL-17A and accelerate liver regeneration through IL-22. Moreover, dectin-1 is upregulated in hepatic γδ T cells in a regenerating liver. Dectin-1 ligation induces IL-22 and IL-17A production in hepatic γδ T cells. Therefore, the dectin-1–γδ T cells–IL-17A/IL-22 axis promotes liver regeneration. These findings may be helpful in understanding the roles of hepatic γδ T cell in the maintenance of physiological homeostasis in the liver. Interestingly, evidence suggests that the microbiota not only enhance hepatic IL-17A-producing γδ T cell homeostasis but also promote liver regeneration [25,68]. Therefore, the role of the microbiota in liver regeneration may depend on hepatic γδ T cells.

Conclusions and perspectives

γδ T cells exhibit strong immune defenses against tumors and viral infections and have been employed in treating cancers and infectious diseases [69,70]. In the liver, γδ T cells not only protect the liver against infections and carcinogenesis but also contribute to immune-mediated liver damage. Although these findings have significantly enhanced our understanding of the roles of γδ T cells in liver diseases, further studies are still required to elucidate the following: (1) subsets of hepatic γδ T cells other than IFN-γ- and IL-17A-producing γδ T cells, (2) the interaction of hepatic γδ T cells with other intrahepatic cells during the response, (3) the contribution of hepatic γδ T cells to hepatic immune-tolerant status in physiology, (4) the presence and the specific marker(s) of liver-resident γδ T cells, (5) the origin and development of liver-resident γδ T cells, and (6) the tissue-specific regulators of functional polarization of liver-resident γδ T cells. Clarification on the basic biology and functions of hepatic γδ T cells is essential for the development of improved γδ T cell-based therapeutic strategies for liver diseases.

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Compliance with ethics guidelines

Xuefu Wang and Zhigang Tian declare no conflicts of interests. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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