Infection with hepatitis C virus (HCV) often results in chronic disease. There is clear evidence that the human immune system critically determines the outcome of infection and it is widely accepted that chronic evolution of hepatitis C is associated with an ineffective adaptive immune response. However, emerging data suggest that the innate immune system may also play a role.

Natural killer (NK) cells, a heterogeneous sub-population of lymphocytes, represent a central part of the innate immune system. NK cells have a strong cytotoxic potential and are able to rapidly attack target cells without prior immunization. Moreover, NK cells secrete cytokines including IFN-γ and TNF-α and can cross-talk with other immuno-competent cells such as dendritic cells. Thus, NK cells are also involved in the regulation of adaptive immune responses [1].

Based on the expression of CD56 human NK cells have been divided into two different functional subsets. In humans, the vast majority of circulating NK cells belong to the CD56dim subset, which is characterized by moderate to high expression levels of FcyRIIIA (CD16) and perforin, as well as having a high cytotoxic capability. CD56bright NK cells, in contrast, display rather poor cytolytic activity, and are considered to function as immunoregulatory cells via secretion of cytokines [1].

Of note, NK cells are enriched in the liver. In contrast to the peripheral blood that contains about 5–10% NK cells, intra-hepatic lymphocytes contain about 30% NK cells and the percentage of NK cells in the liver may increase >50% in hepatic diseases [2]. Thus, NK cells are not only in the right location but also display the functional capacity needed to control a hepatotropic virus such as HCV.

Accordingly, immunogenetic analyses suggest that NK cells may influence the outcome of acute HCV infection as well as immuno-pathogenesis in chronic hepatitis C [3,4] and in vitro studies indicate that NK cells have the potential to recognize and kill HCV-infected hepatocytes in vivo [5].

The exact role of NK cells in HCV infection, however, remains elusive as current studies have yielded inconsistent results regarding phenotype and function of natural killer cells [6–10]. In addition, little is known regarding the role of NK cells in acute hepatitis as only a few studies addressed this question.

In the current issue of the Journal of Hepatology, Alter and co-workers add another piece to the puzzle [11]. Analyzing the phenotype and function of NK cells during various stages of HCV infection with different clinical outcomes, they showed that acute hepatitis C is associated with an expansion of NK cells which resembles recent findings in humans infected with hanta-virus [12]. Moreover, the authors observed a reduction in the CD56dim NK cell subset in acute HCV patients compared to healthy controls and similar results have been reported previously [13,14]. In contrast, acute Puumala hantavirus infection has been shown to be associated with a rapid expansion of CD56dim NK cells [12], underpinning key differences in NK cell responses during acute infection with different viruses in humans.

Whether low frequency of the CD56dim subset in acute hepatitis C is the result of reduced survival or altered compartmentalization of this NK cell subpopulation remains unclear at the moment.

However, Alter and co-workers show that distribution of NK cells subsets in responders did not differ significantly from that seen in patients with acute or chronic infection [11]. Therefore, percentages of CD56bright, CD56dim, and CD56neg in the bulk NK cell population seemed not to influence the outcome of the infection.

The function of NK cells is tightly regulated by a balance between signals delivered by activating and inhibitory NK cell receptors. Specific NK cell activation receptors have been shown to play a role in the control of viral infections [15,16]. Studies on NK cell receptor expression in chronic hepatitis C have yielded conflicting results. While most groups reported up-regulated expression of the inhibitory NKG2A receptors, data regarding NK cell activation receptors Nkp30, Nkp46, and NKG2D are controversial [7–10].

Alter et al. observed chronic hepatitis C to be associated with a decline in the proportions of Nkp30- and Nkp46-expressing NK cells but expansion of NKG2A-positive NK cells. Interestingly, they also showed that increased levels of NKG2A+ NK cells and reduced percentages of NKG2D+, Nkp30+ and Nkp46+ NK cells could already be detected in patients with acute HCV infection.
In line with two recent reports [13,14], these data clearly indicate that significant alterations of NK cell receptor expression already occur early in HCV infection and are maintained throughout chronic HCV infection.

Interestingly, functional experiments demonstrated increased cytotoxic activity and IFN-γ production of circulating NK cells in patients with acute hepatitis C, indicating that an early impairment of peripheral NK cell function is unlikely to play a major role in the development of chronic HCV infection.

Do NK cells contribute to clearance of HCV infection?

Recent studies failed to reveal any significant association between phenotypical/activity of NK cells in the acute phase and outcome of infection [13,14], which would suggest that NK cells may have little effect and/or rather indirectly affect anti-HCV immunity.

However, these studies were limited by a rather small number of patients that were included and, therefore, may have had limited power to detect differences. Moreover, immunogenetic studies suggested the inhibitory killer cell immunoglobulin-like receptor (KIR) KIR2DL3 and group 1 HLA-C to be protective against evolution of chronic HCV infection [3]. This association is thought to be the result of weaker inhibitory signals generated by KIR2DL3 as compared to KIR2DL1, which enables faster activation of KIR2DL3 expressing NK cells compared with those expressing KIR2DL1 [17]. Of note, Alter and co-workers found significantly up-regulated expression of KIRs recognizing HLA-C molecules in patients who cleared the virus and Amadei et al. recently observed a trend toward a higher de-granulation activity in KIR2DL3-positive NK cells from self-limited as compared with chronically evolving infections [14]. Thus, increased frequencies of NK cells expressing HLA-C-binding KIRs may be associated with HCV clearance.

In addition, Alter et al. demonstrated that in the acute phase lower frequencies of NK cells expressing the activating receptors NKp30, NKp46, and NKGD2 as well as a low proportion of CD161+ NK cells were associated with a self-limited course of infection.

As both direct and indirect stimulation of NK cells resulted in down-regulation of the natural cytotoxicity receptors (NCRs), NKp30, and NKp46, respectively, the authors concluded that early activation of NK cells, marked by a loss of NCRs (and NKGD2, and CD161) may predict spontaneous HCV clearance. A role of NK cells in the control and clearance of HCV is further supported by Pelletier et al. who observed a correlation between NK cell activity and T cell activity in acute hepatitis C, suggesting a coordinated innate and adaptive immune response to acute HCV infection [13]. However, we must be careful not to jump to conclusions and there are still many questions to be resolved.

Different NK cell subsets are characterized by specific expression patterns of chemokines receptors [18]. As these surface molecules are critically involved in lymphocyte migration, altered composition/phenotype of circulating NK cells may just be the result of hepatic recruitment of specific NK cell subsets.

Moreover, intra-hepatic NK cells may behave differently to peripheral blood NK cells due to the specific environment in the liver. For instance, murine intra-hepatic NK cells have been shown to be hypo-responsive as they displayed lower cytotoxic activity and reduced IFN-γ secretion but produced greater levels of immuno-regulatory cytokines such as interleukin-10 than circulating NK cells [19].

Thus, it would be important to analyze phenotype and function of intra-hepatic NK cell subsets in the acute phase of HCV infection. However, due to ethical reasons these data will hardly be obtained.

Alternatively, altered surface expression of NK cell receptors in patients that subsequently clear the virus might be an epiphemomenon of an effective anti-viral immune-response. Cytokines such as IFN-α have been shown to effectively activate NK cells and to affect the NK cell phenotype [10,20]. Thus, changes in cytokine secretion by other immuno-competent cells might affect NK cell receptor expression in early HCV infection.

Taken together there is clear evidence that phenotypical and functional alterations of NK cells occur early in HCV infection, suggesting that NK cells may play a role in HCV immunopathogenesis. However, much more has to be learnt to exactly define the specific contribution of NK cells to the outcome of hepatitis C.

Conflict of interest

The author declares that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References


