Hepatic NKT cells: friend or foe?

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ABSTRACT

The innate immune system represents a critical first line of host response to infectious, injurious and inflammatory insults. NKT cells (natural killer T-cells) are an important, but relatively poorly understood, component of the innate immune response. Moreover, NKT cells are enriched within the liver, suggesting that within the hepatic compartment NKT cells probably fulfill important roles in the modulation of the immune response to infection or injury. NKT cells are characterized by their rapid activation and secretion of large amounts of numerous types of cytokines, including those within the Th1-type, Th2-type and Th17-type groups, which in turn can interact with a multitude of other cell types within the liver. In addition, NKT cells are capable of participating in a wide array of effector functions with regards to other cell types via NKT cell-surface-molecule expression [e.g. FASL (FAS ligand) and CD40L (CD40 ligand)] and the release of mediators (e.g. perforin and granzyme) contained in cellular granules, which in turn can activate or destroy other cells (i.e. immune or parenchymal cells) within the liver. Given the huge scope of potential actions that can be mediated by NKT cells, it has become increasingly apparent that NKT cells may fulfill both beneficial (e.g. clearance of virally infected cells) and harmful (e.g. induction of autoimmunity) roles in the setting of liver disease. This review will outline the possible roles which may be played by NKT cells in the setting of specific liver diseases or conditions, and will discuss the NKT cell in the context of its role as either a 'friend' or a 'foe' with respect to the outcome of these liver disorders.

INTRODUCTION

NKT cells [NK (natural killer) T-cells] have been increasingly recognized as major contributors in the development of a diverse array of inflammatory responses. NKT cells were originally named as such because of their co-expression of cell-surface markers typical of conventional T-cells [i.e. TCRs (T-cell receptors)] as well as those expressed on NK cells [1]. Conventional T-cells recognize antigens (namely peptides) presented to them in the context of cell-surface proteins encoded by the MHC. However, NKT cells recognize antigen presented by the MHC class I-related antigen CD1 [1,2]. CD1 molecules (CD1d in the rat and mouse) are adapted for the presentation of lipid antigens (mainly glycolipids) and, hence, NKT cells are activated by lipid antigens which are presented to them by CD1 [2]. NKT cells have been divided into two subtypes. The major subtype of NKT cells, termed Type I or iNKT cells (invariant NKT cells), have a highly conserved invariant αβ TCR encoded by the Vα14 (Vα24 in humans) and Jα18 genes paired with a set of Vβ chains (mainly Vβ8.2, Vβ7 and Vβ2 in mice, and Vβ11 in humans [2]). In contrast, Type II NKT cells (non-invariant NKT cells) express a more diverse TCR repertoire [2,3]. In general, most studies to date have focused upon iNKT cells and, therefore, in this review, when discussing NKT cells, iNKT cells will be implied unless otherwise stated.

NKT cells are an important component of the innate immune response and, as such, respond to infections or...
Hepatic NKT cells are activated by glycolipid antigen (endogenous or exogenous) which has been processed and expressed on the surface of APC (e.g. DCs) in conjunction with the MHC class I-like molecule CD1d. Activated NKT cells are capable of rapidly secreting cytokines contained within the Th1-type (e.g. IFN-γ and TNF-α), Th2-type (e.g. IL-4, IL-5 and IL-13) and Th17-type (e.g. IL-17) groups. Cytokines released from activated NKT cells can have beneficial (e.g. viral clearance) or harmful (e.g. autoimmunity) effects within the liver. MMP, matrix metalloproteinase; PMN, polymorphonuclear cell.

Although NKT cells are known to be activated by glycolipid antigens, the identification of specific NKT-activating antigens has been difficult. α-GalCer (α-galactosylceramide), a glycolipid derived from a marine sponge, was identified over a decade ago and is the most widely used activator of NKT cells [2,11]. More recently, the endogenous lysosomal glycosphingolipid iGb3 (isoglobotrihexosylceramide) has been suggested as being an endogenous activator of NKT cells [12]; however, this has recently been questioned [13]. In addition, a number of exogenous glycolipid NKT cell ligands have recently been identified and include glycolipids derived from some Gram-negative LPS (lipopolysaccharide)-negative bacteria and from the spirochete Borrelia burgdorferi [2,14]. IL-12 derived from activated DCs (dendritic cells) also plays an important role in NKT cell activation [2,15].

NKT cells have been implicated in immune responses against infectious agents and tumours, and in regulating a wide variety of autoimmune and inflammatory diseases [1,2,16]. Although NKT cells can be detected wherever conventional T-cells are found, the highest NKT cell/conventional T-cell ratio is found in the liver [17]. Furthermore, the relative frequency of iNKT cells in the livers of humans and mice differ significantly; specifically, in humans iNKT cells represent approx. 12% and in mice approx. 25–40% of intrahepatic lymphocytes [3,18,19]. In the liver, NKT cells reside mainly within the sinusoids (Figure 3) and can be visualized using intravital microscopy as patrolling through the hepatic sinusoids, crawling at rates of up to 20 μm/min [20]. Moreover, upon T-cell-antigen activation, hepatic NKT cells abruptly stop moving [20]. The reason for the relative enrichment of NKT cells in the liver is unclear, but may reflect in part the high expression of CD1d on Kupffer cells, sinusoidal endothelial cells and hepatocytes [2]. In addition, the cell-surface molecule CD11a appears to be important for the accumulation of NKT cells within the liver, as mice deficient in CD11a have a profound liver-specific reduction in NKT cell numbers [21]. Chemokines are small chemotactic proteins which potently regulate leucocyte trafficking, including the movement of NKT cells [22–24]. NKT cells have high surface expression of a number of chemokine receptors, including CXCR3 and CXCR6 [23,24]. Interestingly, mice deficient in CXCR3 or CXCR6 have striking reductions in hepatic
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Figure 2  Immunoregulatory functions of hepatic NKT cells
Activated NKT cells express CD40L and FASL on their cell surface. FASL can interact with FAS, which is highly expressed on hepatocytes leading to hepatocyte apoptosis or, alternatively, to hepatocyte mitosis in the setting of liver regeneration. CD40L expressed on the surface of activated NKT cells can interact with CD40 expressed on hepatic DCs, leading to DC semi-maturation and tolerance induction, as well as the release of IL-12 from DCs, which induces further activation of NKT cells. Activated NKT cells can also release perforin and granzyme from cytoplasmic granules which can destroy other cells.

Figure 3  Localization of NKT cells within liver sinusoids
Liver section from a CXCR6\(^{\text{gfp}}\) mouse showing GFP\(^{\text{hi}}\) CD1d-restricted NKT cells (bright green cells with white arrows) within the liver sinusoids (yellow arrows). This Figure was reproduced from Geissmann, F., Cameron, T.O., Sidobre, S., Manlongat, N., Kronenberg, M. et al. (2005) Intravascular immune surveillance by CXCR6\(^{+}\) NKT cells patrolling liver sinusoids. PLoS Biol. 3(4), e113. doi:10.1371/journal.pbio.0030113.

NKT cell numbers, suggesting that these chemokine receptors play important roles in the hepatic recruitment and/or retention of NKT cells [20,25]. IL-15 is a novel cytokine which is indispensable for the proliferation, survival and homoeostasis of NKT cells [26]. Recently, Ito cells (hepatic stellate cells) have been identified as important players in the promotion of hepatic NKT cell homoeostatic proliferation through their production and release of IL-15 [27], thereby implicating the Ito cell/IL-15/NKT cell communication pathway in the relative enrichment of NKT cells within the liver.

NKT cells are enriched within the liver and rapidly secrete large amounts of a number of cytokines upon appropriate stimulation (Table 1). Therefore NKT cells are capable of fulfilling a number of immunomodulatory and regulatory roles within the liver during a diverse array of pathological processes and, thereby, may represent a ‘friend’ or ‘foe’ with regards to overall host outcome in response to these insults.

THE HEPATIC NKT CELL AS A ‘FRIEND’

Infection
A role for NKT cells in antimicrobial defence has been suggested by the recent identification of bacterial components as NKT cell ligands [2,14]. However, with regards to liver cell destruction as a consequence of infection, liver damage caused by the hepatitis B and C viruses are of major worldwide concern [28]. Certainly, in keeping with their innate nature, NKT cells are involved in responses to viruses although, unlike bacteria, viruses only contain host lipids [14]. Interestingly, in the mouse, virus infection can down-regulate CD1d expression on DCs, implying a possible viral evasion strategy from
Factors influencing the differential production of Th1- or Th2-type cytokine patterns in NKT cells

NKT cells [29]. In the setting of hepatitis B infection, much of our information comes from the experimental mouse hepatitis B transgenic model. Using this model, an important role for IFNγ secreted from activated hepatic NKT cells (and subsequently transactivated NK cells) has been documented for the inhibition of hepatitis B viral replication [30]. In further studies using this mouse model of hepatitis B infection, Baron and co-workers [31] identified increased numbers of activated IFNγ-producing hepatic NKT cells within the liver. Moreover, they also demonstrated that non-classical CD1d-restricted, but not α-GalCer-reactive, hepatic NKT cells are activated in response to hepatitis B viral antigen-expressing hepatocytes, implicating a possible role for this cell type in hepatitis B viral clearance [31]. Interestingly, in patients, NKT cells appear to be important in the development of an adequate immune response following hepatitis B vaccination [32]. However, in hepatitis-B-infected patients, NKT cells do not appear to be important for a therapeutic response to IFNα therapy [33].

The role of NKT cells in hepatitis C infection and clearance is poorly understood. Numbers of NKT cells appear to be increased within the livers of patients with chronic hepatitis C infection, and these cells express markers suggestive of cellular activation [34,35]. In further studies, increased numbers of non-classical CD1d-reactive IFNγ-producing NKT cells were documented within the livers of hepatitis-C-infected individuals in conjunction with up-regulated CD1d expression within the liver, implying a potential role for these non-classical NKT cells in the clearance of hepatitis-C-infected liver cells [36,37].

Autoimmunity

Given their potent immunomodulatory properties, NKT cells have been implicated in the pathogenesis of a number of autoimmune diseases [38]. IFNγ secreted from NKT cells would be expected to augment autoimmune phenomena, whereas activation of NKT cells to produce increased amounts of Th2-type cytokines has been associated with an improvement in a number of experimental models of autoimmune disease, including EAE (experimental autoimmune encephalomyelitis) and diabetes [38,39]. Moreover, a cross-talk between NKT cells and T<sub>reg</sub> cells (regulatory T-cells) has been suggested, with NKT-cell-derived IL-2 driving increased proliferation of T<sub>reg</sub> cells and enhanced surface expression of CTLA-4 [40]. Given the well-documented immune-suppressing effects of T<sub>reg</sub> cells, increased T<sub>reg</sub> cell numbers would be expected to inhibit autoimmune responses [41]. In addition, activated NKT cells up-regulate surface CD40L (CD40 ligand) expression, which can interact with CD40 expressed on DCs [42]. CD40 stimulation drives the subsequent semi-maturation of DCs, which plays an important role in the development of tolerance and possibly regulates the ultimate predisposition to autoimmune liver disease [43]. However, clinically, the potential role of NKT cells in autoimmune liver diseases has not been well characterized [44]. Interestingly, NKT cell numbers appear to be increased within the liver in the autoimmune liver disease PBC (primary biliary cirrhosis) [45] (although this has been challenged [46]), in association with decreased hepatic T<sub>reg</sub> cell numbers [47]. These observations suggest that defects in NKT cell/T<sub>reg</sub> cell cross-talk with regards to recruitment or maintenance of T<sub>reg</sub> cell populations within the liver may contribute to the development of this autoimmune liver disease and may represent a fruitful area for future investigation.

Tumour rejection

NKT cells have an important role in tumour surveillance, and cancer patients have been reported to have a decrease in the size of their NKT cell pool, a decrease in NKT cell IFNγ production or a decrease in NKT cell proliferative responses to α-GalCer stimulation [48]. Moreover, stimulation of NKT cells protects mice from cancer liver metastasis and suppresses the development of
hepatocellular carcinoma following the adoptive transfer of hepatoma tumour lines in mice [49–51]. This protective effect of NKT cells is attributable to their release of IFNγ upon activation, as well as to NKT-cell-mediated transactivation of NK cells and their subsequent release of IFNγ [49,52]. It is this phenomenon that has sparked clinical interest in the treatment of cancer patients with α-GalCer and with α-GalCer-loaded DCs (to give maximal NKT cell activation) [53–55].

Liver regeneration

The role of NKT cells in hepatic regeneration is somewhat controversial. After partial hepatectomy in the mouse, hepatic NKT cell numbers are increased [56], and decreased hepatocyte mitosis has been observed in hepatectomized CD1d-knockout mice which lack NKT cells [57]. Moreover, activation of hepatic NKT cells with α-GalCer post-hepatectomy increases hepatocyte proliferation and improves hepatic regeneration via a pathway which involves TNFα and FAS/FASL [57]. These findings are consistent with other experimental observations which have also implicated TNFα and FAS activation as playing beneficial roles in hepatic regeneration [58–60]. However, these observations have been challenged by Ito et al. [61], who suggested that activated hepatic NKT cells can cause severe liver injury (as reflected by serum alanine aminotransferase levels, an indirect marker of liver cell damage) post-partial hepatectomy via a TNFα-driven mechanism [61]. Interestingly, IFNγ has been identified as a negative regulator of hepatic regeneration in the murine partial hepatectomy model [62], and hepatic NKT cells as well as NK cells transactivated after NKT cell activation produce significant quantities of IFNγ (as described above). Therefore activated NKT cells may also theoretically inhibit liver regeneration by increasing liver IFNγ levels.

THE HEPATIC NKT CELL AS A ‘FOE’

Infection

Although NKT cells appear to play an important role in the host capacity to deal with infection, NKT cell responses during infection do not always appear to be beneficial. Central to immune clearance of hepatotropic viruses is the elimination of infected hepatocytes during the immune response. Specifically, cytokine- and/or FASL-mediated killing of infected hepatocytes driven by NKT cells, by definition, leads to liver cell death and, if overly robust, could potentially lead to severe liver inflammation and even possibly fulminant liver failure. Moreover, viral hepatitis is characterized pathologically by liver cell death, regeneration and often fibrosis [28]. NKT cells have also been negatively implicated in the hepatic repair and regeneration process. Specifically, using the hepatitis B transgenic mouse model, NKT cells were shown to negatively regulate the regenerative response of the liver to partial hepatectomy, mainly through an IFNγ-mediated effect upon hepatocytes [63]. This finding suggests that activated NKT cells could potentially adversely affect hepatic repair processes in the setting of hepatotrophic viral infection.

The host response to liver cell destruction in the setting of chronic viral hepatitis often results in the deposition of collagen, leading to the development of hepatic fibrosis and ultimately cirrhosis [64,65]. Examination of liver specimens from hepatitis-B- and C-infected patients has revealed increased hepatic NKT cell numbers in chronically infected livers [66]. Moreover, these NKT cells had significant alterations in their effector functions demonstrated by a skewing in their cytokine-producing profiles to a more Th2-type consisting of IL-4 and IL-13 production, cytokines linked to the development of hepatic fibrosis [66]. Interestingly, the increase in hepatic NKT cell numbers in chronic hepatitis-B- and C-infected livers was associated with a striking up-regulation of CD1d expression in APCs (antigen-presenting cells) in cirrhotic livers [66]. These observations suggest that hepatic NKT cells in patients with chronic viral hepatitis may contribute to the development of progressive liver fibrosis via a mechanism that involves an NKT cell CD1d-associated enhancement of pro-fibrinogenic cytokine secretion.

As mentioned above, NKT cells can be activated by exogenous bacterial antigens presented in the context of CD1d [14], and this response would be expected to be of benefit to help with the resolution of infection. However, NKT cell responses have also been implicated in hepatic damage associated with bacterial challenge. Salmonella infection can be associated with the development of hepatitis [67]. Moreover, in a mouse model of Salmonella infection, NKT cells have been directly implicated in the development of elevated serum alanine aminotransferase levels, as well as pathological lesions in the liver, during the course of infection [68]. Further investigations using this model showed that TLR2 (Toll-like receptor 2) expressed on the surface of hepatic NKT cells may be activated during Salmonella infection, and that TLR2 activation leads to enhanced FASL expression on hepatic NKT cells. Increased FASL expression on the surface of NKT cells can then lead to hepatocyte death, presumably by interacting with FAS expressed on the hepatocyte cell surface and the induction of hepatocyte apoptosis [69].

Autoimmunity

NKT cells have been broadly implicated in the regulation of a variety of autoimmune disorders, including lupus, diabetes and multiple sclerosis [38]. However, NKT cells have been directly linked to the development of liver damage in a number of animal models of autoimmune hepatitis, as well as in patients with autoimmune hepatitis and the autoimmune liver disease
PBC. The ConA (concanvalin A) model is a widely utilized mouse model which mimics many aspects of human autoimmune hepatitis [44,70–72]. Using this model, hepatic NKT cells have been directly implicated in the severe hepatitis caused by ConA administration. Specifically, the development of hepatitis after ConA treatment is completely prevented in mice that genetically lack NKT cells [73]. Moreover, hepatic NKT cell production of both IFNγ and TNFα has been implicated in the development of ConA-induced hepatitis [70,72,74,75]. The critical role of NKT cell activation in the development of liver damage in the ConA model of hepatitis has been supported by experimental findings in a second murine model of hepatitis which results from the direct activation of NKT cells within the liver by the specific NKT cell ligand α-GalCer [76]. α-GalCer-induced hepatitis, similarly to ConA-induced hepatitis, is considered to be an experimental model of human autoimmune hepatitis [76].

IL-4, which is rapidly released from activated NKT cells, has also been implicated in liver cell destruction in ConA-induced hepatitis [75,77], a finding which parallels observations in children with autoimmune hepatitis [78]. These observations suggest that, although IL-4 is considered a prototypic Th2-type (i.e. anti-inflammatory) cytokine, in the setting of liver disease IL-4 has pro-inflammatory properties [79]. This suggestion is supported by the findings that IL-4 directly induces hepatocyte apoptosis in vitro [80] and in vivo [81]. In addition, IL-4 produced by NKT cells within the liver up-regulates FASL expression on the NKT cell surface in an autocrine fashion [77]. FASL expressed on hepatic NKT cells subsequently interacts with FAS expressed on hepatocytes, which can lead to hepatocyte apoptosis [71,74,82]. In addition, IL-4 has been directly linked to the production of IL-5 within the liver during the course of ConA-induced hepatitis (with hepatic NKT cells representing a significant source of IL-5 [83]), and IL-5 produced in this manner plays a critical role in the subsequent recruitment of eosinophils into the liver, which contribute directly to the development of ConA-induced hepatitis [83,84]. These findings in the ConA-induced hepatitis model have potential implications for liver transplantation in humans in that increased IL-5 production and the hepatic recruitment of activated eosinophils have been identified in the setting of liver graft rejection [85,86].

PBC is considered to be a classical autoimmune disease affecting the liver [87]. Hepatic NKT cell numbers are increased in patients with PBC [45], and mice that lack NKT cells have defective clearance of Sphingomonas (a ubiquitous Gram-negative bacteria which does not contain endotoxin) from the liver [88,89]. In addition, glycolipids derived from Sphingomonas have been shown to be capable of activating NKT cells, and patients with PBC are seropositive for antibodies against Sphingomonas [90], suggesting that NKT cell/Sphingomonas interplay may contribute to the pathogenesis of PBC.

Recently a novel T-cell subset has been identified that is capable of inducing tissue inflammation and autoimmunity, namely Th17 or IL-17-producing T-cells [91,92]. IL-17 acts in mouse models, both in vivo and in vitro, as a potent inflammatory cytokine [93,94]. Interestingly, NKT cells are capable of producing IL-17 [7,8], suggesting that NKT cell secretion of IL-17 may potentially play a role in hepatic inflammation in the setting of liver disease. Moreover, higher serum IL-17 levels have recently been associated with an increasing severity of hepatitis in the clinical setting [95]. Obviously the potential role of IL-17-producing NKT cells in the development of hepatic autoimmunity warrants further investigation.

**Toxic/metabolic liver disease**

Alcohol-related liver disease is a commonly encountered clinical problem and is characterized by hepatic steatosis, hepatitis and fibrosis [96]. NKT cells have been implicated in the development of alcohol-related liver injury in a mouse model. Specifically, in the mouse model of chronic ethanol feeding, increased numbers of hepatic NKT cells have been documented in association with the development of liver injury; an effect that was temporally attenuated in NKT-cell-deficient mice [97]. Moreover, activation of NKT cells by treatment of mice with α-GalCer, in the setting of experimental alcohol-related liver injury, leads to marked liver cell destruction and subsequent animal death [97]. Maximal hepatic damage induced by activated hepatic NKT cells in this model appears to require a combination of FAS and TNFα signalling pathways [97].

NAFLD (non-alcoholic fatty liver disease) closely mimics alcohol-induced liver injury pathologically and is becoming exceedingly common in developed countries [98]. Interestingly, in contrast with the observations made in murine alcohol-induced liver injury, hepatic NKT cell numbers appear to decrease in fatty livers of ob/ob mice and in mice with diet-induced fatty livers (mouse models of NAFLD) [99,100]. This decrease in hepatic NKT cell numbers appears to be associated with the development of a hepatic Th1-type cytokine profile, which promotes hepatic inflammation and enhances the liver’s sensitivity to the damaging effects of endotoxin [99]. Importantly, the observed decreases in hepatic NKT cell numbers in these murine models of NAFLD probably reflect the activation-induced down-regulation of NKT cell-surface markers as opposed to a true depletion of NKT cell numbers within the liver [101]. In contrast with the observations outlined above, the adoptive transfer of NKT cells into ob/ob mice leads to a decrease in hepatic fat content and an improvement in glucose tolerance in these mice [102] (impaired glucose tolerance is considered to be a major predisposing factor for the development of NAFLD in patients [83]). Therefore the precise role of NKT cells in human NAFLD awaits further delineation.
Acetaminophen hepatotoxicity is an important cause of severe liver injury in North America and Europe, commonly resulting in hospitalization and even death [103]. Traditionally, hepatic damage associated with excess acetaminophen ingestion was felt to be due to a toxic metabolite produced during the metabolism of acetaminophen within the liver [104]. However, recently, an important role of the innate immune system has been identified in acetaminophen-induced liver damage in the mouse [105,106]. Specifically, acetaminophen-induced hepatic damage was shown to be dependent upon the cross-talk between hepatic NK and NKT cells, and their resultant production of IFNγ [105]. These observations suggest that therapeutics targeting hepatic NKT cell activation may potentially be beneficial in the treatment of acetaminophen-induced liver injury in the clinical setting.

Wilson’s disease is a rare, but potentially devastating, congenital defect of copper excretion which commonly affects the liver [107]. Interestingly, increased numbers of hepatic INKT cells have been identified in liver biopsy specimens of patients with Wilsonian hepatitis, one form of liver disease associated with this disorder [108]. Moreover, these same authors used the LEC rat model of Wilson’s disease to show that, in the setting of hepatitis, hepatic NKT cell numbers were increased [108]. These observations suggest that NKT cells may play a pathological role in this form, and potentially other forms, of metabolic liver disease and warrants further exploration.

SUMMARY AND CONCLUSIONS

NKT cells are innate immune cells and, as such, rapidly react as part of the first wave of the immune response to injurious or infectious insults. However, the diverse biological repertoire of NKT cells allows them to fulfil a spectrum of regulatory functions in the response to hepatic injury, from pro-inflammatory effects to the suppression of inflammation. This ‘Jekyll and Hyde’ existence is very apparent in the context of the roles identified to date for NKT cells in the pathogenesis of liver diseases, where clinical as well as experimental observations suggest strongly that NKT cells play an important role. Therefore NKT cells appear to represent an attractive potential therapeutic target for the treatment and control of a number of liver diseases, from viral hepatitis to autoimmune hepatitis. However, it will be important to remember that NKT cells fulfil diverse immunoregulatory functions within the liver and that attempts to therapeutically drive NKT cell behaviour in a specific direction, in an effort to treat a specific hepatic disease, may result in biological effects which are unexpected and potentially very important. A fuller understanding of the spectrum of NKT cell biological behaviours will allow us to better regulate NKT cells within the liver to hopefully one day help in the clinical management of patients with liver disease.

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