NKG2D and KIR receptors and their role in allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia

ABSTRACT

NK cells (from Natural Killer) play an important role in the fight against viral infections or cancer. These immune cells are also able to recognize cells without HLA (human leukocyte antigen) proteins and, unlike T cells, can eliminate cells that try to escape immune surveillance by internalizing these molecules. For example, leukaemia stem cells, which are thought to be responsible for leukaemia relapse, are able to do this.

The activity of NK cells is controlled by inhibitory and activating receptors. Among the best studied are the KIR (killer-cell immunoglobulin-like receptor) receptors, which can be both inhibitory and activating and whose ligands are primarily HLA molecules. The most prominent activating receptor is NKG2D (natural killer group 2-D), whose ligands are the stress-induced proteins MICA and MICB (MHC class I-related chain-A or -B) and ULBP (human cytomegalovirus Unique Long 16-binding protein).

In the first part of this study, we aimed to describe whether the Czech population corresponds in allele frequency and polymorphisms of KIR and NKG2D receptors and MICA and MICB ligands to other populations of Caucasian origin. In both cases we observed the same results as in other studies.

In the second part, we focused on studying the presence of specific MICA, MICB or NKG2D polymorphisms or HLA-KIR matching and the effect of these changes/interactions on transplant outcome. We observed that a graft from a donor with at least one MICA-14 Gly allele was statistically significantly associated with worse overall patient survival. We also observed a negative effect of the MICB-58 Glu allele on relapse-free survival. The result with MICB-58 was not statistically significant in multivariate analysis. On the other hand, we observed no effect of the already known MICA-129, MICB-98 and HNK/LNK (high NK/low NK) polymorphisms in NKG2D on transplantation outcome.

In the analysis of KIR receptor matching and mismatch with HLA ligand, we observed that the higher the match between KIR and HLA in inhibitory receptors (2-3 vs. 5), the higher the risk of relapse and the worse the overall survival of patients. After comparing all individual KIRs that had sufficient HLA for statistical analysis, we observed that KIR2DL1-HLA matching led to a higher risk of relapse. However, the effect did not translate into overall survival, although the same trend as for relapse-free survival was observed.

Our study demonstrated the effect of MICA and MICB polymorphisms and the degree of matching between KIR and HLA on the outcome of hematopoietic cell transplantation. Knowledge of NK cell receptor polymorphisms may serve as an

additional criterion for donor selection and contribute to better transplantation outcomes in the future.