



Are KIR-HLA Polymorphisms Relevant for the Outcome of Chronic Infected Hepatitis C Virus Patients?

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Abstract

Natural killer (NK) cells play an important role in viral clearance and in the elimination of neoplastic cells. Recent cellular and genetic studies revealed that NK cells modulate the immune response against hepatitis C virus (HCV). Improving our understanding of NK cells could help us gain further insight into the virus-host interaction and the mechanisms of viral persistence. Previous studies mention the role of Killer cell Immunoglobulin-like Receptors (KIRs) and their Human Leukocyte Alleles (HLA) ligands in disease progression of chronic HCV infected patients. Specific HLA class I and class II alleles may influence the susceptibility or resistance to persistent HCV infection. In the last few years, progress has been made in the link between KIR-HLA gene polymorphisms and susceptibility to immune-mediated diseases such as chronic HCV infection. Many studies have shown the importance of NK cells in the outcome of chronic HCV patients. The immune response against HCV is affected by certain KIR genes and HLA genes. There is a great potential for the use of KIR genes as a prognostic tool for the development of complications such as liver cirrhosis and HCC.

Keywords: Chronic HCV; NK cells; *KIR* genes; HLA alleles; Spontaneous clearance; Viral replication; Viral persistence

Abbreviations: HCV-Hepatitis C Virus; NK-Natural Killer; KIR-Killer-cells Immunoglobulin-like Receptors; HLA-Human Leukocyte Antigens; MHC-Major Histocompatibility Complex; HCC-Hepatocellular Carcinoma; SVR-Sustained Virological Response; Peg-IFN-Pegylated Alpha Interferon; IFNL3-Interferon Lambda-3

Introduction

HCV is a major public health problem worldwide with an estimated population of 71 million people suffering from chronic hepatitis C infection. Approximately 3,99,000 people die each year from hepatitis C, mostly from complications like cirrhosis and hepatocellular carcinoma (HCC) [1]. HCV prevalence varies around the world. Regarding HCV genotypes in Europe, the most common subtype is 1b whilst in America the most frequent subtype is 1a. In the Middle East, North and Central Africa, the most prevalent genotype is 4 and in Asia, it is genotype 3 [2,3]. HCV infection has two possible outcomes: spontaneous clearance or chronic infection [4]. Memory T helper cells and/or cytotoxic T lymphocytes can provide protection against HCV and contribute to spontaneous clearance [5]. A significant number of chronic HCV-infected patients could develop complications such as cirrhosis and hepatocellular carcinoma (HCC) in the late stages [6].

Natural killer cells are a type of lymphocyte involved in the innate anti-viral immune response. They were first mentioned in the 1970s. NK cells have a crucial role in the prevention and progression of cancer and in immune surveillance as well [7-11]. The function of the NK cell is controlled by killer-cell immunoglobulin-like receptors

(KIR), a family of type I transmembrane glycoproteins which recognize HLA class I molecules [12,13]. According to the “missing self” hypothesis, one important function of NK cells is to detect and eliminate cells if they fail to express normal self-antigens. [14]. A strategy to discriminate between normal and infected cells is the interaction with major histocompatibility complex (MHC) class I proteins [15]. MHC class I molecules are expressed on the surface of all nucleated cells. Both virus-infected cells and neoplastic cells have a decreased expression of MHC-class I and therefore are targets for NK cells [16].

Human KIR haplotypes are encoded by chromosome 19q13.4. They are divided into two groups: group ‘A’ and group ‘B’. The ‘A’ haplotype consists mostly of KIR genes for inhibitory receptors and the ‘B’ haplotype contains genes for both activating and inhibitory receptors [17,18]. If none of the following *KIR* genes: *KIR2DL2*, *KIR2DL5*, *KIR3DS1*, *KIR2DS1*, *KIR2DS2*, *KIR2DS3*, *KIR2DS5* are present, the genotype is AA. If any of these genes are present, the haplotype is B. When we can’t distinguish between AB and BB genotypes, the genotype is known as Bx [19]. The interaction between KIR and HLA-C molecules is the dominant control mechanism of human NK cells. A minority of HLA-A and HLA-B alleles function as KIR ligands [20]. Scientists are particularly interested in certain combinations of activating or inhibitory KIR and their HLA ligands could have implications in the clinical outcome of chronic HCV infection.

Association of Chronic HCV Infection Outcome with KIR-HLA Class I Genes

Many studies have shown the influence of KIR-HLA combinations in the outcome of chronic HCV infection. Certain HLA class I molecules are associated with HCV spontaneous clearance. *KIR2DL1*

receptors recognize HLA-C group 2 antigens (that present amino acid lysine in position 80), *KIR2DL2/3* receptors recognize HLA-C group 1 antigens (that present amino acid asparagine in position 80) and *KIR3DL1* is the receptor for HLA Bw4 molecules [21-23]. In regards to inhibitory genes, a link between *KIR2DL2* and chronic persistent HCV infection was observed [24,25]. The affinity of the *KIR2DL2* to the HLA-C ligand is higher than that of *KIR2DL3*, which has a stronger inhibition of the NK cell [13,25,26].

NK cells contribute to the resolution of HCV infection through KIR2DL3/HLA-C1 interaction. Several studies have revealed the combination of group 1 HLA-C genes with *KIR2DL3* homozygosity has been associated with HCV clearance [26,27] and has also been associated with a sustained viral response to antiviral therapy [28,29]. A better outcome was observed in individuals with this combination of receptor and ligand (KIR2DL3/HLA-C1). One possible explanation might be exposure to virus. The beneficial effect of KIR2DL3/HLA-C1/C1 was only seen in the non-transfusion group, suggesting that NK cells may be an important part of the immune response when there is a limited exposure to virus [26,27].

Studies that compare patients who spontaneously resolved infection and patients who developed chronic HCV have been revealed that *KIR2DS3* gene is significantly more prevalent in patients with chronic HCV infection [30-32]. The association of *KIR2DS3* with chronic infection was influenced by the HLA-C genetic background. *KIR2DS3* was only significantly increased in patients with chronic HCV infection and a HLA-C2+ genetic background [30,31]. This suggests that certain KIR-haplotypes were more common in patients with chronic HCV infection. Vasconcelos et al. also described in the Brazilian population an association of *KIR2DS3* (either alone or together with *KIR2DL2* and *KIR2DS2*) with chronic HCV infection [28]. Related to KIR genes involved in susceptibility to chronic HCV infection and to viral load levels, the data has shown a difference between viremia levels in *KIR2DS3+/KIR2DS5-* patients versus other combinations of these two genes. Patients with *KIR2DS3* but not *KIR2DS5* gene have lower levels of viremia [33]. However, in a recent study, conducted by Podhorzer et al. *KIR2DS3* expression was correlated with high viral load levels [34]. The contribution of this gene to chronic HCV infection requires further studies in ethnically different populations.

In a study looking at the risk of developing HCC and lymphoproliferative disease progression in Italian patients with chronic HCV infection showed *KIR2DS5* gene has a protective effect against disease progression when associated with *KIR2DS3* gene. These results suggest that low expression of activating *KIR* genes 2DS3 and 2DS5 leads to a reduction in the activation of NK cells in lymphoproliferative disorders. An increased risk of HCC was associated with a reduction of HLA-Bw4+KIR3DS1+ in the same cohort study [20].

Another study in Japan looking at the risk of hepatitis C virus-related HCC in young patients showed associations between KIR2DL2-HLA-C1 and KIR2DS2-HLA-C1 were significantly higher in younger patients who developed HCC. This study also revealed that patients with chronic hepatitis C had a significantly higher incidence rate of KIR3DL1-HLA-Bw4 pairs [35].

The following HLA alleles configuration HLA-A*03, B*27, DRB1*01:01, DRB1*04:01 are strongly associated with HCV viral clearance while DQB1*02:01 is associated with chronic infection [28].

Correlations between KIR - HLA Class II Alleles and Chronic HCV Infection Outcome

Particularly DRB1 and DQB1 alleles are associated with spontaneous resolution of HCV infection. Some associations were tested in the Caucasians, Asians and Hispanic populations. KIR-HLA polymorphisms also influence the susceptibility to chronic HCV and response to antiviral therapy. The importance of interferon lambda and innate immunity in the outcome of HCV infection was also described by Frias et al. Interferon lambda-3 (IFNL3) genotype was found in patients with self-limiting acute HCV infection [36].

A rapid reduction in viremia by direct acting antiviral therapy improves the response to PegIFN in patients who had previously failed to respond to standard PegIFN/ribavirin (RBV) therapy [37].

In Caucasians, HLA-DRB1*16:01 was associated with higher rates of spontaneous clearance, while DRB4*01:01, HLA-DRB1*07 and DRB1*07:01 were associated with lower rates of spontaneous HCV clearance [35]. HLA-DRB1*0701 was also reported as being correlated with a lack of response to antiviral therapy and higher viral loads [38].

Other studies investigated whether HLA class II alleles influenced the clinical outcome of HCV infection and response to interferon therapy in the Egyptian population. It was revealed that the DQB1*02, DQB1*06, DRB1*13, DRB1*15, DRB1*13:01, DRB1*13:61 and DRB1*13:69, may act as positive predictors for response to interferon treatment. These alleles were more frequently present in responders than in non-responders [29].

Conclusion

Many studies have shown that NK cells are linked to their KIR genotypes and they have a protective role against the HCV viral loads. Different interactions between KIR and HLA class I and class II molecules have an influence on the immunopathogenesis of chronic HCV and have a significant impact on NK cell function [27,28,35]. These HLA molecules in association with *KIR* genes may be used as predictors for response to interferon treatment or for the outcome of chronic HCV infection. KIR-HLA polymorphisms are clinically relevant for the course of chronic HCV infection, affecting patient's clinical status and potential development of a liver tumor. HCV recurrence is lower among patients with a larger number of activating *KIR* genes [31,35]. The immune response against HCV is complex. Interactions between NK cells-KIR genes and HLA genes are challenging and could offer more answers for the different outcomes of HCV infected patients. Further research is required to shed some light on HCV immunopathogenesis.

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