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Editorial
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Role of KIR and HLA in Donor Selection for HSCT

*Svetlana Vojvodić**

Department for Laboratory Diagnostics, Institute for Blood Transfusion of Vojvodina, Serbia

Editorial

Majority of the patients with hematological diseases lacking human leukocyte antigen (HLA) matched sibling donors are treated by hematopoietic stem cells transplantation (HSCT) from HLA matched unrelated donors. Polymorphisms of HLA genes represent a major barrier to HSCT because HLA-A, -B, -C and DRB1 incompatibilities confer a higher risk of acute graft-versus-host disease (aGVHD) and mortality. HLA compatibility is a crucial parameter that influences the clinical outcome of HSCT. Whereas it is technically simple to assess genotypic HLA compatibility in a related HSCT setting, the situation becomes more complex for unrelated donor selection, since there are non-HLA immunogenetic markers that are of great importance for the HSCT outcome. Years of intensive research in humans have shown a special importance of NK cells in the hematological diseases and in mediating favorable HSCT outcomes.

Natural killer (NK) cells are one of the first cells to recover following allogeneic HSCT and are believed to play an important role in facilitating engraftment or preventing post-transplant infection and tumor recurrence. Several studies have provided novel insights into the mechanisms by which NK cells mediate these highly clinically relevant immunological functions. In particular, the ability of NK cells to reduce the risk of graft versus host disease (GVHD) by eliminating dendritic cells and increase the graft versus leukemia effect (GVL) by eliminating leukemic clones in the setting of HLA haploidentical HSCT highlights their clinical potentials. Conventional human NK cells are identified by the expression of CD56, NKp46 and by the absence of CD3. Other cell surface receptors commonly expressed in NK cells fall within three families. They are, 1) killer immunoglobulin like receptors (KIR), 2) NKG2A-C that form a heterodimer with CD94, and NKG2D, which is expressed as a homodimer and relies on DAP10 and DAP12 adaptor proteins, and 3) natural cytotoxicity receptors (NCR).

KIRs have either activating or inhibitory function by interacting with HLA class I, HLA-C alleles and Bw4 alleles, present on normal cell surface. Inhibitory KIRs recognize epitopes shared by groups of HLA-class I alleles (KIR ligands): KIR2DL1 recognizes HLA-C group 2 alleles, KIR2DL2 and KIR2DL3 recognize HLA-C group 1 alleles, and KIR3DL1 is the receptor for HLA-Bw4 alleles. Fifteen KIR genes can be categorized into inhibitory (KIR A-haplotype) or activating haplotypes (KIR B haplotype) based on their gene content. These haplotypes can be further divided as telomeric and centromeric parts, which contain either A- or B-motifs according to the presence or absence of A- or B-haplotype defining KIR genes. Since the KIR and HLA alleles segregate independently, even in the setting of fully matched HLA transplants, there is a high likelihood that KIR genes are mismatched. In unrelated transplants, this likelihood increases, as only 0.24% of unrelated individuals will have matching KIR.

An array of diverse KIR-associated HSCT outcomes in the literature owes itself largely to the differences in transplant protocols across various centers, and partly to the ways NK cell alloreactivity is inferred. According to the 'Perugia model', the D-R KIR-ligand incompatibility leads to stronger NK cell mediated graft versus leukemia (GVL) effect resulting in protection from leukemia relapse. The 'Memphis model' (or the missing ligand model) imparts NK cell alloreactivity to one or more missing HLA ligands in the recipient for the donor inhibitory KIR. The 'KIR haplotype model' proposed by the Minnesota group, apportions higher NK alloreactivity to high number of activating KIR genes (haplotype B) in the donor. According to this model, in non-ATG conditioned HSCT, use of donors carrying KIR-B haplotypes leads to better overall and relapse-free survival among the recipients carrying one or two C1 bearing HLA-C epitopes..

NK cells following HLA-haploidentical or half-matched HSCT significantly reduces the relapse of acute myeloid leukemia (AML), decreased GVHD, improved engraftment and the overall survival as reported by some groups. When this principle was applied to other types of transplants the results have varied significantly. In some studies, KIR-ligand mismatches demonstrate an improved

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Correspondence:
Svetlana Vojvodić, Department for Laboratory Diagnostics, Institute for Blood Transfusion of Vojvodina, Tissue Typing Compartment, Hajduk Veljkova 9a, 21000 Novi Sad, Serbia, Tel: +381-21-4877-963; Fax: +381-21-4877-978; E-mail: svetlana.vojvodic021@gmail.com

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overall survival, however, this wasn't observed in other studies. In the majority of studies, KIR-ligand mismatch was associated with increased acute GVHD. Several studies demonstrate a reduced risk of relapse with missing KIR-ligand; however, one study demonstrated an increase in relapse. Heterogeneity in the treatment procedures (conditioning regimen, graft composition and post-transplant immune suppression) and in the patient population (disease, risk category) might explain the conflicting results concerning KIR ligand incompatibility. More specifically, unrelated grafts contain more T cells than haploidentical grafts and this has been shown to be associated with poor reconstitution of potentially alloreactive NK cells.

To conclude, the interactions between donor KIR and recipient HLA class I can be used to inform donor selection to improve the HSCT outcome. Many studies did not perform KIR genotyping, but used an algorithm to predict KIR-HLA mismatches. Not always the presence of the corresponding HLA ligand means inhibition as the KIR gene may be absent. Another factor that may be related to the survival of these patients is the presence of activating KIRs, which is information only available from genotyping. High resolution sequencing of KIR genes is also proving useful to predict the HSCT outcome by identifying the real alleles involved in the rejection process, GvHD and relapse, all factors that affect survival rates.