Arch. Immunol. Ther. Exp. (2011) 59:449–455
DOI 10.1007/s00005-011-0145-y

REVIEW

NK Cells Prevalence, Subsets and Function in Viral Hepatitis C

Jan Żeromski · Iwona Mozer-Lisewska · Mariusz Kaczmarek · Arleta Kowala-Piaskowska · Jan Sikora

Received: 18 April 2011 / Accepted: 4 July 2011 / Published online: 5 October 2011

Abstract Innate immunity appears to play an important role in the pathogenesis of viral hepatitis C. Among various cell subsets of this immunity natural killer (NK) cells raised particular interest. These cells are abundant in liver, possess significant cytotoxic potential and show links with adaptive immunity. They play important role, particularly in the acute phase of viral infections, including hepatitis C. They exhibit various types of receptors, either inhibitory or activating, that are able to react with distinct ligands on infected cells. Homozygosity of some receptors, namely KIR2DL3 reacting with recipient HLA-C1 antigens is a herald of good prognosis in hepatitis C virus (HCV) infection. In the early stage of the latter, both the prevalence and the cytotoxicity of NK cells are increased. Their inhibitory receptors are down regulated whereas activating ones are up regulated. Interferon-γ secreted by $NK56^{+bright}$ NK cells has a direct cytotoxic effect on infected hepatocytes. In contrast, in the chronic phase of HCV liver disease both, the prevalence and function of NK cells are impaired. Nevertheless, their cytotoxicity contributes to liver injury. Cells show change in the polarization profile from NK1 to NK2, manifested by secretion of immunosuppressive cytokines. Some HCV peptides are inhibitory for NK cells leading to the reduction of their antiviral activity. The unwanted effects of HCV peptides can be at least partly reversed by the antiviral therapy.

J. Żeromski (✉) · M. Kaczmarek · J. Sikora
Chair and Department of Clinical Immunology, University of Medical Sciences, Rokietnicka 5D, 60-806 Poznan, Poland
e-mail: jzeromski@ump.edu.pl

I. Mozer-Lisewska · A. Kowala-Piaskowska
Chair and Department of Infectious Diseases, University of Medical Sciences, Poznan, Poland

Keywords NK cells · Viral hepatitis C · NK receptors · NK cytotoxicity · Antiviral therapy · HCV-mediated NK immunosuppression

Introduction

Large granular lymphocytes, later called natural killer (NK) cells constitute about 10–20% lymphocytes in peripheral blood of man. Their immunophenotype is usually described as $CD56^{+}$, $CD16^{+}$, and $CD3^{-}$. According to the expression of CD56, CD16 differentiation antigens and functional features, NK cells are further subdivided to several subsets. Thus, $CD56^{+dim}CD16^{+}$ cells constitute the majority of NK and are known to be the main cytotoxic effectors. $CD56^{+bright}CD16^{+}$ cells comprise about 10% of total NK cells and are producers of interferon (IFN)-γ and other immunoregulatory cytokines. The division of these two main subsets is not absolute, because it has been shown that $CD56^{+bright}$ cells may transform into $CD56^{+dim}$ ones. Moreover, the latter can also produce above mentioned cytokines. In addition, $CD56^{-}CD16^{+}$ subset of NK cells may also be found, but their function remains unclear (Björkström et al. 2010; Cooper et al. 2001). Recent data suggest that CD56-negative NK cells exhibit functional skewing manifested by low capacity to produce IFN-γ, and to degranulate, but may release significant amounts of chemokines such as MIP-1α, MIP-1β, and RANTES (Fig. 1).

In principle, the function of NK cells is to sense pathogen infected and/or transformed cells, and following the activation, to eliminate these from the body. In contrast to T and B cells, the NK cells do not require prior sensitization. To prevent unwanted cytotoxicity, the NK cells are equipped into various receptors, allowing them to recognize self from non-self and unchanged healthy cells. This phenomenon has

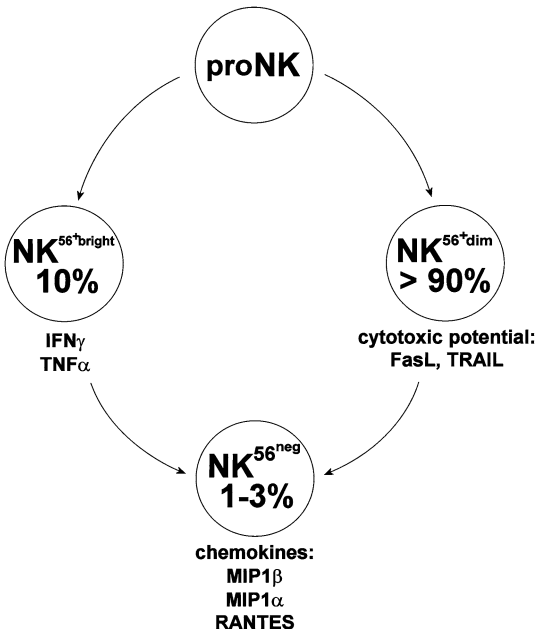

Fig. 1 NK cell subsets

been termed the "missing-self hypothesis" (Ljunggren and Kärre 1990). In addition to CD16 (FcγRIII) three groups of NK cell receptors have been distinguished: killer immunoglobulin-like receptors (KIRs), lectin-like receptors and natural cytotoxicity receptors. KIRs and lectin-like receptors are both activating and inhibitory, while natural cytotoxicity receptors have only activating function. Ligands of KIRs are predominantly alleles of MHC class I molecules such as HLA, mainly HLA-C antigens. Ligands of lectin-like (CD94-NKG2A-F) receptors are HLA-E antigens connected with HLA-A, -B, -C or -G leader peptide and also MICA, MICB (class I-related stress proteins). Natural cytotoxicity (NKp30, p44, p46, p80) receptors have various ligands, some unknown, but the most important are apparently viral hemagglutinins. In molecular terms, the difference between activating and inhibitory receptors is expressed in the cell cytoplasmic tails—the long immunoreceptor tyrosine-based inhibition motifs (ITIMs) mediate inhibitory signals, while the short immunoreceptor tyrosine-based activation motifs (ITAMs) are responsible for activating signals (Tomasello et al. 2000).

Moreover, NK cells appear to be involved in a close bidirectional cross-talk with dendritic cells (DCs). Activated NK cells enhance DC maturation and production of interleukin (IL)-12. Reciprocally, DCs augment cytotoxicity of NK cells. These interactions are mainly cell-contact dependent (Fernandez et al. 1999; Gerosa et al. 2002). Plasmacytoid DCs when activated by virus or CpG-ODN express the ligand for glucocorticoid-induced tumor necrosis factor receptor (GITR). The latter, in synergy with IL-2, IFN-α and some KIR receptors triggers NK cell cytotoxicity and IFN-γ secretion due to GITR expression on NK cells (Hanabuchi et al. 2006).

NK cells are considered to play a major role in viral infections, predominantly in the early phase. Following recognition of infected cells as non-self via activating receptors, the response of NK cells is further enhanced by at least two cytokines—IL-12 released by DCs and monocytes, and IFN-γ secreted by T cells and activated NK cells themselves. Furthermore, type I IFNs secreted by virus-infected cells augment NK cell cytotoxicity.

For many years, NK cells were considered as crucial mediators of innate immunity. Moreover, their role in performing immune surveillance against malignant transformation, by differentiating self/non self, perpetuated this opinion. Recently this dogma has been challenged, as it had been found, that at least in mice, NK cells possess features of adaptive immunity, such antigen-specific recall responses to some haptens. The antigen specificity appeared to be supported by some RAG-1 and RAG-2 (recombination-activating genes)-independent mechanisms and consequently mice were able to express NK cells memory following viral infection (Paust et al. 2010; Sun and Lanier 2009).

NK Cells in Normal Human Liver

Normal uninfected human liver contains about 10^9–10^{10} lymphocytes. Within this pool NK cells constitute about 30% of resident lymphoid cells. In liver disease the percentage of NK cells within intrahepatic lymphocyte pool may reach up to 90% (Doherty and O'Farrelly 2000). The remaining lymphocyte population includes T cells (63%) and B cells (6%). T cells can be subdivided to conventional ($CD4^+$ and $CD8^+$ ones) and unconventional (NKT cells, TCR$\gamma\delta$ T cells). NKT cells express T-cell receptor (TCR) and T-cell marker CD3 and express NK cell differentiation antigen, CD56. TCR repertoire of the NKT cells is very restricted and the MHC class I molecule CD1d is used for the recognition of mostly glycolipid antigens. NKT cells are beyond the scope of this article.

Intrahepatic NK cells are distributed between endothelial cells of liver sinusoids and have been previously called "pit" cells (Vanderkerken et al. 1993). In comparison to blood natural killers, their granules are smaller and have lower density. Functional properties of intrahepatic NK cells differ from their blood counterparts, presumably because of "tolerogenic" microenvironment of liver. They are less cytotoxic, produce lower amounts of IFN-γ. In contrast, they release greater quantities of immunosuppressive cytokines such as IL-10 (Lassen et al. 2010). In addition, intrahepatic NK cells express anti-fibrotic activities by the inhibition of hepatic stellate cells (HSC). The latter effect is manifested in two ways: by functional HSC

inhibition exerted by IFN-γ and by direct induction of HSC apoptosis (Melhem et al. 2006).

NK Cells in Viral Hepatitis C: General Data

Viral hepatitis C and more precisely, hepatitis C virus (HCV) is responsible for more than 170 million infections worldwide. Most patients after mild or symptomless acute phase succumb to chronic phase leading to liver cirrhosis and/or even to hepatic carcinoma (Lavanchy 2009). A vaccine is still unavailable due to the high polymorphism and variability of HCV genome. Current day antiviral treatment may significantly reduce the viral load but cannot totally eliminate it from the body. However, the immune system may recognize the virus and mount specific humoral and cell-mediated immune responses both. The cell-mediated immune response is usually too late and too weak to cope with the high burden of viral particles and/or virally infected cells. It has been claimed that in an acute phase of hepatitis C, HCV-sensitized $CD8^+$ T lymphocytes are induced after an unexpectedly long interval after virus exposure. Furthermore, $CD8^+$ T lymphocytes can be inefficient due to poor IFN-γ production (Cox et al. 2005). In the chronic phase of HCV infection only 1–2% of T cells fulfill the criteria of HCV specificity (Rehermann and Nascimbeni 2005). The virus has several means to block the specific antiviral response and becomes invisible to cytotoxic T cells. This issue has been recently discussed by us in the context of pattern recognition receptors (Mozer-Lisewska et al. 2010).

An interesting aspect of the role of NK cells in the HCV infection is the expression of particular forms of KIR receptors in combination with HLA-C allotypes and its relation to the disease outcome. It has been demonstrated by several authors that homozygosity of KIR2DL3 and HLA-C1 confers partial resistance to viral hepatitis C (CHC). The infected individuals often remain seronegative and aviremic. For example, when infected, these patients may spontaneously resolve infection, while when undergoing antiviral treatment, are more likely to manifest a sustained virological response (SVR). This observation was confirmed in different ethnic groups (Gendzekhadze et al. 2009; Knapp et al. 2010; Romero et al. 2008). Possible explanation of this phenomenon is the lower avidity of the binding of KIR2DL3 to HLA-C that results in down regulated activity of the inhibitory receptor and the enhanced function of KIR2DL2 activating receptor (Fadda et al. 2010; Moesta et al. 2008).

NK Cells in the Acute Phase of Hepatitis C

Following infection with HCV peripheral blood NK cells become more prevalent and activated. There is an increase in the number of $CD56^{+bright}$ and a relative reduction of $CD56^{+dim}$ NK cells. Both cell types show an increased expression of NKG2D receptor. IFN-γ production and cytotoxicity of NK cells are greater than observed in healthy controls (Amadei et al. 2010). This is associated with an increased NK cell degranulation (irrespective of the outcome of the infection), but correlated with the specific T cell response. Expression of NKG2A inhibitory receptor in NK cells is lower. In contrast, NKG2D activating receptor expression is upregulated. Production of IFN-γ is augmented, but the rise is lower in intravenous drug users, presumably due to inhibitory effect of drugs such as opium (Pelletier et al. 2010). Activation status of NK cells tends to decline in those individuals, who clear HCV, but usually persists in those progressing to a chronic phase. It has been reported that lower prevalences of NK cells expressing activating receptor as NKp30, NKp46, CD161 and NKG2D were found in patients who were able later to clear HCV infection over time, compared to patients, who progressed to a chronic phase (Alter et al. 2011).

Several cytokines have been implicated in NK cell activation and function, such as IL-12, IL-18 and IFN-γ. There has been much interest in type III IFN IL-28 (IFN-γ3) that is considered as a mediator of HCV clearance (Rauch et al. 2010; Thomas et al. 2009). It has been postulated that IFN-γ-mediated viral clearance is probably more efficient than the elimination of infected hepatocytes by cytotoxic effector cells. A possible explanation of this difference may be related to the mechanism of cytotoxicity that requires a 1:1 contact between effector cell and hepatocyte, whereas IFN-γ released by single NK cell may be cytotoxic to 100-fold liver cells (Guidotti and Chisari 1996). In addition, it is generally accepted that there is some functional redundancy of the above listed cytokines in the acute phase.

NK Cells in Chronic Phase of Hepatitis C

In general, NK cells in the chronic phase of HCV infection are down-regulated, both in number and function. The total number of lymphocytes, absolute number and percentage of NK cells in peripheral blood are decreased. Several authors reported reduced NK prevalence in peripheral blood of HCV patients that was usually associated with the decline of IFN-γ production (Dessouki et al. 2010; Morishima et al. 2006). One of the possible reasons for this observation could be the lack of IL-15 necessary for NK development and function (Jinushi et al. 2003; Meier et al. 2005). With regard to NK subsets, there is a general consensus that the relative increase of $CD56^{+bright}$ cells is not associated with $CD56^{+dim}$ cell increase. Upregulation of tumor necrosis factor-related apoptosis-inducing ligand

(TRAIL) contributing to damage of hepatocytes in situ has been shown in NK cells. It has been postulated that the decrease of $CD56^{+dim}$ NK cells is due to the effect of endogenous and/or therapeutic IFN-α. In contrast, $CD56^{-}CD16^{+}$ NK cell subset becomes expanded. The $CD56^{-}CD16^{+}$ NK cells, however, are considered to be in the terminal stage of differentiation and function. They produce small amounts of IFN-γ and release some chemokines such as MIP-1. Their significance remains to be elucidated (Gonzalez et al. 2009).

The impaired function of NK cells in the course of HCV infection is particularly evident in their interactions with DCs (Mavilio et al. 2006). Although DCs are able to produce IL-15, the production is deficient, apparently due to the inhibitory effect of IFN-α. NK cells normally activate DCs, however, in the chronic HCV infection the activating effect is poor. This results in impaired antigen presentation by DCs. Several alterations of NK receptor expression and function during chronic HCV infection have been described. For example, an increase of NKG2A inhibitory receptor expression was shown both on intrahepatic and peripheral blood NK cells (Bonorino et al. 2009; Harrison et al. 2010). NKG2A was shown, however, to be hypofunctional, because their ligand MICA (nonpolymorphic MHC class I chain related) protein expression is impaired on HCV-infected hepatocytes and DCs. This results in lower DCs activation (Jinushi et al. 2004). Furthermore, NK cells have shown decreased KIR expression with an increased expression of some activating receptors. Although there are conflicting reports concerning NKG2D activating receptors, the general consensus is that there is the activating receptors such as NKG2C, NKp30, NKp44 and NKp46 are up regulated. This could explain why the cytotoxicity of NK cells in chronic HCV was reported intact or increased (Yoon et al. 2009). Some authors noticed the change in the polarization profile of NK cells, from NK1 secreting IFN-γ, tumor necrosis factor (TNF), etc. to NK2 secreting IL-10, transforming growth factor (TGF)-β, IL-4, IL-13 (Peritt et al. 1998). This shift is probably due to the impact of IL-10 secreted by T cells infiltrating infected liver (Abel et al. 2006). On the other hand, there are experimental data hinting to the suppression of full cycle HCV infection in human hepatocytes. Wang et al. (2008) have shown that when NK cells culture supernatants (SN) were added to HCV infected hepatocytes, this resulted in significantly lower concentrations of HCV RNA and protein as compared to control cells. This effect could be abolished by the antibody to IFN-γ. SN treated hepatocytes produced high quantities of type I IFN and expressed IFN regulatory factors-3 and -7. The SN also enhanced signal transducer and activator of transcription (STAT-1 and -2), transcription factors crucial for IFN-mediated antiviral activities (Wang et al. 2008) (Fig. 2).

Reactivity of NK Cells in the Course of Antiviral Therapy of Hepatitis C

Standard therapies with IFN-α and ribavirin appears to modify the number and function of NK cells in HCV infected patients. IFN-α is known to increase cytotoxicity of NK cells. Studies from Australia and Egypt have shown that the antiviral therapy increased proportions of $CD56^{+bright}$ NK cells, while declined slightly $CD56^{+dim}$ ones (Fathy et al. 2010; Lee et al. 2010). The $CD56^{+dim}$ cells manifested a lower expression of CD16 and perforin. The authors concluded that this may be advantageous to the patient, because an increased secretion of IFN-γ by $CD56^{+bright}$ NK has an antiviral effect, while down-regulation of cytotoxic properties of $CD56^{+dim}$ cells prevented or limited damage of hepatocytes (Lee et al. 2010).

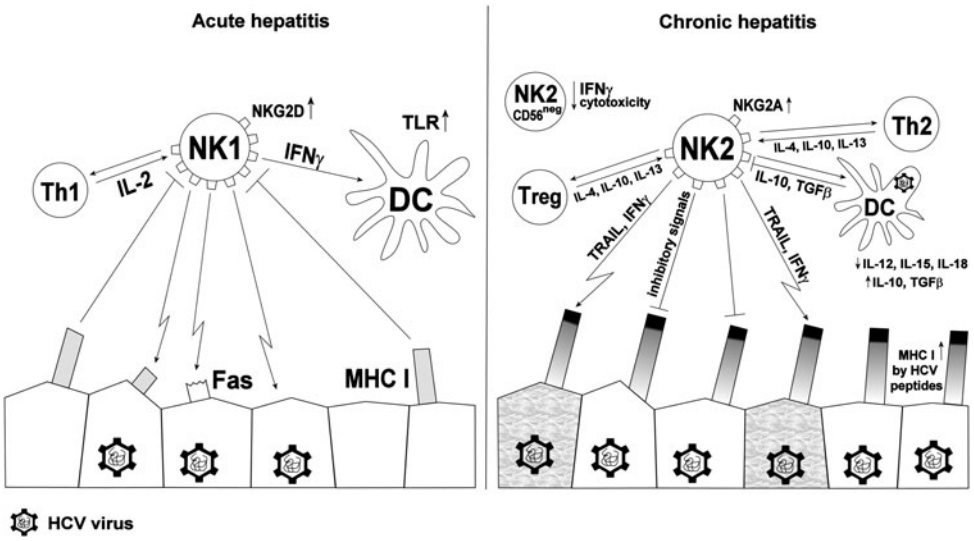

Fig. 2 NK cell function in acute and chronic hepatitis C

A different study from Japan has found that adverse effects on NK cells due to HCV infection such as a reduction of NK frequency and suppression of IFN-γ synthesis were reversed after therapy (Dessouki et al. 2010). Harrison et al. (2010) have shown that antiviral therapy leads to down-regulation of NKG2A receptor on $CD56^{dim}$ NK cells from HCV infected patients. Those who reached SVR had, however, greater numbers of NKG2A-positive, KIR-negative NK cells than the patients without SVR (Harrison et al. 2010). Thus, it appears that numerous NK cells with down-regulated inhibitory receptors are of an advantage in the course of CHC. The number of tested patients was, however, too low ($n = 12$) to draw the definitive conclusions. In the study of children with chronic hepatitis C, after antiviral therapy lasted 48 weeks we have observed significant fall of white blood cell count and in particular, effector cells with cytotoxic potential, including NK cells (Mozer-Lisewska et al. 2007).

One of the effects of IFN-α therapy in CHC is the induction on NK cells of TRAIL. Stegmann et al. (2010) have demonstrated that patients who responded to pegylated-IFN-α therapy had higher levels of TRAIL on $CD56^{+dim}$ cells than those who did not. There was a reverse correlation between TRAIL and viral load. The TRAIL was also expressed on $CD56^{+bright}$ cells and this expression was significantly higher than on the cells from control subjects. Thus, TRAIL appears to be an important marker linked to the response to antiviral therapy and in inducing apoptosis. However, TRAIL appears to be partly responsible for the injury of the liver as manifested by various types of necrosis seen by pathologists in liver sections. Some NK cell receptors appear to have predictive value for response to antiviral therapy. For example, a high numbers of $CD56^{-}$ NK cells are associated with poor response. These cells are known to have low expression of IFN-γ, TNF-α and poor CD107a degranulation, the latter corresponding to cell cytotoxicity (Gonzalez et al. 2009). It has been shown that the absence of KIR2DS2 and ND KIR2DL2 on NK and NKT cells was associated with poor response to antiviral therapy (Peg/RBV) in patients with recurrent CHC after liver transplantation (Askar et al. 2009). The difference in response between patients who had the cells expressing the above mentioned receptors and the patients who did not, was highly significant. This suggests that the determination of KIR expression on NK cells prior to the onset of the therapy may be of value in the planning of treatment strategy. There are data suggesting that activation status of NK cells shows correlations with the intensity of the liver inflammatory process. Oliviero et al. (2009) have demonstrated inverse correlation of NK cell NKGD2 expression with alanine aminotransferase (ALT) activity. Another inverse correlation has been shown between the number of NKG2A positive NK cells and viremia (Bonorino et al. 2009). The role and the significance of NK cells in various stages of hepatitis C and during antiviral therapy have been recently reviewed (Cheent and Khakoo 2011).

HCV Strategies to Evade NK Cell Response

Hepatitis C virus has evolved several strategies to prevent or abolish antiviral activity of NK cells. It can, for example, inhibit IFN-γ production by IL-12 activated NK, the effect mediated by the engagement of cellular tetraspanin CD81 by HCV envelope glycoprotein E2. In contrast, the production of another cytokine, IL-8 permissive for HCV infection, was increased by NK cells. Such modulation in the cytokine profile secreted by NK cells during HCV infection is definitely advantageous for viral spread (Crotta et al. 2010). Another strategy used by HCV appears to down-regulate the ligands of NKG2D activating receptor of NK cells. A reduced expression of ligands has been shown to be dependent on the activity of HCV protease NS3/4A (Wen et al. 2008). Furthermore, it has been reported that NS5A protease of HCV stimulates monocytes via Toll-like receptor 4 to IL-10 and TGF-β production. TGF-β decreases expression NKG2D on NK cells, and this results in impaired effector activity (Séne et al. 2010). At the same time TGF-β enhances activation of HSCs, resulting in the proliferation of fibroblasts and ultimately in liver fibrosis. It has been also demonstrated CD94-NKG2A ligand, HLA-E becomes upregulated by a peptide derived from HCV core (HCV_{core} 35-44) that leads to the inhibition of NK cells (Nattermann et al. 2006).

Concluding Remarks

The beneficial role of NK cells in the acute phase of HCV infection is beyond doubt. However, later in the disease process, in the chronic stage the virus exerts powerful inhibitory effect on various aspects of NK cells function and their antiviral activity declines significantly. High cytotoxic potential of NK cells warrants, however, consideration as to how their impairment in the course of chronic hepatitis C might be overcome. One possible way would be to boost NK cells function with exogenous cytokines such IL-12 and IL-15. IL-15 might be particularly beneficial as it is known to be pivotal for NK cells development and function. Such attempts are already underway (Doskali et al. 2011). A different strategy is demonstrated by the recent experiments aiming to inhibit or even eliminate HSCs by transfection with specific inhibitory KIR small interfering RNA in order to activate NK cells. This approach resulted in a significant reduction of liver fibrosis in mice (Muhanna et al. 2011).

Acknowledgments This work was supported by the Grant no NN 401535740 from the Polish National Science Centre (to I. Mozer-Lisewska).

Conflict of interest The authors declare that none of them has any competing interests whatsoever.

References

Abel M, Sene D, Pol S et al (2006) Intrahepatic virus-specific IL-10-producing CD8 T cells prevent liver damage during chronic hepatitis C virus infection. Hepatology 44:1607–1616

Alter G, Jost S, Rihn S et al (2011) Reduced frequencies of $NKp30^{+}NKp46^{+}$, $CD161^{+}$ and $NKG2D^{+}$ NK cells in acute HCV infection may predict viral clearance. J Hepatol 55:278–288

Amadei B, Urbani S, Cazaly A et al (2010) Activation of natural killer cells during acute infection with hepatitis C virus. Gastroenterology 138:1536–1545

Askar M, Avery R, Corey R et al (2009) Lack of killer immunoglobulin-like receptor 2DS2 (KIR2DS2) and KIR2DL2 is associated with poor responses to therapy of recurrent hepatitis C virus in liver transplant recipients. Liver Transpl 15:1557–1563

Björkström NK, Ljunggren HG, Sandberg JK (2010) CD56 negative NK cells: origin, function, and role in chronic viral disease. Trends Immunol 31:401–406

Bonorino P, Ramzan M, Camous X et al (2009) Fine characterization of intrahepatic NK cells expressing natural killer receptors in chronic hepatitis B and C. J Hepatol 51:458–467

Cheent K, Khakoo SI (2011) Natural killer cells and hepatitis C: action and reaction. Gut 60:268–278

Cooper MA, Fehniger TA, Caligiuri MA (2001) The biology of human natural killer-cell subsets. Trends Immunol 22:633–640

Cox AL, Mosbruger T, Lauer GM et al (2005) Comprehensive analyses of $CD8^{+}$ T cell responses during longitudinal study of acute human hepatitis C. Hepatology 42:104–112

Crotta S, Brazzoli M, Piccioli D et al (2010) Hepatitis C virions subvert natural killer cell activation to generate a cytokine environment permissive for infection. J Hepatol 52:183–190

Dessouki O, Kamiya Y, Nagahama H et al (2010) Chronic hepatitis C viral infection reduces NK cell frequency and suppresses cytokine secretion: Reversion by anti-viral treatment. Biochem Biophys Res Commun 393:331–337

Doherty DG, O'Farrelly C (2000) Innate and adaptive lymphoid cells in the human liver. Immunol Rev 174:5–20

Doskali M, Tanaka Y, Ohira M et al (2011) Possibility of adoptive immunotherapy with peripheral blood-derived $CD3CD56^{+}$ and $CD3^{+}CD56^{+}$ cells for inducing antihepatocellular carcinoma and antihepatitis C virus activity. J Immunother 34:129–138

Fadda L, Borhis G, Ahmed P et al (2010) Peptide antagonism as a mechanism for NK cell activation. Proc Natl Acad Sci USA 107:10160–10165

Fathy A, Eldin MM, Metwally L et al (2010) Interferon therapy shifts natural killer subsets among Egyptian patients with chronic hepatitis C. Braz J Infect Dis 14:398–405

Fernandez NC, Lozier A, Flament C et al (1999) Dendritic cells directly trigger NK cell functions: cross-talk relevant in innate anti-tumor immune responses in vivo. Nat Med 5:405–411

Gendzekhadze K, Norman PJ, Abi-Rached L et al (2009) Co-evolution of KIR2DL3 with HLA-C in a human population retaining minimal essential diversity of KIR and HLA class I ligands. Proc Natl Acad Sci USA 106:18692–18697

Gerosa F, Baldani-Guerra B, Nisii C et al (2002) Reciprocal activating interaction between natural killer cells and dendritic cells. J Exp Med 195:327–333

Gonzalez VD, Falconer K, Björkström NK et al (2009) Expansion of functionally skewed CD56-negative NK cells in chronic hepatitis C virus infection: correlation with outcome of pegylated IFN-alpha and ribavirin treatment. J Immunol 183:6612–6618

Guidotti LG, Chisari FV (1996) To kill or to cure: options in host defense against viral infection. Curr Opin Immunol 8:478–483

Hanabuchi S, Watanabe N, Wang YH et al (2006) Human plasmacytoid predendritic cells activate NK cells through glucocorticoid-induced tumor necrosis factor receptor-ligand (GITRL). Blood 107:3617–3623

Harrison RJ, Ettorre A, Little AM et al (2010) Association of NKG2A with treatment for chronic hepatitis C virus infection. Clin Exp Immunol 161:306–314

Jinushi M, Takehara T, Tatsumi T et al (2003) Autocrine/paracrine IL-15 that is required for type I IFN-mediated dendritic cell expression of MHC class I-related chain A and B is impaired in hepatitis C virus infection. J Immunol 171:5423–5429

Jinushi M, Takehara T, Tatsumi T et al (2004) Negative regulation of NK cell activities by inhibitory receptor CD94/NKG2A leads to altered NK cell-induced modulation of dendritic cell functions in chronic hepatitis C virus infection. J Immunol 173:6072–6081

Knapp S, Warshow U, Hegazy D et al (2010) Consistent beneficial effects of killer cell immunoglobulin-like receptor 2DL3 and group 1 human leukocyte antigen-C following exposure to hepatitis C virus. Hepatology 51:1168–1175

Lassen MG, Lukens JR, Dolina JS et al (2010) Intrahepatic IL-10 maintains NKG2A + Ly49- liver NK cells in a functionally hyporesponsive state. J Immunol 184:2693–2701

Lavanchy D (2009) The global burden of hepatitis C. Liver Int 29(suppl 1):74–81

Lee S, Watson MW, Flexman JP et al (2010) Increased proportion of the CD56(bright) NK cell subset in patients chronically infected with hepatitis C virus (HCV) receiving interferon-alpha and ribavirin therapy. J Med Virol 82:568–574

Ljunggren HG, Kärre K (1990) In search of the 'missing self': MHC molecules and NK cell recognition. Immunol Today 11:237–244

Mavilio D, Lombardo G, Kinter A et al (2006) Characterization of the defective interaction between a subset of natural killer cells and dendritic cells in HIV-1 infection. J Exp Med 203:2339–2350

Meier UC, Owen RE, Taylor E et al (2005) Shared alterations in NK cell frequency, phenotype, and function in chronic human immunodeficiency virus and hepatitis C virus infections. J Virol 79:12365–12374

Melhem A, Muhanna N, Bishara A et al (2006) Anti-fibrotic activity of NK cells in experimental liver injury through killing of activated HSC. J Hepatol 45:60–71

Moesta AK, Norman PJ, Yawata M et al (2008) Synergistic polymorphism at two positions distal to the ligand-binding site makes KIR2DL2 a stronger receptor for HLA-C than KIR2DL3. J Immunol 180:3969–3979

Morishima C, Paschal DM, Wang CC et al (2006) Decreased NK cell frequency in chronic hepatitis C does not affect ex vivo cytolytic killing. Hepatology 43:573–580

Mozer-Lisewska I, Dworacki G, Sluzewski W et al (2007) Alterations in immunophenotype of peripheral blood mononuclear cells in children with chronic viral hepatitis following anti-viral therapy. J Pediatr Infect Dis 2:141–146

Mozer-Lisewska I, Sikora J, Kowala-Piaskowska A et al (2010) The incidence and significance of pattern-recognition receptors in chronic viral hepatitis types B and C in man. Arch Immunol Ther Exp 58:295–302

Muhanna N, Abu Tair L, Doron S et al (2011) Amelioration of hepatic fibrosis by NK cell activation. Gut 60:90–98

Nattermann J, Feldmann G, Ahlenstiel G et al (2006) Surface expression and cytolytic function of natural killer cell receptors is altered in chronic hepatitis C. Gut 55:869–877

Oliviero B, Varchetta S, Paudice E et al (2009) Natural killer cell functional dichotomy in chronic hepatitis B and chronic hepatitis C virus infections. Gastroenterology 137:1151–1160 (1160 e1–7)

Paust S, Senman B, von Andrian UH (2010) Adaptive immune responses mediated by natural killer cells. Immunol Rev 235:286–296

Pelletier S, Drouin C, Bédard N et al (2010) Increased degranulation of natural killer cells during acute HCV correlates with the magnitude of virus-specific T cell responses. J Hepatol 53:805–816

Peritt D, Robertson S, Gri G et al (1998) Differentiation of human NK cells into NK1 and NK2 subsets. J Immunol 161:5821–5824

Rauch A, Kutalik Z, Descombes P et al (2010) Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. Gastroenterology 138:1338–1345 (1345 e 1–7)

Rehermann B, Nascimbeni M (2005) Immunology of hepatitis B virus and hepatitis C virus infection. Nat Rev Immunol 5:215–229

Romero V, Azocar J, Zuniga J et al (2008) Interaction of NK inhibitory receptor genes with HLA-C and MHC class II alleles in Hepatitis C virus infection outcome. Mol Immunol 45:2429–2436

Séne D, Levasseur F, Abel M et al (2010) Hepatitis C virus (HCV) evades NKG2D-dependent NK cell responses through NS5A-mediated imbalance of inflammatory cytokines. PLoS Pathog 6:e1001184

Stegmann KA, Bjorkstrom NK, Veber H et al (2010) Interferon-alpha-induced TRAIL on natural killer cells is associated with control of hepatitis C virus infection. Gastroenterology 138:1885–1897

Sun JC, Lanier LL (2009) Natural killer cells remember: an evolutionary bridge between innate and adaptive immunity? Eur J Immunol 39:2059–2064

Thomas DL, Thio CL, Martin MP et al (2009) Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 461:798–801

Tomasello E, Bléry M, Vély F et al (2000) Signaling pathways engaged by NK cell receptors: double concerto for activating receptors, inhibitory receptors and NK cells. Semin Immunol 12:139–147

Vanderkerken K, Bouwens L, De Neve W et al (1993) Origin and differentiation of hepatic natural killer cells (pit cells). Hepatology 18:919–925

Wang SH, Huang CX, Ye L et al (2008) Natural killer cells suppress full cycle HCV infection of human hepatocytes. J Viral Hepat 15:855–864

Wen F, Brown KE, Britigan BE et al (2008) Hepatitis C core protein inhibits induction of heme oxygenase-1 and sensitizes hepatocytes to cytotoxicity. Cell Biol Toxicol 24:175–188

Yoon JC, Shiina M, Ahlenstiel G et al (2009) Natural killer cell function is intact after direct exposure to infectious hepatitis C virions. Hepatology 49:12–21