KIR (Killer Ig-like Receptor) Mismatch

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Killer Ig-like Receptor (KIR) is the most polymorphic NK receptor family in humans. KIR comprises activating and inhibitory receptors and the interaction of inhibitory KIRs with HLA class I during NK cell maturation is crucial for NK cell education and generation of self-tolerant NK cells. Hence, NK cells do not kill autologous cells as long as expressing the corresponding HLA class I ligand. However, downregulation of HLA class I expression induce the killing of autologous cells through a mechanism of ‘missing self-recognition’. In hematopoietic stem cell transplantation (HSCT), particularly in haploidentical HSCT, a KIR-ligand mismatch in the graft-versus-host (GVH) direction can occur. In this situation, we expect that the donor-driven alloreactive NK cells eliminate residual leukemic cells and thus reduce the incidence of tumor relapse and also remove host dendritic cells (DCs) and T cells, reducing GVHD and graft rejection.

In this regards, presence of alloreactive NK cells subsets in HSCT grafts would be an important feature which needs to be considered for optimal allogeneic HSCT donor selection. Although the mismatches between donor and recipient based on ‘missing self-recognition’ is the prerequisite to exert alloreactivity, the models predicting NK cell alloreactivity varies depending on the clinical settings which were evaluated by different groups. Missing-self/KIR-Ligand mismatch or ligand-incompatibility model, receptor-ligand mismatch model, missing ligand model and activating KIR model have been investigated. To get the complete information about mismatches of ligand-ligand, receptor-ligand and receptor-receptor between the donor and recipient or identifying activating KIR in the donor, high resolution genotyping and phenotyping of HLA and KIR should be performed.

The effect of KIR is affected by transplantation setting such as haplo-HSCT and unrelated donor (URD) HSCT, or use of pretransplant ATG. In contrary to the beneficial effect in haplo-HSCT, the worse outcomes have been reported in URD HSCT with KIR-ligand mismatch. Missing-ligand model with donor HLA types reflects more accurate interaction between donor NK cells and recipient cells, thus are predictive for outcome. Donor with at least one activating KIR haplotype, B/x has contributed to significant lower relapse. Although KIR licensing is known as an important factor for more efficient killing of tumor, depending on the clinical studies, it’s not been clearly estimated in vivo HSCT setting. It is obvious that the NK cell alloreactivity can change the reconstitution environment after haplo-HSCT and URD-HSCT regardless of sources and HLA matching level. However, to overcome the heterogeneity of algorithms and to optimize the KIR effect, larger multicenter prospective trials may be warranted.
References


