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Editorial Open Access

Relevance of *HLA-KIR* Genes in Chronic Hepatitis C Virus Infection Outcome

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Editorial

Hepatitis C Virus (HCV) is responsible for over 170 million chronically infected worldwide people, most patients develop a lifetime chronic infection that can lead to severe liver pathology [1].

Substantial research evidences suggest that the innate immune response significantly contributes to HCV outcome [2,3]. Natural Killer (NK) cells have efficient anti-viral functions including direct cytotoxicity of infected cells and production of inflammatory cytokines [4]. Killer cell immunoglobulin-like receptors (KIRs) play a major role in regulating the activity of NK cells involved against viral infections, autoimmune diseases, cancers or post-transplantation [5-7].

Many recent studies have reviewed the importance of NK cells in chronic HCV infection outcome and the interactions between the *KIR* and *HLA* genes. Both molecules have structural polymorphisms which could be referred to a particular clinical condition [5-11].

Interaction between KIR and HLA-C molecules is the dominant control mechanism of the host NK cells. Genetic studies reveal that, in the early phase of HCV infection, specific KIR and HLA-C pairs are associated with the spontaneous resolution of HCV infection [8,9].

KIR2DL1 receptors recognize HLA-C group 2 antigens (lysine in position 80), KIR2DL2/3 receptors recognizes HLA-C group 1 antigens (asparagine in position 80) and KIR3DL1 is the receptor for HLA Bw4 molecules [10,11].

KIR2DL3-mediated inhibition of NK cells protects from HCV persistence, since KIR2DL3 has a lower affinity for its HLA-C ligand than other KIRs [12]. KIR2DL3 binds HLA-C1 with a weaker affinity compared with KIR2DL2 binding of HLA-C1. NK cells in HCV carriers with this combination of receptors and ligands could be more easily activated during HCV infection resulting in a better outcome [8,11].

Activatory *KIR2DS3* gene interaction with *HLA-C2* is significantly increased in HCV patients having a role in the development of chronic viral infection [12]. The authors of this study identify a strong influence of KIR B haplotype (and HLA-C2) for the activation of NK cells. In other previous study, a beneficial effect of a KIR A haplotype (with *HLA-C1*) was observed [8,13].

The role of *KIR* genes in susceptibility to chronic HCV infection and viral load level variations were revealed in different *KIR2DS3-KIR2DS5* genotypes combinations.

Kusnierczyk et al. have found that in patients with KIR2DS3+/KIR2DS5- the HCV viremia levels was 2.6 times lower than in patients with other KIR genotypes [14]. In contrast, a study conducted by Podhorzer et al. has shown that KIR2DS3 expression was correlated with high viral load levels [15].

Our unpublished data, show on HCV Romanian infected patients, that in *KIR2DS3+/KIR2DS5-* genotype HCV viremia mean values were 2.2 times lower than in other genotypes.

All these evidence-based results underline that the immune response against HCV is complex. Interactions between NK activatory-inhibitory *KIR* genes and HLA alleles are important and challenging. These insights could offer more information related to different outcomes in HCV chronically infected individuals. Variable interactions between KIRs and HLA class I and class II molecules have a relevant influence on immunopathogenesis of HCV and have a significant impact on NK cells function.

Understanding HCV immunopathogenesis for an improved clinical management of chronic hepatitis C is further required.

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