

Role of gamma-delta T cells in liver inflammation and fibrosis

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Abstract

Conventional adaptive T cell responses contribute to liver inflammation and fibrogenesis, especially in chronic viral infections and autoimmune hepatitis. However, the role of unconventional gamma-delta ($\gamma\delta$) T cells in liver diseases is less clear. In the past two decades, accumulating evidence revealed that $\gamma\delta$ T cell numbers remarkably increase in the liver upon various inflammatory conditions in mice and humans. More recent studies demonstrated that the functional effect of $\gamma\delta$ T cells on liver disease progression depends on the subsets involved, which can be identified by the expression of distinct T cell receptor chains and of specific cytokines. Fascinatingly, $\gamma\delta$ T cells may have protective as well as pathogenic functions in liver diseases. Interferon γ -producing $\gamma\delta$ T cells, for example, induce apoptosis in hepatocytes but also in hepatic tumor cells; while interleukin-17-expressing $\gamma\delta$ T cells can downregulate pathogenic effector functions of other immune cells and can promote apoptosis of fibrogenic stellate cells. However, the results obtained in human liver disease as well as murine models are not fully conclusive at present, and the effects of $\gamma\delta$ T cells on the outcome of liver disease might vary dependent on etiology and stage of disease. Further definitions of the $\gamma\delta$ T cell subsets in-

involved in acute and chronic liver inflammation, as well as their effector cytokines might uncover whether interference with $\gamma\delta$ T cells could be a useful target for the treatment of liver disease.

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Core tip: The liver is particularly enriched in unconventional T cells expressing the gamma-delta T cell receptor and the functional role of these gamma-delta ($\gamma\delta$) T cells in liver diseases is being intensively investigated at present. $\gamma\delta$ T cells accumulate in inflamed liver and their function appears highly dependent on the distinct subsets. In principle, $\gamma\delta$ T cells can be protective as well as pathogenic in the context of liver inflammation. This review summarizes the current knowledge of $\gamma\delta$ T cell effector functions and the cytokines produced by these cells in human liver diseases and murine experimental models of acute and chronic liver injury.

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INTRODUCTION

Despite its various metabolic functions, the liver is also an important immunological organ. The blood coming from the gastrointestinal tract *via* the portal vein carries manifold potential antigens, derived from the commensal microflora of the gut, food or invading pathogens^[1]. Hepatic leukocytes are able to either mount immune responses against pathogenic antigens or to induce tolerance against harmless substances^[2]. Innate immune cells are important

triggers of hepatic inflammation and it is well known that the liver is selectively enriched in macrophages (Kupffer cells), natural killer (NK) and natural killer T (NKT) cells, and also one of the richest sources for gamma/delta T cells ($\gamma\delta$ T cells) in the body^[3,4]. About 15%-25% of the hepatic T cells express the gamma/delta T cell receptor (TCR), indicating that this specific lymphocyte population might exert important functions in liver homeostasis and diseases. Moreover, the liver is also a site of extrathymic generation of $\gamma\delta$ T cells during human fetal development, where the first transcripts of $\gamma\delta$ TCR genes appear before a functional thymus is developed^[5]. $\gamma\delta$ T cells are a specific subpopulation of non-conventional T cells that are identified by expression of the $\gamma\delta$ TCR instead of the $\alpha\beta$ TCR^[6,7]. In secondary lymphoid organs they account for only 2%-3% of all CD3⁺ cells, while the highest abundance of $\gamma\delta$ T cells is seen in the gut mucosa^[8].

$\gamma\delta$ T cells are often described to link innate and adaptive immunity as they share features with innate immune cells as well as with conventional T cells of the adaptive immune system^[9,10]. In contrast to $\alpha\beta$ T cells, $\gamma\delta$ T cells leave the thymus after their maturation as mature T cells with a defined functional potential in a so-called pre-activated status^[11]. Although $\gamma\delta$ T cells are able to recognize antigens presented on MHC molecules, they express only a restricted TCR repertoire and also recognize a lot of non-peptide ligands without the need for TCR engagement^[12,13]. In the periphery, $\gamma\delta$ T cells can also be sufficiently activated through cytokines without TCR engagement, allowing them to respond much faster than $\alpha\beta$ T cells. Similar to conventional T cells, $\gamma\delta$ T cells can kill target cells *via* death receptor mediated apoptosis or release of cytolytic granules^[14,15]. They also produce large amounts of immunomodulatory cytokines, including interferon (IFN) γ , interleukin (IL)-17, IL-4, IL-5, IL-10, IL-13, TGF β and GM-CSF^[16].

According to their functional potential, $\gamma\delta$ T cells can be subdivided into different effector populations. $\gamma\delta$ T cells expressing a specific cytokine or with particular tissue localization often show a bias towards use of the same TCR V gene segments. IFN γ secreting $\gamma\delta$ T cells, for example, often express V δ 1 or V γ 9V δ 2 chains^[17-19], while $\gamma\delta$ T cells expressing V γ 4 are frequently associated with production of IL-17^[20,21] and/or IL-10^[19]. In mice, these subtypes can also be distinguished by expression of surface markers, with the IFN γ secreting subpopulation expressing NK1.1 and CD27^[11,22], while the IL-17⁺ subpopulation expresses CCR6 and CD25^[22]. Interestingly, $\gamma\delta$ T cells have been shown to be the major source of IL-17 in different immune-mediated diseases, often producing much higher amounts of this cytokine than (conventional) CD4⁺ Th17 cells, even if responding in similar or lower numbers than Th17 cells^[23,24].

The functional role of $\gamma\delta$ T cells during the pathogenesis of inflammatory disorders seems to be very diverse as they have been associated with pathogenic as well as protective functions, depending on the inflamed organ and disease model studied. In experimental glomerulonephritis, collagen-induced arthritis or

experimental silicosis, for example, $\gamma\delta$ T cells promote disease progression through production of IL-17^[25-27]. In contrast, during adriamycin-induced nephropathy or concanavalin A-induced hepatitis, $\gamma\delta$ T cells play a protective role through downregulation of the pathogenic functions of CD4⁺ or NKT cells, respectively^[20,28].

In recent years, a number of studies using material from patients with liver diseases as well as experimental models of liver injury revealed that $\gamma\delta$ T cell subsets are altered during the progression of liver diseases, indicating that this unconventional lymphocyte population might be of utmost importance for determining the fate of inflammatory processes in the liver. In this review article, we aim to present and discuss the current knowledge about the functional role of $\gamma\delta$ T cells and their subsets in the pathogenesis of liver disease in mice and humans, as well as possible mechanisms of their pro- or anti-inflammatory activities in the context of liver diseases (Table 1).

AUTOIMMUNE LIVER DISEASE

$\gamma\delta$ T cells were already implicated in human autoimmune liver diseases two decades ago. Patients with primary sclerosing cholangitis or autoimmune hepatitis have been shown to display elevated numbers of $\gamma\delta$ T cells in blood and liver when compared to healthy controls^[29]. In the liver, $\gamma\delta$ T cells were predominantly found in portal infiltrates and areas of bile duct proliferation or fibrogenesis, but the exact contribution of these cells to liver immunopathology remained elusive. Further insight into the functional role of $\gamma\delta$ T cells in autoimmune hepatitis was provided more recently in a study of Zhao *et al.*^[20] by using the mouse model of concanavalin A (ConA)-induced fulminant hepatitis. This disease model of rapid liver inflammation and necrosis is dependent on the activation of CD4⁺ T cells^[30] and the role of IL-17 in this condition is controversially discussed (reviewed in^[31]). In this study, the authors suggest a protective role of IL-17 produced by V γ 4⁺ $\gamma\delta$ T cells through downregulation of the pathogenic function of NKT cells. NKT cells accumulate early after injury in the liver and promote the initiation of inflammatory responses and subsequent tissue damage by releasing pro-inflammatory cytokines^[32]. V γ 4⁺ $\gamma\delta$ T cells were the primary source of IL-17 in ConA-induced hepatitis and adoptive transfer of wild type (wt) $\gamma\delta$ T cells was able to reduce the aggravated disease phenotype in $\gamma\delta$ T cell deficient mice, associated with higher liver damage and IFN γ levels, to the level of wt mice. This function was critically dependent on IL-17 as this effect could not be observed when TCR δ ^{-/-} mice were reconstituted with IL-17^{-/-} $\gamma\delta$ T cells^[20]. These data indicate possible protective functions of IL-17⁺ $\gamma\delta$ T cells *via* NKT cell inhibition in immune-mediated liver diseases such as autoimmune hepatitis (Table 1).

VIRAL INFECTION

The essential role of T cell mediated immune responses

Table 1 Role of gamma-delta T cells in human and experimental liver disease

Species	Liver disease	TCR usage	Cytokine production	Other markers	Effector function(s)	Ref.
Protective functions of $\gamma\delta$ T cells						
Mouse	Concanavalin A-induced hepatitis	V γ 4	IL-17		$\gamma\delta$ T cells inhibit NKT cell function	[20]
Mouse	Experimental fibrosis	V γ 4?	IL-17, IL-22	CCR6, CD95L	$\gamma\delta$ T cells induce stellate cell apoptosis and limit collagen production	[47]
Mouse	Listeria monocytogenes infection	V γ 4	IL-10		$\gamma\delta$ T cells downregulate CD8 ⁺ T cell effector function	[39]
		V γ 4/V γ 6	IL-17		$\gamma\delta$ T cells are protective during early infection	[24]
Human	Liver metastasis of colon cancer	V δ 1	IFN γ , TNF α , IL-2	CD56, CD161	hepatic $\gamma\delta$ T cells are cytotoxic against tumor cell lines in culture	[17]
Human	Pediatric tumor cell culture	V γ 9V δ 2	?		$\gamma\delta$ T cells are cytotoxic against hepatoma cells in culture	[18]
Mouse	Adenoviral infection	V γ 4	IL-17		$\gamma\delta$ T cells are critical for establishment of functional adaptive immune responses	[21]
Pathogenic functions of $\gamma\delta$ T cells						
Mouse	<i>Schistosoma japonicum</i> infection	?	IL-17		$\gamma\delta$ T cells contribute to immune-mediated pathology	[40]
Mouse	Adenoviral infection	?	IFN- γ	CXCR3	$\gamma\delta$ T cells contribute to hepatocyte apoptosis <i>via</i> FasL engagement and recruitment of cytotoxic T cells	[37]
Mouse	MHV infection	?	TNF- α , IFN- γ , IL-17, IL-2	CD69, CD44	$\gamma\delta$ T cells induce hepatocyte apoptosis <i>via</i> TNF- α -signaling	[38]
Human	HCV infection	V δ 1	IFN- γ	H L A - D R , CD95, CD45-RO	Activated $\gamma\delta$ T cells contribute to HCV-mediated immunopathology	[19]

$\gamma\delta$ T cells: Gamma-delta T cells; IFN: Interferon; IL: Interleukin; TNF: Tumor necrosis factor; MHV: Mouse hepatitis virus; HCV: Hepatitis C virus.

in either clearing viral hepatitis or allowing persistent chronic infections is well established^[33]. However, less data exist on $\gamma\delta$ T cells in hepatitis B or C. In patients with chronic hepatitis B virus (HBV) infection, intra-hepatic as well as peripheral $\gamma\delta$ T cell numbers inversely correlate with disease severity^[34]. Wu *et al*^[34] showed that mainly V δ 2⁺ $\gamma\delta$ T cells are reduced and that these cells display an effector-memory phenotype with expression of CD45RA, MHC class II molecule human leukocyte antigens (HLA)-DR and CD38. Furthermore, these cells produce high levels of IFN γ but not IL-17 and are able to inhibit cytokine production of pathogenic CD4⁺ Th17 cells through cell contact- as well as IFN γ -dependent mechanisms. Therefore, the authors concluded that reduced numbers of $\gamma\delta$ T cells account for decreased inhibition of Th17 cells, resulting in higher liver damage and pathology.

In contrast, several studies have shown that $\gamma\delta$ T cells are enriched in the livers of patients with chronic hepatitis C virus (HCV) infection when compared to healthy controls or peripheral blood^[19,35,36]. Agrati and colleagues demonstrated that these $\gamma\delta$ T cells are predominantly V δ 1⁺ and display an effector-memory phenotype as they express HLA-DR and CD95^[19]. These cells also produce increased levels of IFN γ during HCV infection and therefore very likely contribute to HCV-induced immunopathology in the liver. Furthermore, an additional study by Tseng *et al*^[36] showed that $\gamma\delta$ T cells isolated from livers of HCV patients are cytotoxic against primary human hepatocytes in culture, suggesting that $\gamma\delta$ T cells might contribute to HCV-triggered liver injury.

A similar effect is seen in mice with adenoviral infection. IFN- γ -producing $\gamma\delta$ T cells accumulate around infected hepatocytes and contribute to hepatocyte death through Fas-mediated apoptosis^[37]. Furthermore,

IFN γ production induces the release of chemokines like CXCL9 by hepatocytes, which further recruits $\gamma\delta$ T cells and CD8⁺ cytotoxic T cells. The importance of $\gamma\delta$ T cells for these pathogenic processes is underlined by the fact that $\gamma\delta$ T cell deficient mice are protected from adenovirus-induced liver injury. However, these mice show no difference in viral clearance. Another study by Hou *et al*^[21] shows that IL-17 producing $\gamma\delta$ T cells also increase in adenovirus-infected murine liver. Consistent with the results obtained in ConA-induced hepatitis, V γ 4⁺ $\gamma\delta$ T cells are the major IL-17 producers and IL-17 secretion by these cells is critical for the development of a functional antiviral immune response and subsequent clearance of the virus.

In mouse hepatitis virus (MHV) infection, $\gamma\delta$ T cells play a clearly pathogenic role but *via* a different mechanism^[38]. Although IFN γ - and IL-17- producing $\gamma\delta$ T cells accumulate in the liver also in this model, their function seems to be rather dependent on tumor necrosis factor (TNF) α -production. Activated hepatic $\gamma\delta$ T cells are cytotoxic against MHV infected hepatocytes but this effect does not require cell-cell contact or IFN γ -/IL-17-signaling, while blockade of TNF α leads to markedly reduced hepatocytotoxicity^[38].

Taken together, the functional role of $\gamma\delta$ T cells during viral infection of the liver seems to be highly dependent on the subset involved. While V δ 1⁺ and V δ 2⁺ T cells are associated with production of IFN γ and progression of liver immunopathology, the V γ 4⁺ IL-17 producing subset of $\gamma\delta$ T cells seems to be rather important for viral clearance. The fact that liver injury during MHV infection is dependent on TNF- α production by $\gamma\delta$ T cells might suggest that a third subset of $\gamma\delta$ T cells is functionally involved in viral-induced liver diseases.

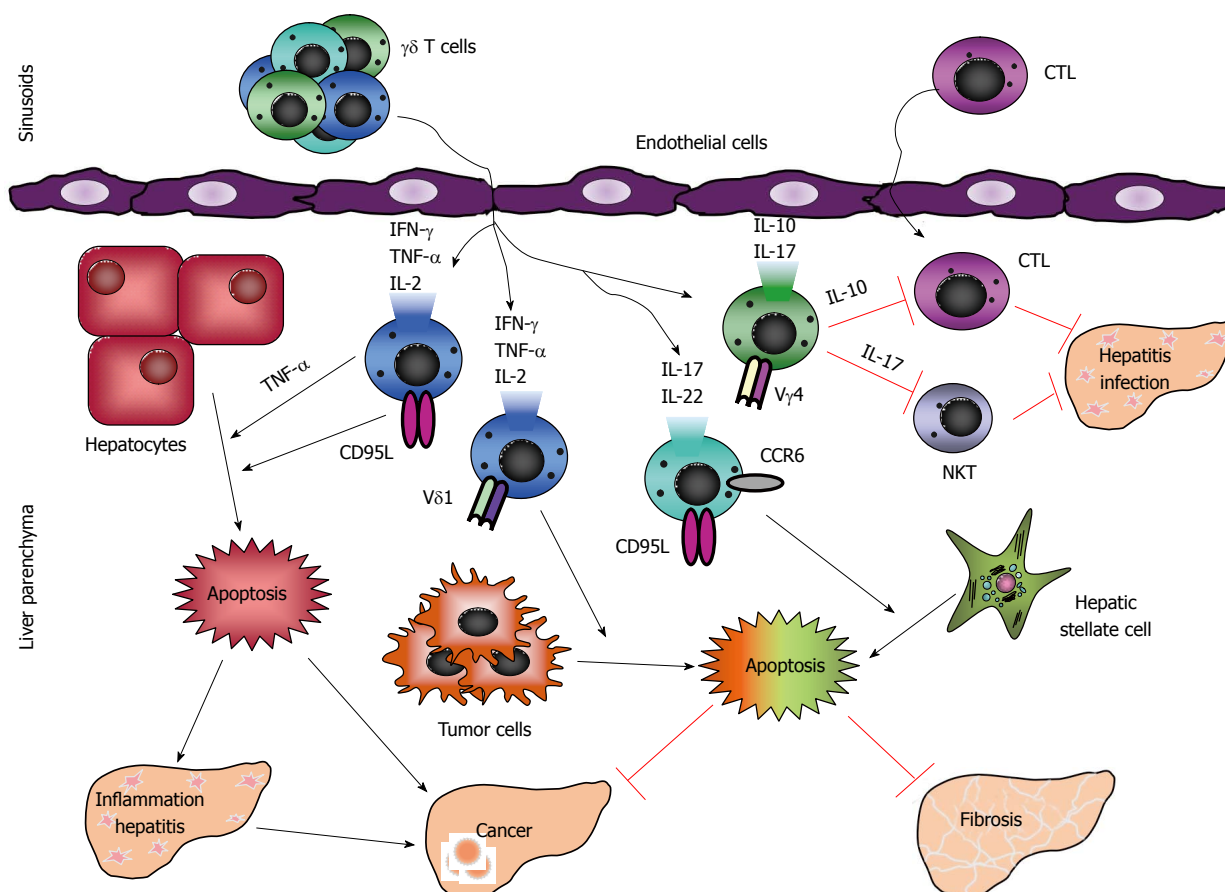


Figure 1 Role of gamma-delta T cells in liver disease. Upon liver damage several subsets of gamma-delta ($\gamma\delta$) T cells are recruited to the liver, where they can exert different functions on numerous cell types, ultimately resulting in protective or pathogenic effects on the outcome of liver disease. Pathogenic effects include induction of hepatocyte apoptosis by interferon (IFN) γ - and/or tumor necrosis factor (TNF) α -producing $\gamma\delta$ T cells, mediated via death receptor signaling (TNF receptors or Fas/CD95). However, the $\text{V}\delta 1^+$ $\text{IFN}\gamma$ -producing subset can also have beneficial functions as they drive tumor cells apoptosis. Other protective functions can be attributed to $\text{V}\gamma 4^+$ T cells, which produce interleukin (IL)-17 and IL-10, and can downregulate pathogenic effector functions of other lymphocytes like natural killer T (NKT) cells or cytotoxic T cells, respectively. IL-17 $^+$ $\gamma\delta$ T cells have also been shown to induce Fas-mediated apoptosis of hepatic stellate cells (the main producer of collagen during hepatofibrogenesis), thereby limiting liver fibrosis.

BACTERIAL AND PARASITIC LIVER INFECTIONS

$\gamma\delta$ T cells have been shown to exert protective functions in bacterial infections of the liver. $\gamma\delta$ T cell deficient mice infected with *Listeria monocytogenes* develop increased liver pathology which is caused by infiltrating $\text{CD}8^+$ T cells producing high levels of $\text{TNF-}\alpha$ ^[39]. This pathogenic effect can be prevented through adoptive transfer of $\text{V}\gamma 4^+$ $\gamma\delta$ T cells. These cells produce high levels of IL-10, which in turn downregulates $\text{TNF-}\alpha$ production in $\text{CD}8^+$ T cells (Figure 1). Furthermore, $\text{V}\gamma 4^+$ T cells are also the major IL-17 producing cell type during *Listeria* infection and $\gamma\delta$ T cell-derived IL-17 is critically needed for protective immunity during early infection^[24]. IL-17 deficient mice reconstituted with $\gamma\delta$ T cell-deficient bone marrow, meaning that $\gamma\delta$ T cells are able to produce IL-17 but $\gamma\delta$ T cells are not, show a much higher bacterial burden in the liver than mice reconstituted with wt bone marrow^[24]. In contrast, during *Schistosoma japonicum* infection IL-17 production by $\gamma\delta$ T cells seems to have a more pathogenic role^[40]. Although $\gamma\delta$ T cells are the major IL-17 produc-

ing cell type also in this model, neutralization of IL-17 reduced liver inflammation and pathology in this case.

During malaria infection, however, $\gamma\delta$ T cells play only a minor role as long as conventional adaptive T cell responses are intact, demonstrated by the fact that $\gamma\delta$ T cell deficient mice survive plasmodium infection without extensive organ failure^[41]. $\gamma\delta$ T cells are needed for protective immunity against the parasite only in mice deficient for $\gamma\delta$ T cells. In this case, depletion of $\gamma\delta$ T cells leads to severe immunopathology because development of the parasite is not inhibited, an effect that can be reversed through adoptive transfer of $\gamma\delta$ T cells^[41].

As described above, $\gamma\delta$ T cells can have opposing effects in different infection models. This further underlines the functional heterogeneity of the different $\gamma\delta$ T cell subsets distinguished by cytokine production or usage of specific receptor chains. The impact that $\gamma\delta$ T cells have on the outcome of different infectious diseases might also be influenced by the nature of the adaptive immune response induced by the microorganism itself as this could change the local cytokine milieu dramatically.

LIVER FIBROSIS

Independent from the underlying etiology of liver disease, such as viral hepatitis, alcoholic and non-alcoholic steatohepatitis or other origins, chronic liver diseases characteristically progress from tissue injury to chronic hepatitis and fibrosis to liver cirrhosis as the end-stage of chronic liver diseases^[42]. Persistent inflammation in the liver is considered the driving force for disease progression. Over recent years, several studies have emphasized the crucial role of various immune cell subsets for controlling inflammation and fibrogenesis in the liver and the interplay between the different leukocyte populations, including monocytes, Kupffer cells, NK/NKT or T lymphocytes, appears to be tightly regulated by cytokines and chemokines^[43,44]. Although IL-17 has been recognized as an important regulatory cytokine in hepatic inflammation^[31], relatively few data exist on the contribution of $\gamma\delta$ T cells to the pathogenesis of liver fibrosis. $\gamma\delta$ T cells accumulate in fibrotic liver and contribute to IL-17 production in different experimental models of chronic liver injury, as well as liver samples of patients with chronic hepatitis^[45,46]. Interestingly, IL-17 itself, produced mainly by $\alpha\beta$ T cells and neutrophils, was found to promote fibrosis progression through activation of hepatic stellate cells (HSC) and Kupffer cells.

In contrast, hepatic $\gamma\delta$ T cells can be associated with protective functions in murine chronic liver injury but these functions appear to be independent from the signature cytokine IL-17. We recently showed that specifically the CCR6 expressing subtype of $\gamma\delta$ T cells, producing IL-17 and IL-22, accumulates in fibrotic livers of mice subjected to experimental liver injury models^[47]. These cells are capable of limiting fibrosis progression through induction of apoptosis in HSC, the major collagen producing cell type in the liver. Nevertheless, this effect does not depend on their IL-17 or IL-22 production but is rather mediated through Fas/Fas-ligand (FasL) interactions. IL-17 deficient $\gamma\delta$ T cells are able to limit liver fibrogenesis to the same extent as wt $\gamma\delta$ T cells and blockade of IL-22 could not reduce HSC apoptosis, while use of a FasL-blocking antibody significantly inhibited HSC apoptosis (Figure 1). Thus, these data indicate that $\gamma\delta$ T cells, at least its CCR6 expressing subset, represent an important anti-fibrotic pathway in hepatic inflammation by ameliorating the inflammatory reaction and the activation of collagen-producing stellate cells in chronically injured liver.

LIVER CANCER

More than two decades ago the first studies showed that $\gamma\delta$ T cells accumulate in tumor bearing liver. Patients with hepatic malignancies as well as tumor bearing mice show elevated levels of $\gamma\delta$ T cells in the liver when compared to healthy controls^[17,48]. Usually these cells display an activated phenotype with expression of CD56, CD161 and LFA-1 and are cytotoxic against hepatoma cells and Daudi targets in culture^[17,18]. Furthermore, murine V δ 1⁺

$\gamma\delta$ T cells induced in response to cytomegalovirus (CMV) infection have been shown to inhibit development of liver metastases in a colon cancer model^[49]. These findings suggest that $\gamma\delta$ T cells might contribute to anti-tumoral immune responses, likely by promoting direct cytotoxic responses to malignant parenchymal cells (Figure 1). However, tumor cells can escape $\gamma\delta$ T cell responses through downregulation of the respective ligands^[18].

Although detailed mechanistical studies on anti-tumoral responses of $\gamma\delta$ T cells in the liver are still lacking, further insight into these mechanism might be provided by a recent study on recruitment of $\gamma\delta$ T cells in the B16 melanoma model^[50]. In this model, $\gamma\delta$ T cells inhibit tumor growth as $\gamma\delta$ T cell-deficient mice develop larger tumors than their wild type counterparts. A similar effect is seen in CCR2- as well as CCL2-deficient mice, which display reduced $\gamma\delta$ T cell infiltrates in B16 lesion and a higher tumor growth rate. Moreover, this study also shows that murine as well as human peripheral $\gamma\delta$ T cells migrate toward CCL2 *in vitro*^[50]. Since this effect could only be observed with V δ 1⁺ but not V δ 2⁺ $\gamma\delta$ T cells, this mechanism might very well also play a role in hepatic malignancies.

CONCLUSION

$\gamma\delta$ T cells have been shown to accumulate in the liver upon various inflammatory conditions which lead to hepatic fibrosis and other types of immunopathology when becoming chronic. The exact contribution of these lymphocytes to liver inflammation seems to be highly dependent on the subsets involved, which can be identified by the specific cytokines they produce and their expression of different T cell receptor chains. $\gamma\delta$ T cells producing IFN γ often co-express TNF α and the V δ 1 chain but usually do not produce IL-17, which is often co-expressed with V γ 4 chains. The effect of these subsets on the outcome of liver disease also depends in part on the underlying liver disease etiology. Accordingly, the IFN γ ⁺ subset is able to induce apoptosis in different cell types, which might have pathogenic or beneficial effects on liver immunopathology depending on whether hepatocytes or tumor cells are affected. In contrast, IL-17 producing $\gamma\delta$ T cells are often associated with protective functions in liver inflammation as they can inhibit pathogenic effector functions of cytotoxic T cells or NKT cells, as well as limit hepatofibrogenesis through inhibition of hepatic stellate cells. Nevertheless, the results obtained in human liver disease as well as murine models are not fully conclusive at present as many studies lack detailed analysis on the correlation of cytokine production with specific surface markers such as TCR chains. Therefore, it is not clear whether the diverse functions that $\gamma\delta$ T cells have during different liver diseases are executed by very few subsets according to the cytokines they produce or by a huge variety of $\gamma\delta$ T cells with redundant cytokine profiles. Thus, it is of utmost importance to further define $\gamma\delta$ T cell subsets in acute and chronic liver inflammation as well as the cytokines they produce in order to assess

whether interference with $\gamma\delta$ T cells might be useful as a therapeutic target for the treatment of liver disease.

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