Single-nucleotide polymorphisms in MICA and MICB genes could play a role in the outcome in AML patients after HSCT

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INTRODUCTION

NK cells play important role in the allogeneic hematopoietic stem cell transplantation (HSCT); therefore, it is crucial to understand their regulation. NKG2D and its ligands, MICA and MICB, are known as the key regulators of NK cells. The NKG2D receptor is strongly evolutionarily conserved but its ligands are highly polymorphic genes with the main variability in the exons 2–4 encoding extracellular (receptor-binding) domains α1, α2, and α3. The best-known functional polymorphisms with a role in HSCT are in exon 3 of MICA and MICB, called MICA-129 and MICB-98. Here we describe the role of polymorphisms within the exon 2 – MICA-14 and MICB-58.

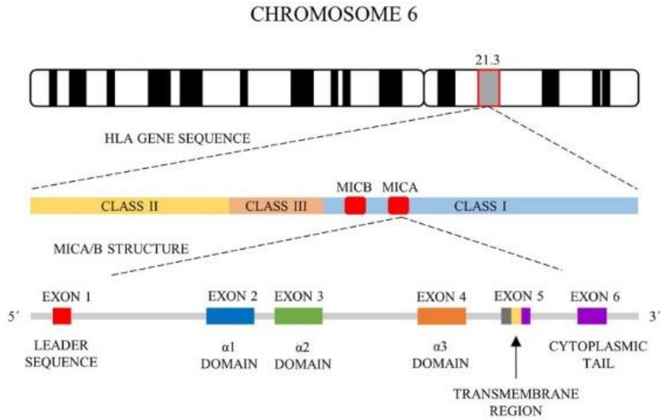

Figure 1. Schematic representation of MICA and MICB structure

METHODS

Clinical data were collected from 124 patients with myeloid malignancies (95% AML, 5% MDS) after HSCT (with related donors in 20%, haploidentical in 28% and unrelated in 52% cases) at the Department of Hematology and Oncology, University Hospital Pilsen. Donors' and patients' DNA samples were sequenced for exons 2-4 of MICA and MICB and translated into amino acids. Analyses of OS and RFS and visualizations were performed using Kaplan–Meier analysis and log-rank testing. Statistically significant clinical parameters from univariate analysis were then used for multivariate Cox regression.

RESULTS

Donor's MICA-14 plays a role in the overall survival

We found that graft from a donor with at least one MICA allele containing glycine (instead of tryptophan) at position 14 (MICA-14Gly) is significantly associated with deterioration of patient's overall survival (with $p < 0.01$ for univariate analysis and $p < 0.05$ for multivariate analysis with HR = 2.254 (95% CI, 1.058–4.801)) compared to patients with graft without MICA-14Gly (Figure 2A).

Patient's MICB-58Lys can be linked to a lower risk of relapse

We observed the role of the MICB-58 polymorphism. The patients without the MICB-58Glu had a significantly lower risk of relapse than patients with MICB-58Glu in univariate analysis ($p < 0.01$) (Figure 2B), but this observation was not confirmed by multivariate analysis ($p = 0.069$ with HR = 3.764, 95% CI, 0.902–15.707). The reason why the result of multivariate analysis is not statistically significant can lie in higher representation of patients transplanted with active disease in the group of patients with MICB-58Glu (51%) versus the patients with MICB-58Lys only (19%).

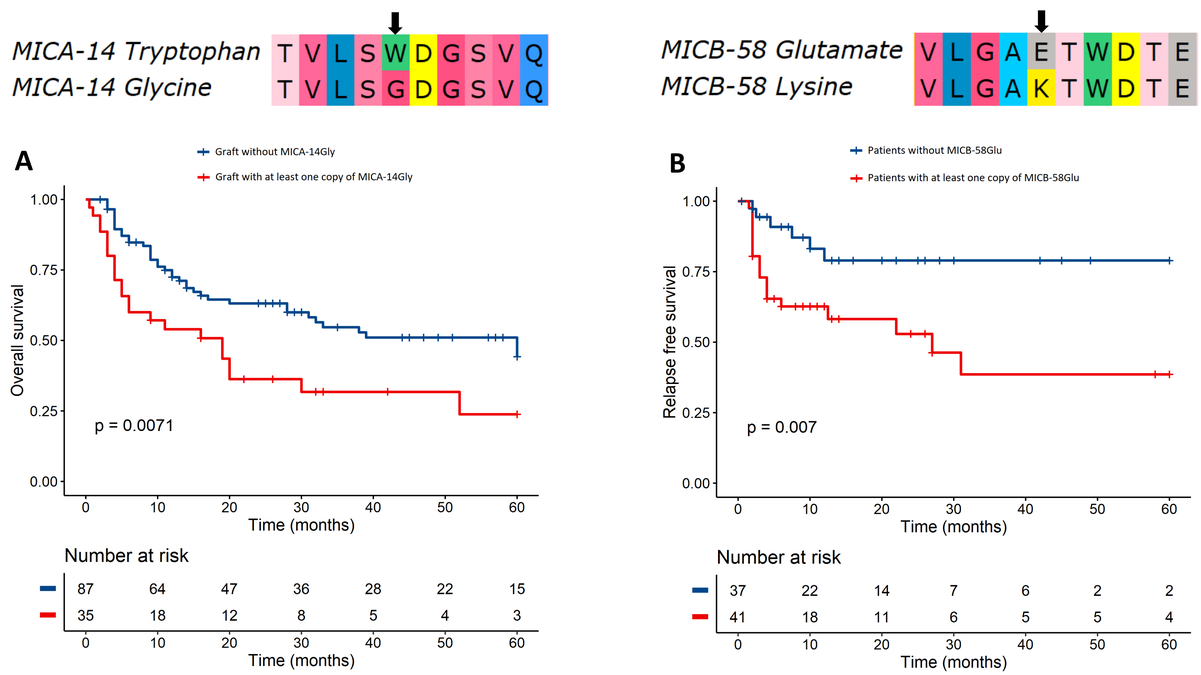

Figure 2.

A
OS of patients transplanted with graft containing at least one copy of MICA-14Gly versus grafts lacking MICA-14Gly group of MICA exon 2.

B
Univariate analysis – RFS of patients with at least one copy of MICB-58Glu versus patients lacking MICB-58Glu group of MICB exon 2.

CONCLUSION

We found a new polymorphism in donors (MICA-14Gly) influencing OS in our cohort of patients undergoing HSCT for AML/MDS and MICB-58 with a potential role on relapse.

FUNDING

The study was funded by the Ministry of Health of the Czech Republic—Czech Health Research Council (project no. NV18-03-00277).

Machuldova A, et al. J Clin Med. 2021;10(20):4636. doi:10.3390/jcm10204636