OncoImmunology 2:12, e26622; December 2013; © 2013 Landes Bioscience

KIR/HLA immunogenetic background influences the evolution of hepatocellular carcinoma

Elisabetta Cariani[1] and Gabriele Missale[2,*]

[1]Clinical Pathology-Toxicology; Ospedale S Agostino-Estense; Modena, Italy;
[2]U.O. Infectious Diseases and Hepatology; Azienda Ospedaliero-Universitaria di Parma; Parma, Italy

Keywords: CD56, HCC, HLA, immunotherapy, killer cell Ig-like receptor, natural killer cell

Natural killer (NK) cells play a major role in antitumor immune responses. Recent results from our laboratory demonstrate the impact of the immunogenetic background on the activity of NK cells and hence on the outcome of hepatocellular carcinoma, disclosing perspectives for the development of NK-cell based therapies.

NK cells represent 30–50% of all hepatic lymphocytes in humans and they are involved not only in immunoregulatory mechanisms but also in fibrosis, regeneration, as well as in the response to acute and chronic liver infection. In addition, NK cells play an important role in controlling hepatic tumorigenesis. In patients with hepatocellular carcinoma (HCC), an enrichment in $CD56^+$ cells among tumor-infiltrating lymphocytes has been correlated with improved clinical outcomes,[1] even though the liver microenvironment, especially in the cirrhotic liver, can limit cancer immunosurveillance by different mechanisms. Immunosurveillance is mainly mediated by the recognition of MHC class I molecules by killer cell Ig-like receptors (KIRs) and by NK-cell activating receptors such as killer cell lectin-like receptor subfamily K, member 1 (KLRK1, best known as NKG2D) that can bind non-classical MHC class I-like molecules such as MHC class I polypeptide-related sequence A (MICA), MICB and UL16-binding proteins (ULBPs), which are upregulated on the surface of transformed cells.[2,3] Inhibitory KIRs (which inhibit the cytotoxic activity of NK cells), interact with classical MHC class I molecules. In line with this model, the downregulation of MHC class I molecules on target cells promotes the activation of NK cells and their cytotoxic activity.

Because KIR and HLA molecules are encoded on different chromosomes, several combinations of KIR and HLA alleles are possible. In particular, a specific KIR may be expressed in the absence of the cognate HLA molecule. Moreover, KIR/HLA interactions can exhibit different binding affinities. For instance, the binding between inhibitory KIR2DL3 and HLA-C1 is characterized by a lower affinity than that between KIR2DL1 and HLA-C2, while KIR3DL1 binds with high affinity HLA-BW4 molecules containing isoleucine at position 80 (BW4I80) as compared with threonine (BW4T80).[2] Considering that there are 15 genetic loci coding for KIRs and that many of these loci have several alleles, various KIR/HLA combinations can be present in a given individual, and this is expected to influence NK-cell effector functions.

A strong interaction between inhibitory KIRs and HLA molecules could play a negative role in protection against virus-infected or transformed cells. However a process of education (licensing) occurs during development of the mature pool of NK cells. The recognition of MHC class I molecules by inhibitory receptors shapes the effector functions of NK cells, leading to efficient responses in the case of high-affinity interactions and to hyporesponsiveness when the KIR/HLA binding is weak or missing.[4] By contrast, the concurrence of activating KIRs and their ligands, such as KIR2DS1 and HLA-C2, results in reduced NK-cell functional competence.[5]

Several immunogenetic studies have demonstrated that specific KIR/HLA compound genotypes increase or reduce the susceptibility to infectious, autoimmune or malignant disorders.[6] We have recently reported a strong association between the KIR/HLA genotype and the clinical outcome of HCC patients after therapeutic ablation.[7] In particular, activating KIR2DS5, homozygous HLA-C1 and HLA-BW4I80 were associated with improved patient survival, whereas HLA-C2 and HLA-BW4T80 were linked to dismal disease outcome. In addition the cytotoxic activity of NK cells was more pronounced in subjects bearing HLA-C1 alone or combined with specific inhibitory KIR ligands (i.e., KIR2DL2 and KIR2DL3). Our results are consistent with the licensing model, i.e., the acquisition of a full functional competence only by NK cells that express inhibitory receptors that recognize self MHC molecules. The relevance of NK-cell functions for the prognosis of HCC patients is supported by the survival advantage exhibited by subjects carrying both inhibitory KIRs and their cognate ligands (**Fig. 1**). Conversely, the low-affinity interactions between activating KIR2DS1 and

*Correspondence to: Gabriele Missale; Email: missale@tin.it
Submitted: 09/25/2013; Accepted: 09/26/2013; Published Online: 10/21/2013
Citation: Cariani E, Missale G. KIR/HLA immunogenetic background influences the evolution of hepatocellular carcinoma. OncoImmunology 2013; 2:e26622; http://dx.doi.org/10.4161/onci.26622

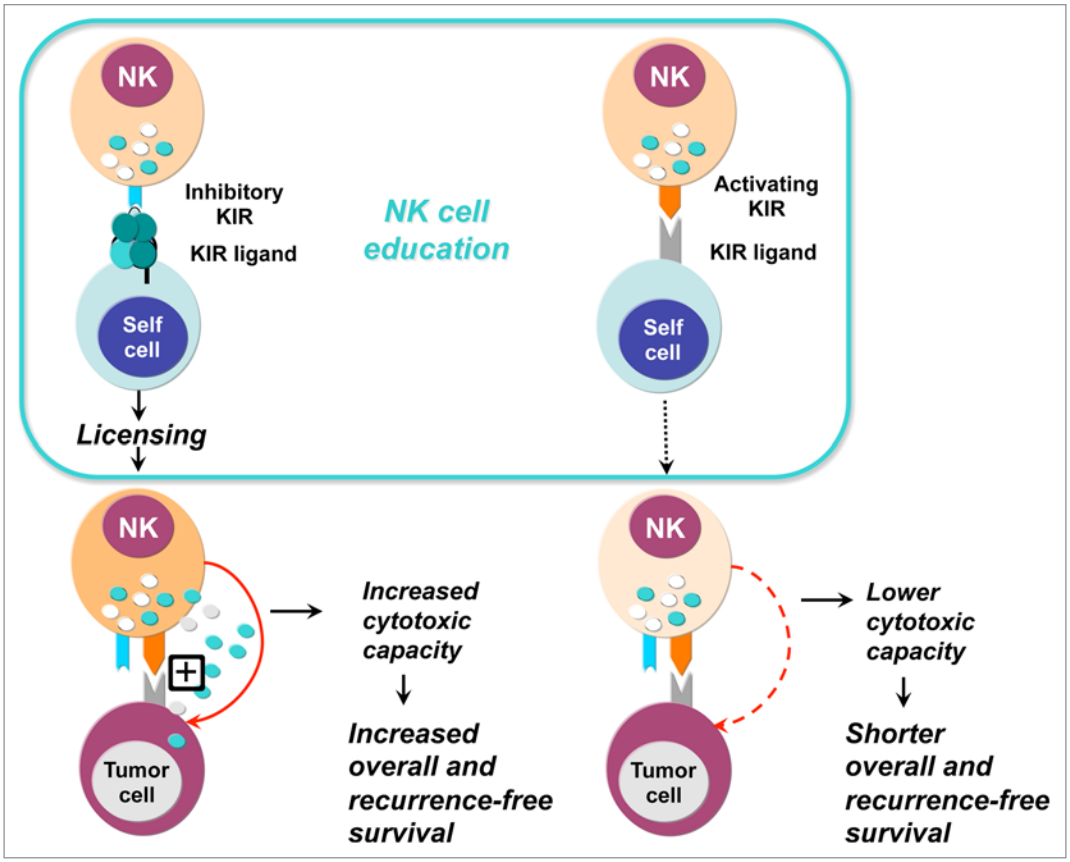

Figure 1. Potential impact of the interactions between killer cell Ig-like receptors (KIRs) and their ligands on the clinical outcome of hepatitis C virus (HCV)-linked hepatocellular carcinoma (HCC). The high-affinity binding of inhibitory KIRs and their ligands during development enhances the functions of natural killer (NK) cells through a process known as licensing. Conversely, the activity of NK cells expressing activating KIRs that bind self ligands is decreased, as it has been described for the interaction between KIR2DS1 and HLA-C2. These observations may provide a key for the interpretation of the functional and clinical correlates of KIR/HLA genotypes HCV-linked HCC.

HLA-C2 would lead to a hyporesponsiveness of NK cells,[5] at least in part explaining the reduced cytotoxic activity of NK cells isolated from HLA-C2-expressing HCC patients, who exhibited poor overall survival (**Fig. 1**).

The significance of KIR2DS5 as a predictor of extended overall and recurrence-free survival is open to speculation, since the specific ligand of this receptor remains unknown. KIR2DS5 is present in a fraction of KIR B haplotypes, which are characterized by a higher number of genes encoding activating KIRs as compared with the A haplotype.[2] Thus, KIR2DS5 might either impact on the activity of NK cells in a direct fashion, or represent a surrogate marker for a KIR haplotype that influences disease outcome in HCC patients.

The KIR haplotype of NK cells can influence the outcome of infectious diseases and malignancies in opposite ways. In the specific setting of chronic hepatitis C virus (HCV) infection, the KIR2DL3/HLA-C1 genotype has been associated with the spontaneous resolution of infection and increased NK-cell cytotoxicity, whereas HLA-C2 was frequently detected among patients exhibiting chronic disease. Homozygous KIR2DL3/HLA-C1 has also been implicated in the response to the treatment of chronic HCV infection, whereas homozygous HLA-C2 was associated with resistance to therapy. In addition, the KIR3DS1/HLA-BW4I80 genotype and HLA-C1 are considered protective against the development of HCV-related HCC (reviewed in ref. 8). Our study, which was focused on predictors of disease outcome, confirmed the relevance of these genotypes in the evolution of HCC after treatment. Taken together, these observations confirm the involvement of the same KIR/HLA profiles both in the immune response to HCV infection and in its long-term consequences such as HCC development and prognosis.

The implication of our work is 2-fold: apart from identifying mechanisms that may govern the evolution of HCC, the genetic backgrounds that we observed to influence disease outcome in HCC patients appear to have functional correlates amenable to therapeutic correction.

In patients with HCC and other cancers,[1,9] NK cells are often functionally impaired. Our findings suggest that restoring the activity of NK cells could reduce the risk of disease recurrence upon ablative therapy or surgery, potentially impacting on the survival of HCC patients. Different strategies have been undertaken to implement NK cell-based therapies, including the administration of immunostimulatory thalidomide derivatives, the adoptive transfer of allogeneic NK cells, the activation or genetic engineering of autologous NK cells in vitro followed by their reinfusion, and the

use of monoclonal antibodies that block the interaction between inhibitory KIRs and their ligands.[9,10] These approaches might be particularly useful in HCC patients, who generally have dismal prognosis even upon curative treatments.

References

1. Tian Z, Chen Y, Gao B. Natural killer cells in liver disease. Hepatology 2013; 57:1654-62; PMID:23111952; http://dx.doi.org/10.1002/hep.26115
2. Purdy AK, Campbell KS. Natural killer cells and cancer: regulation by the killer cell Ig-like receptors (KIR). Cancer Biol Ther 2009; 8:2211-20; PMID:19923897; http://dx.doi.org/10.4161/cbt.8.23.10455
3. El-Gazzar A, Groh V, Spies T. Immunobiology and conflicting roles of the human NKG2D lymphocyte receptor and its ligands in cancer. J Immunol 2013; 191:1509-15; PMID:23913973; http://dx.doi.org/10.4049/jimmunol.1301071
4. Höglund P, Brodin P. Current perspectives of natural killer cell education by MHC class I molecules. Nat Rev Immunol 2010; 10:724-34; PMID:20818413; http://dx.doi.org/10.1038/nri2835
5. Fauriat C, Ivarsson MA, Ljunggren HG, Malmberg KJ, Michaëlsson J. Education of human natural killer cells by activating killer cell immunoglobulin-like receptors. Blood 2010; 115:1166-74; PMID:19903900; http://dx.doi.org/10.1182/blood-2009-09-245746
6. Kulkarni S, Martin MP, Carrington M. The Yin and Yang of HLA and KIR in human disease. Semin Immunol 2008; 20:343-52; PMID:18635379; http://dx.doi.org/10.1016/j.smim.2008.06.003
7. Cariani E, Pilli M, Zerbini A, Rota C, Olivani A, Zanelli P, Zanetti A, Trenti T, Ferrari C, Missale G. HLA and Killer Immunoglobulin-like Receptor Genes as outcome predictors of hepatitis C virus-related hepatocellular carcinoma. Clin Cancer Res 2013; (Forthcoming); PMID:23938290; http://dx.doi.org/10.1158/1078-0432.CCR-13-0986
8. Jamil KM, Khakoo SI. KIR/HLA interactions and pathogen immunity. J Biomed Biotechnol 2011; 2011:298348; PMID:21629750; http://dx.doi.org/10.1155/2011/298348
9. Fregni G, Perier A, Avril MF, Caignard A. NK cells sense tumors, course of disease and treatments: Consequences for NK-based therapies. Oncoimmunology 2012; 1:38-47; PMID:22720210; http://dx.doi.org/10.4161/onci.1.1.18312
10. Oberoi P, Wels WS. Arming NK cells with enhanced antitumor activity: CARs and beyond. OncoImmunology 2013; 2:e25220; http://dx.doi.org/10.4161/onci.25220

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.