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## Role of $\gamma\delta$ T cells in liver diseases and its relationship with intestinal microbiota

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### Abstract

$\gamma\delta$ T cells are unconventional T lymphocytes that bridge innate and adaptive immunity. Based on the composition of T cell receptor and the cytokines produced,  $\gamma\delta$ T cells can be divided into diverse subsets that may be present at different locations, including the liver, epithelial layer of the gut, the dermis and so on. Many of these cells perform specific functions in liver diseases, such as viral hepatitis, autoimmune liver diseases, non-alcoholic fatty liver disease, liver cirrhosis and liver cancers. In this review, we discuss the distribution, subsets, functions of  $\gamma\delta$ T cells and the relationship between the microbiota and  $\gamma\delta$ T cells in common hepatic diseases. As  $\gamma\delta$ T cells have been used to cure hematological and solid tumors, we are interested in  $\gamma\delta$ T cell-based immunotherapies to treat liver diseases.

**Key words:**  $\gamma\delta$ T cells; Liver diseases; Viral hepatitis; Autoimmune liver disease; Non-alcoholic fatty liver disease; Liver cirrhosis; Liver cancer; Intestinal microbiota

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**Core tip:**  $\gamma\delta$ T cells are unconventional T lymphocytes that bridge innate and adaptive immunity. These cells are enriched in epithelial layers of different tissues and the peripheral blood. They have been used in hematological and solid tumors for immunotherapies. The effects of  $\gamma\delta$ T cells in liver diseases depend on subsets, mechanisms and different stages of diseases. We herein discuss the distribution, subsets, functions of  $\gamma\delta$ T cells and the relationship between the microbiota and  $\gamma\delta$ T cells in common hepatic diseases.

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## INTRODUCTION

The liver receives approximately 1.5 L of blood from the portal vein and hepatic artery<sup>[1]</sup>. The liver is the major location of immune responses, metabolic activities and the clearance of toxins<sup>[2]</sup>. It acts as a sentinel, guarding against pathogen components such as lipopolysaccharide from the gut, and is enriched in innate immune cells, including Kupffer cells, natural killer (NK) cells and natural killer T (NKT) cells and adaptive immune cells, such as T lymphocytes, as well as the cytokines they secrete<sup>[3]</sup>. In dysregulated hepatic immune conditions, patients die from infections that occur in end-stage liver diseases, such as acute and chronic liver failure (ACLF), liver cirrhosis and liver cancer. Moreover, tumor cells escape immune surveillance, leading to metastasis.  $\gamma\delta$ T cells account for a tiny proportion of immune cells in peripheral blood; however, they are abundant in the human liver. These cells are both protective and pathogenic in different liver diseases<sup>[4]</sup>. In recent years,  $\gamma\delta$ T cells have attracted increasing attention. In this review, we will explore the properties and roles of  $\gamma\delta$ T cells in the peripheral blood and liver in diverse hepatic diseases (Table 1).

## $\gamma\delta$ T CELLS

$\gamma\delta$ T cells develop before other T cells in all vertebrates. They serve as neonatal protectors when the functions of  $\alpha\beta$ T cells are impaired and act as antigen presenting cells<sup>[5]</sup>.  $\gamma\delta$ T cells are 15%-25% of the T lymphocyte population and 3%-5% of total lymphocytes in the liver; however, the highest frequency of  $\gamma\delta$ T cells is seen in the gut mucosa<sup>[6]</sup>. The frequency of  $\gamma\delta$ T cells in the liver outnumbers that in the peripheral blood<sup>[1]</sup>.  $\gamma\delta$ T cells are unconventional T lymphocytes with unique properties that bridge the innate and adaptive immunity. They express  $\gamma\delta$ T cell receptor (TCR) and do not require antigen presentation with the help of major histocompatibility complex<sup>[7]</sup>. These cells recognize major histocompatibility complex class I chain-related antigens A and B (MICA and MICB) and nonpeptide metabolites of isoprenoid biosynthesis<sup>[7]</sup>.  $\gamma\delta$ T cells are also activated by cytokines without TCR stimulation, which allows them to act earlier than  $\alpha\beta$ T cells.

Human  $\gamma\delta$ T cells can be divided into three groups according to their  $\delta$  chain expression<sup>[7]</sup>. Approximately 56.4% of hepatic  $\gamma\delta$ T cells express V $\delta$ 2+ chains, whereas approximately 8.9% of hepatic  $\gamma\delta$ T cells express V $\delta$ 1+ chains<sup>[8]</sup>. The V $\delta$ 1+ chain usually combines with V $\gamma$ 2, $\gamma$ 3, $\gamma$ 4, $\gamma$ 5 and  $\gamma$ 8 chains<sup>[9]</sup>, and the abovementioned subsets are mainly located in the epithelial layer of the gut, dermis, liver and spleen to maintain the integrity of epithelial tissue<sup>[9,10]</sup>. The CD1 family members are the ligands for V $\delta$ 1 T cells. Moreover, intestinal epithelial V $\delta$ 1 recognizes MICA or MICB through the TCR and NKG2D<sup>[9]</sup>. V $\delta$ 1 T cells usually proliferate during intracellular infections, fungal infections, viral infections and celiac disease<sup>[11]</sup>. V $\delta$ 2 T cells exclusively pair with the V $\gamma$ 9 chain (also termed V $\gamma$ 9V $\delta$ 2 T cells), which are mainly present in the peripheral blood and make up over 90% of peripheral circulating  $\gamma\delta$ T cells<sup>[11]</sup> and 1%-5% of circulating T cells<sup>[7]</sup>. V $\delta$ 2 T cells usually expand during microbial infections<sup>[11]</sup>. V $\delta$ 2+ T cells can be divided into V $\gamma$ 9+V $\delta$ 2+ and V $\gamma$ 9-V $\delta$ 2+ subsets<sup>[11]</sup>. The ligands for V $\gamma$ 9V $\delta$ 2 T cells are phosphoantigens on microbes and transformed cells. Intermediate metabolites of microbial isoprenoid biosynthesis, (E)-4-Hydroxy-3-methyl-but-2-enyl pyrophosphate, an isopentenyl pyrophosphate that is produced *via* the mevalonate pathway by transformed cells, activate these cells in a TCR-dependent manner. F1-ATPase expressed by tumor cells and butyrophilin3A1 are antigen-recognition molecules essential to V $\gamma$ 9V $\delta$ 2 T cells activation<sup>[9]</sup>. Toll-like receptors (TLRs) and natural killer receptors coordinate with the TCR to stimulate V $\gamma$ 9V $\delta$ 2 T cells. For example, pathogen-associated molecular patterns activate V $\gamma$ 9V $\delta$ 2 T cells through TLRs and induce cytokines and chemokines. V $\gamma$ 9V $\delta$ 2 T cells can also recognize MICA/MICB and UL-16 binding protein through NKG2D. DNAM-1, a kind of natural killer receptor that recognizes nectin-like-5, also participates in V $\gamma$ 9V $\delta$ 2 T cells activation. Toxic shock syndrome toxin and staphylococcal enterotoxins are

Table 1 The roles of  $\gamma\delta$ T cells in liver diseases

Liver diseases	Mechanisms of $\gamma\delta$ T cells	Functions
Viral hepatitis	Production of IFN- $\gamma$ , TNF- $\alpha$ ; Expression of CD107a; Downregulation of IL-17, IL-22	Amelioration
	Exhaustion of CD8+T cells; Production of IL-17 and TNF- $\alpha$	Aggravation
Liver bacterial, fungal and parasitic infections	Production of IL-9, IL-17, TNF- $\alpha$	Protection
Autoimmune liver diseases	Production of IL-10 and granzymes; Expression of CD39, CD73, NKG2D; Downregulation of NKT cells	Amelioration
	Expression of IL-17; Apoptosis of Tregs	Aggravation
Nonalcoholic fatty liver disease	Expression of IL-17	Aggravation
Liver fibrosis and cirrhosis	Expression of IL-17	Aggravation
	Apoptosis of HSC	Amelioration
Liver tumors	Expression of Ia and LFA-1, CD56 and CD161; Production of IFN- $\gamma$ , perforin	Anti-tumor

IFN- $\gamma$ : Interferon- $\gamma$ ; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; IL-17: Interleukin-17; NKT: Natural killer T; HSC: Hepatic stellate cells.

superantigens that are involved in V $\gamma$ 9V $\delta$ 2 T cell activation<sup>[9]</sup>. Zoledronate is used to stimulate V $\gamma$ 9V $\delta$ 2 T cells as an immunotherapy against solid tumors and is receiving increasing attention<sup>[1]</sup>. Activated V $\gamma$ 9V $\delta$ 2 T cells not only play an important role in cytotoxicity and promoting inflammatory processes, but also induce differentiation and maturation of innate immune cells *via* chemoattractant cytokine ligand 3 (CCL3), CCL4 and chemokine (C-X-C motif) ligand 10 (CXCL10)<sup>[1,12]</sup>. The third group of  $\gamma\delta$ T cells are V $\delta$ 3 T cells, which are approximately 0.2% of circulating T cells. These cells are rich in the liver in healthy individuals and in patients with chronic viral infections, such as cytomegalovirus (CMV) and HIV, and leukemias<sup>[9]</sup>. Some V $\delta$ 3 T cells recognize glycolipids presented by CD1d<sup>[1]</sup>.

Based on the diverse cytokines produced by  $\gamma\delta$ T cells<sup>[6]</sup>, they can be divided into different functional subsets through stimulation. Differentiation requires transcription factors such as T-bet and eomesodermin for interferon- $\gamma$  (IFN- $\gamma$ ) expression and retinoic acid-related orphan receptor and Runx1 for interleukin-17 (IL-17) expression<sup>[13-15]</sup>. The IFN- $\gamma$ -producing subset express the V $\delta$ 1 or V $\gamma$ 9V $\delta$ 2 chains<sup>[6]</sup>. Qureshi *et al*<sup>[16]</sup> support the observations that  $\gamma\delta$ T cells and NK cells are the producers of IFN- $\gamma$  in the early immune response, which is followed by the cellular immune response.  $\gamma\delta$ T cells also act as T regulatory cells (termed  $\gamma\delta$ Treg cells). These cells inhibit peripheral blood mononuclear cell proliferation<sup>[9]</sup>. Approximately 70%-90% of  $\gamma\delta$ T cells express CD27, and 10%-30% of  $\gamma\delta$ T cells are CD27<sup>-</sup><sup>[15]</sup>. IL-17-secreting  $\gamma\delta$ T cells, also called  $\gamma\delta$ T17 cells, are mainly located in lymphoid organs and peripheral tissues<sup>[17,18]</sup>.  $\gamma\delta$ T17 cells are CD27<sup>-</sup> but express C-C motif receptor 6 (CCR6) and CD25<sup>[15,19]</sup>.  $\gamma\delta$ T17 cells play a pathogenic role in infection and autoimmune diseases. Scavenger receptor SCART2<sup>high</sup>  $\gamma\delta$ T cells belong to a new subset of activated  $\gamma\delta$ T17 cells<sup>[20]</sup> and appear under noninflammatory conditions.

## T CELLS IN THE IMMUNE SYSTEM

As a kind of unique population,  $\gamma\delta$ T cells act as a bridge between innate and adaptive immunity. Their roles in immune responses depend on many aspects, such as the existing locations, the stimuli used to activate and the period of responses<sup>[21]</sup>. Their pleiotropy, such as Th1 and Th2 phenotypes, is determined by specific stimuli and cytokines in the microenvironment, and is exhibited at different stages of immune responses<sup>[22,23]</sup>. Most of the  $\gamma\delta$ T cells are Th1 phenotype. During the early stage of innate immune response,  $\gamma\delta$ T cells sense the stressed epithelial cells or dendritic cells (DCs), then recruit innate cells, including neutrophils and macrophages, by producing IL-17 and CCL2, respectively<sup>[24]</sup>. During the middle stage of enhanced adaptive response, the interaction between  $\gamma\delta$ T cells and DCs is intensive, leading to the proliferation and polarization of  $\gamma\delta$ T cells and maturation of DCs<sup>[24,25]</sup>.  $\gamma\delta$ T cells regulate B cells to produce a large number of immunoglobulins in the absence of  $\alpha\beta$ T cells. In addition, human V $\gamma$ 9V $\delta$ 2 T cells act as antigen presenting cells and present antigens to CD4+T cells and CD8+T cells, initiating adaptive responses<sup>[22,26]</sup>. Whereas,  $\gamma\delta$ T cells play the opposite roles and kill macrophages and  $\alpha\beta$ T cells and promote

tissue repair by producing IL-10 during the later stage<sup>[21,24]</sup>.

$\gamma\delta$ T cells are also involved in antitumor immune responses. The activated cells exert cytotoxic effects by secreting perforin, granzymes, IFN- $\gamma$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), *etc.*  $\gamma\delta$ T cells influence DCs and  $\alpha\beta$ T cells which regulate the immune responses in killing tumor cells. The combined regimens consisting of zoledronic acid, IL-2 and V $\gamma$ 9V $\delta$ 2 T cells have shown promising effects in clinical trials<sup>[27]</sup>.

## T CELLS IN LIVER DISEASES

### $\gamma\delta$ T cells in hepatitis B/C and other hepatic virus infections

Hepatitis B virus (HBV) infection is one of the major liver diseases in Asian people. Approximately 90% of infants with acute infection gradually develop chronic hepatitis B (CHB). Only about 5% of adults develop CHB, and the remaining adults are acutely infected<sup>[28]</sup>. Among HBV carriers,  $\gamma\delta$ T cells prevented concanavalin A-induced hepatitis in HBV-transgenic mice, indicating that  $\gamma\delta$ T cells can be used to ameliorate liver injury in HBV carriers<sup>[29]</sup>. Moreover, Jia *et al.*<sup>[30]</sup> showed that the percentage of  $\gamma\delta$ T cells in peripheral blood was low, whereas the percentage of intrahepatic  $\gamma\delta$ T cells in the inflamed lobular area was high. The proportion of  $\gamma\delta$ T cells in blood was inversely correlated with acute hepatitis B severity. Circulating  $\gamma\delta$ T cells in acute hepatitis B with an activated memory TemRA phenotype exhibited enhanced cytotoxicity against HBV by producing IFN- $\gamma$  and TNF- $\alpha$ <sup>[30]</sup>. A study showed that the number of  $\gamma\delta$ T cells, especially V $\delta$ 2 T cells, in the liver and peripheral blood of patients with CHB infection decreased during disease progression and during pegylated IFN- $\alpha$  treatment. V $\delta$ 2 T cells have increased production of TNF- $\alpha$  and increased expression of CD107a which enhanced the cytotoxicity of these cells in the case of IFN- $\alpha$  therapy<sup>[31]</sup>. The number of V $\delta$ 2 T cells in immune-activated (IA) patients was lower than that in immune-tolerant or healthy subjects and was negatively correlated with disease severity. These cells downregulated IL-17 and IL-22 production in the microenvironment and ameliorated liver injury in IA patients with CHB<sup>[32]</sup>. Nevertheless, a previous study showed that in an HBV-carrier mouse model, liver  $\gamma\delta$ T cells facilitated HBV-associated tolerance by indirectly inducing antiviral CD8+T cells exhaustion through myeloid-derived suppressor cells infiltration in the liver in an IL-17-dependent manner<sup>[33]</sup>. Moreover, inhibiting the NKG2A-HLA-E pathway-mediated CD8+T cells response prevented  $\gamma\delta$ T cells from inhibiting HBV replication in CHB patients, while the frequency of  $\gamma\delta$ T cells was negatively correlated with HBeAg seroconversion<sup>[32,34]</sup>. In addition, Chen *et al.*<sup>[35]</sup> showed that  $\gamma\delta$ T cells in the blood of HBV-ACLF patients that produced higher amounts of IL-17 and TNF- $\alpha$  were significantly decreased compared to those of patients with CHB and healthy controls. This finding indicated that  $\gamma\delta$ T cells may take part in the pathogenesis of HBV-ACLF due to their inflammatory and cytotoxic properties. Thus, the functions of  $\gamma\delta$ T cells during HBV infection depend on the cell subsets and different stages of disease.

With regard to hepatitis C virus (HCV) infection, approximately 75%-80% of adults who are acutely infected develop chronic hepatitis C infection<sup>[36]</sup>.  $\gamma\delta$ T cells, especially V $\delta$ 1 T cells with an effector phenotype, accumulated in the liver of patients with chronic HCV infection and HIV/HCV-co-infected patients. These V $\delta$ 1 T cells that originated from the peripheral blood homed to the HCV-infected liver, showed a Th1-cytokine-secreting pattern and led to liver necroinflammation<sup>[10,37,38]</sup>. Whereas, V $\gamma$ 9V $\delta$ 2 T cells were decreased in the peripheral blood of these patients<sup>[39]</sup>. Tseng *et al.*<sup>[37]</sup> showed that  $\gamma\delta$ T cells from these patients can be stimulated and produced IFN- $\gamma$  and TNF- $\alpha$  by a cytokine cocktail *in vitro* and are highly cytotoxic to primary hepatocytes, suggesting a pathogenic role for  $\gamma\delta$ T cells in HCV infection. Moreover,  $\gamma\delta$ T cells isolated from liver tissue with viral infection expanded exclusively in the liver but not in peripheral blood<sup>[37]</sup>. Therefore,  $\gamma\delta$ T cells display pathogenic function in HCV-infected individuals.

Lu *et al.*<sup>[40]</sup> demonstrated that liver TCR  $\gamma\delta$ + CD4-CD8- (double negative, DN) T cells with an activated phenotype of CD25-CD28-CD69+ were markedly increased in murine hepatitis virus strain 3 infection and were activated to produce TNF- $\alpha$ , IFN- $\gamma$ , IL-17A and IL-2. These cells were cytotoxic to murine hepatitis virus strain 3-infected hepatocytes *via* the TNF- $\alpha$  pathway, indicating the critical role of TCR  $\gamma\delta$ +DN T cells in viral clearance. Ajuebor *et al.*<sup>[41]</sup> showed that  $\gamma\delta$ T cells accelerated acute liver injury, which was infected with adenovirus expressing the *Escherichia coli* LacZ gene in a CXCL9-CXCR3-dependent mechanism. The reduced level of IFN- $\gamma$  and CXCL9 due to the lack of  $\gamma\delta$ T cells and hepatocytes, respectively, may contribute to alleviation of liver injury.



### **$\gamma\delta$ T cells in liver bacterial, fungal and parasitic infections**

$\gamma\delta$ T cells were the main producers of IL-17 during *Schistosoma japonicum* infection in the liver, and they were the first line of defense before T helper cell 17 (Th17) reacted. IL-17 contributed to granulomatous inflammation and fibrosis, which were reduced by an anti-IL-17 monoclonal antibody<sup>[42]</sup>. Li *et al*<sup>[43]</sup> showed that IL-9-producing  $\gamma\delta$ T cells played a part in *Schistosoma japonicum* infection in C57BL/6 mouse. Mice that were deficient in  $\gamma\delta$ T cells and infected with *Listeria monocytogenes* developed liver injury due to TNF- $\alpha$  produced by CD8+T cells. This liver pathology was reversed by infusing V $\delta$ 4+  $\gamma\delta$ T cells that secrete IL-10, controlling the proliferation of CD8+ T cells and reducing TNF- $\alpha$  production. Thus,  $\gamma\delta$ T cells protected liver tissue by regulating pathogen-stimulated CD8+ T cells.  $\gamma\delta$ T cells maintained CD8+ T cell homeostasis<sup>[44]</sup>. A study showed that  $\gamma\delta$ T cells were important early in infections, whereas  $\alpha\beta$ T cells played a part later in infection. IL-17 produced by V $\delta$ 4+  $\gamma\delta$ T cells protected against infection. In parasitic infections,  $\gamma\delta$ T cells were also protective.

### **$\gamma\delta$ T cells in autoimmune liver diseases**

Autoimmune liver diseases are chronic liver diseases caused by immune dysfunction. They consist of autoimmune hepatitis (AIH), primary biliary cholangitis, primary sclerosing cholangitis (PSC) and overlap syndrome. AIH is characterized by interface hepatitis, increased transaminase and immunoglobulin G and various autoantibodies<sup>[45]</sup>. Primary biliary cholangitis is characterized by destruction of intrahepatic bile ducts and cholestasis. Without proper treatment it will advance to end-stage liver disease<sup>[46]</sup>. PSC is distinguished by biliary inflammation and fibrosis. The most common symptoms are hepatomegaly and splenomegaly<sup>[47]</sup>.  $\gamma\delta$ T cells have been shown to play immunoregulatory roles in different studies<sup>[48]</sup>, such as in a mouse model of adriamycin-induced nephropathy<sup>[49]</sup>, and in pulmonary fibrosis<sup>[50]</sup>. The number of  $\gamma\delta$ T cells was markedly increased in the blood and portal vein and bile duct proliferation areas in patients with PSC and AIH<sup>[51]</sup>. Peripheral V $\delta$ 1 T cells that produce IFN- $\gamma$  and granzyme B were the main subtype, whereas V $\delta$ 2 T cells were low in AIH patients. In a scurfy transfer model, CD62L<sup>lo</sup>CD44<sup>hi</sup>  $\gamma\delta$ T cells in TCR $\alpha^{-/-}$  mice prevented multi-organ autoimmune diseases before transfer. These cells produced the immunosuppressive cytokine IL-10 and granzymes, and highly expressed CD39 and CD73, which resembled the pattern of ectoenzyme-mediated degradation of ATP to adenosine that was seen in Foxp3+ Tregs cells<sup>[52]</sup>.  $\gamma\delta$ T cells also exerted suppressive functions *via* NKG2D, which is expressed by NK cells, NKT cells and  $\gamma\delta$ T cells.  $\gamma\delta$ T17 cells acted as protectors in autoimmune liver diseases. IL-17A produced by V $\gamma$ 4+  $\gamma\delta$ T cells prevented concanavalin A-induced fulminant hepatitis by downregulating NKT cells and IFN- $\gamma$  production<sup>[6]</sup>. However,  $\gamma\delta$ T17 cells also played an opposite role in the immunopathology of liver diseases<sup>[1]</sup>. IL-17 produced by these cells, rather than Th17 cells, contributed to hepatic inflammation in a mouse model of biliary atresia (BA) and in BA patients<sup>[5]</sup>. The pathogenesis of BA is not fully understood; however, experiments show that the autoimmune process may be involved. Neutralization of IL-17 alleviated the severity of liver inflammation in BA and ultimately protects against liver fibrosis<sup>[5]</sup>.  $\gamma\delta$ T cells also induced Treg cell apoptosis and reversed Treg cell functions to promote effector T cells activities and lead to autoimmune liver diseases<sup>[48]</sup>. The functions of  $\gamma\delta$ T cells vary from situation to situation. These cells serve as promising immunotherapies in clinical trials for cancer, and whether  $\gamma\delta$ T cells can be used in autoimmune liver disease treatment remains to be elucidated.

### **$\gamma\delta$ T cells in non-alcoholic fatty liver disease**

Nonalcoholic fatty liver disease (NAFLD) is one of the metabolic diseases which includes different stages, ranging from hepatic steatosis to steatohepatitis. NAFLD results from multiple factors, and hepatic  $\gamma\delta$ T17 cells that exacerbate steatohepatitis are one of the important mechanisms<sup>[53,54]</sup>. The  $\gamma\delta$ T cells recruited to the liver were mainly  $\gamma\delta$ T17 cells, which aggravated NAFLD by regulating CD4+T cells<sup>[55]</sup>. Although He *et al*<sup>[56]</sup> only mentioned that the expression of IL-17 by Th17 cells declined, hepatic  $\gamma\delta$ T cells also decreased in lentiviral vectors encoding pre-Mir-26a-treated mice after high fat diet feeding, suggesting an improvement in NAFLD. We hypothesize that IL-17 secreted by  $\gamma\delta$ T cells may also play a part in the pathogenesis of NAFLD. Therefore,  $\gamma\delta$ T17 cells promote NAFLD progression.

### **$\gamma\delta$ T cells in liver fibrosis and cirrhosis**

Liver cirrhosis is the outcome of many chronic liver diseases, such as HBV infection in Asia and HCV infection and alcohol abuse in developed countries. The process involves necroinflammation, activation and accumulation of hepatic stellate cells (HSC) and fibrosis<sup>[57]</sup>.  $\gamma\delta$ T cells are a primary cell type found in the portal area of liver cirrhosis patients<sup>[58]</sup>. These cells produce IL-17, which facilitated fibrosis progression by activating HSC and Kupffer cells<sup>[59,60]</sup>. In mice infected with *Schistosoma japonicum*,

Zheng *et al*<sup>[61]</sup> found that  $\gamma\delta$ T cells recruited neutrophils to the liver and caused liver fibrosis by producing IL-17A. Wang *et al*<sup>[62]</sup> also demonstrated that the HMGB1-TLR4-IL23-IL17 axis between macrophages and  $\gamma\delta$ T cells exacerbated liver inflammation. In the presence of IL-23 and IL-1 $\beta$ , the interaction between exosomes and TLR3 in HSCs promoted increased production of IL-17A by  $\gamma\delta$ T cells, which activated HSCs and exacerbated liver fibrosis at an early stage<sup>[63]</sup>. Ni *et al*<sup>[64]</sup> argued that enhanced expression of IL-17A may occur directly from exosomes. Moreover, TLR4 but not TLR3 is expressed in HSCs. A previous study showed that TLR3 is protective against liver fibrosis<sup>[65]</sup>. However, another study showed that CCR6-expressing  $\gamma\delta$ T17 cells in the injured liver hamper liver inflammation and fibrosis by the induction of HSC apoptosis through Fas/Fas-ligand (FasL) interactions<sup>[66]</sup>. In addition,  $\gamma\delta$ T cells, especially IFN- $\gamma$ -producing  $\gamma\delta$ T cells, also exert protective functions against liver fibrosis by killing activated HSCs in a NKp46-, TRAIL- and Fas-ligand-dependent manner directly or indirectly by promoting NK cell-associated cytotoxicity against HSCs<sup>[67]</sup>. Therefore, the opposite effects of  $\gamma\delta$ T cells on liver fibrosis and cirrhosis are associated with the underlying mechanisms.

### **$\gamma\delta$ T cells in liver tumors**

Liver cancers are one of the most common cancers worldwide. Many chronic liver diseases, such as HBV and HCV infection, lead to the pathogenesis of liver cancers<sup>[68]</sup>. Viey *et al*<sup>[69]</sup> showed that  $\gamma\delta$ T cells had the ability to infiltrate tumors. Patients with hepatocellular carcinoma (HCC) had an increased number of CCR2-expressing V $\delta$ 1+  $\gamma\delta$ T cells in the liver<sup>[8,70]</sup>.  $\gamma\delta$ T cells expressed lymphocyte-activation markers Ia and LFA-1, indicating an activated status in hepatic tumor-bearing subjects<sup>[71]</sup>. The expression of CD56 and CD161 also increased, revealing cytotoxicity against hepatic tumors<sup>[72]</sup>.  $\gamma\delta$ T cells lysed hepatoma cells and markedly reduced hepatic tumor cells activity *in vitro*<sup>[73]</sup>. V $\delta$ 1+  $\gamma\delta$ T cells produced IFN- $\gamma$  and exerted cytotoxic effects<sup>[74]</sup>. CMV-stimulated V $\delta$ 1+  $\gamma\delta$ T cells inhibited primary HT-29 colonic cancer and metastatic foci such as in the liver compared to those of control mice<sup>[75,76]</sup>. Activated (CD44<sup>high</sup>) V $\gamma$ 4+  $\gamma\delta$ T cells also participated in tumor immune surveillance by secreting increased IFN- $\gamma$  and perforin in TCR $\delta^{-/-}$  mice due to the high level of eomesodermin in V $\gamma$ 4+  $\gamma\delta$ T cells, suggesting a protective role in the tumor immune response<sup>[77]</sup>. Thus, V $\gamma$ 4+  $\gamma\delta$ T cells might be a novel therapy in liver diseases<sup>[78]</sup>. Recently, it was demonstrated that the ratio of peritumoral HSC to  $\gamma\delta$ T cells can be a valuable predictor of the prognosis of HCC after resection and was always positively correlated with tumor progression. In this study,  $\gamma\delta$ T cells inhibited the behavior of progressive HCC<sup>[79]</sup>. Another study showed that in the HCC group who sequentially used radiofrequency ablation/cellular immunotherapy (CIT), the outcome was efficient and safe compared to that of the group using radiofrequency ablation alone; specifically, NK cells and  $\gamma\delta$ T cells had robust cytotoxicity and may prevent the recurrence of HCC<sup>[80]</sup>. Qian *et al*<sup>[81]</sup> found that the combination of cellular immunotherapy not only favored the progression-free survival of HCV-positive HCC patients but also affected long-lasting viral control. Bispecific antibodies such as MT110 boosted the antitumoral effect of  $\gamma\delta$ T cells. Gustafsson *et al*<sup>[82]</sup> reasonably hypothesized that the presentation of  $\gamma\delta$ T cells and TAA to CD8+ cytotoxic T cells may lead to enhanced killing of tumor cells with the help of activated CD4+ helper T cells. Therefore,  $\gamma\delta$ T cells play an antitumor role in liver cancers<sup>[6,83]</sup>.

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## **RELATIONSHIPS BETWEEN LIVER/INTESTINAL T CELLS AND INTESTINAL MICROBIOTA**

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The microbiota plays an important role in maintaining hepatic  $\gamma\delta$ T17 cells homeostasis. The mechanism underlying the abovementioned phenomenon could be attributed to lipid antigens, components of intestinal microbiota, that were presented by hepatocyte CD1d *via* the portal vein, which activated hepatic  $\gamma\delta$ T cells and produced IL-17A. Activated  $\gamma\delta$ T17 cells have been identified to have pro-inflammation and anti-infection abilities, aggravating liver disease<sup>[84,85]</sup>. For example, the quantity of microbiota affected  $\gamma\delta$ T17 cells in the liver, thus accelerating the development of NAFLD<sup>[2]</sup>. In addition, during cholestatic liver diseases the increased intestinal permeability allowed bacterial translocation to the liver, especially *Lactobacillus gasseri*. Accordingly, hepatic  $\gamma\delta$ T cells responded to the microbial stimulus to secrete IL-17A, exacerbating the cholestatic liver diseases<sup>[86]</sup>. Hepatic  $\gamma\delta$ T17 cells showed an active and mature status by expressing CD44<sup>high</sup>CD62L<sup>-</sup>. A study performed on lung cancer demonstrated that the number of  $\gamma\delta$ T cells in the liver decreased in the absence of commensal microbiota. Li *et al*<sup>[2]</sup> demonstrated that *Escherichia coli* alone could restore hepatic  $\gamma\delta$ T17 cells in a dose-dependent manner.

Moreover, supplementation of  $\gamma\delta$ T cells and IL-17A restored immune surveillance in antibiotic-treated mice<sup>[87]</sup>.

$\gamma\delta$ T cells make up 10%-30% of CD3+ T cells in the intestine of healthy subjects<sup>[11]</sup>.  $\gamma\delta$ T cells are important in maintaining homeostasis of the intestinal barrier in order to kill pathogens and prevent bacteria from translocating to the liver. The commensal microbiota residing on the epithelial surface of the gastrointestinal tract modulated intestinal mucosal  $\gamma\delta$ T cells<sup>[88]</sup>. These microbiota induced- $\gamma\delta$ T cells exert their roles in many pathological processes in the initial stage or in the later stage<sup>[85]</sup>. For example, IL-17A produced by  $\gamma\delta$ T cells affected intestinal immunity. In addition, some studies suggested that IL-17A was protective and maintained barrier functions by regulating the tight junction protein occludin in a DSS-induced colitis model<sup>[89]</sup>. A recent study suggested that *Lactobacillus breves* DM9218 directly stimulated  $\gamma\delta$ T17 cells by expressing TLR2 in the colon, leading to beneficial effects on colitis<sup>[88]</sup>. Another study also suggested that the bacterial consortium markedly stimulated the proliferation of  $\gamma\delta$ T17 cells in the colonic lamina propria. Specific beneficial microorganisms, such as *Bifidobacterium* and *Bacillus spp*, promoted TLR2 expression on  $\gamma\delta$ T cells, which led to enhancement of barrier functions<sup>[90]</sup>. *In vitro*, only the *Bacillus* strains but not *Bifidobacterium* promoted TLR2 and IL-17 expression. However, bacteria constituting the families *Prevotellaceae*, *Rhodospirillaceae*, and *Flavobacteriaceae* were inversely related to  $\gamma\delta$ T17 cells in the intestine. Bacteria in the family *Bifidobacteriaceae* were positively correlated with  $\gamma\delta$ T17 cells<sup>[90]</sup>. The communication between intestinal epithelial cells (IEC) and  $\gamma\delta$  intraepithelial lymphocytes (IEL) relied on microbiota and served to maintain homeostasis of intestinal immunity.  $\gamma\delta$ IEL depended on IL-15 produced by IEC which were stimulated by microbiota to sustain their presence and functions. In turn,  $\gamma\delta$ IEL promoted IEC functions, such as maintenance of the epithelial barrier and lysis of invasive pathogens. Moreover, microbial localization impacted the biological behaviors of  $\gamma\delta$ IEL, for instance, enhanced cytotoxicity against deleterious bacteria<sup>[85]</sup>. Microbiota was also involved in the relationship between  $\gamma\delta$ T cells and cutaneous carcinogenesis. Microbial infection resulted in V $\delta$ 2- $\gamma\delta$ T cells residing in tissue epithelial layers. The V $\delta$ 2- $\gamma\delta$ T cells proliferated and secreted IFN- $\gamma$  upon encountering antigens, leading to cancer cell death. On the other hand, the anti-tumor subset could be transformed into the pro-tumor subset with the help of IL-23. Due to a larger intercellular space and subsequent bacterial translocation,  $\gamma\delta$ T17 cells expanded, causing tumorigenesis. IL-17 also inhibited effector T cells through myeloid-derived suppressor cells indirectly<sup>[85]</sup>.

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## CONCLUSION

In brief, the effects of  $\gamma\delta$ T cells in liver disease depend on subsets, mechanisms and different stages of diseases.  $\gamma\delta$ T cells not only show cytotoxicity against viral hepatitis but also exacerbate CHB and HBV-ACLF. These cells also play an antitumor role in liver cancers. This minority of cells is mainly used to treat hematological and solid tumors through the production of IFN- $\gamma$ , TNF, cytotoxic granules, as well as the functions of  $\gamma\delta$ T17 cells.  $\gamma\delta$ T cells that function as carriers for chimeric antigen receptors are being explored due to their reduced risk of side effects. T cells that are engineered with defined  $\gamma\delta$ TCRs are outstanding in cancer treatment. The functions of  $\gamma\delta$ T cells have also been important in various virus infections, especially CMV. We should emphasize their beneficial roles and engineer this type of immune cell in adoptive immunotherapies, such as targeting specific receptors and expanding cytotoxic anticancer immune cells, and then apply these immune treatments not only for liver diseases but also other systemic diseases.

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