Killer cell immunoglobulin-like receptor and HLA ligand pairs. A role in NK cell licensing in HLA class I mismatched hematopoietic stem cell transplantation for malignancy

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Introduction: NK cells are involved in clearance of cancer cells in certain types of cancers via natural cytotoxicity, (common in hematopoiesis and immune system malignancies and solid tumors). Inhibitory killer cell immunoglobulin-like receptors (iKIRs) function as a protective mechanism for normal autologous cells, provided iKIR engagement by self HLA class I cognate ligands.[1] NK cell licensing effect highly increases the NK cell reactivity against tumor in animal models.[2] NK cell licensing is dependent on the co-expression of iKIRs on NK cells and their cognate HLA class I ligand environment.[3,4]

Objective: We assessed tumor outcomes (progression free survival-PFS and relapse incidence-RI) in N=283 patients including strata with sufficient and deficient NK cell licensing due to HLA class I mismatch.

Methods: Patients underwent HSCT from HLA matched (N=198) and HLA class I single mismatched (N=85) unrelated donors due to myelo- or lymphoproliferative malignancies. HLA class I (A, B and C) alleles and KIR genes in donors were assigned to cognate KIR-HLA ligand pairs. Recipient group with missing HLA class I cognate allele was stratified (N=12).

Results: We found different numbers of licensing KIR-HLA cognate pairs in donors (Table 1). In N=12 recipients single donor's cognate KIR-HLA pair was missing due to HLA mismatch (licensing downward resetting). We found dramatically reduced PFS (52.3% to 8.4%, P=0.00010) and increased RI (17.3% to 30.0%, P=0.013) among patients with the licensing downward resetting status after transplantation from HLA mismatched donor (Figures 1 and 2, respectively). The extremely adverse PFS have withstand the correction when stratified groups were restricted to HLA mismatched donor-recipient pairs (52.0% vs. 8.4%, P=0.00087). Among patients WITHOUT the licensing downward resetting status after transplantation from HLA mismatched donor the PFS and RI were similar to patients transplanted from fully matched donors (Figures 1 and 2, respectively). The incidence of aGvHD was comparable in licensed and downward resetting groups of patients (53.0% vs. 66.7%, OR=0.94, 95%CI 0.83-1.07, p=0.36).

Conclusions: We conclude that anti-tumor function of repopulated donor NK cells is associated with iKIR-HLA-dependent licensing and it can be lost in malignant patients after HSCT if the mismatched HLA ligand in patient does no longer belong to cognate iKIR-HLA pair. The therapeutic effect of NK cell-based tumor immunotherapy is highly dependent on the level of NK cell licensing.

Table 1: Number of NK cell licensing systems in donors (N=283) (C1:KIR2DL2/3, C2:KIR2DL1, Bw4:KIR3DL1, A3/11:KIR3DL2)

Systems	Count (%)
0	1 (<1)
1	21 (7.4)
2	111 (39.2)
3	124 (43.8)
4	26 (9.2)

Figure 1. *Disease Free Survival*

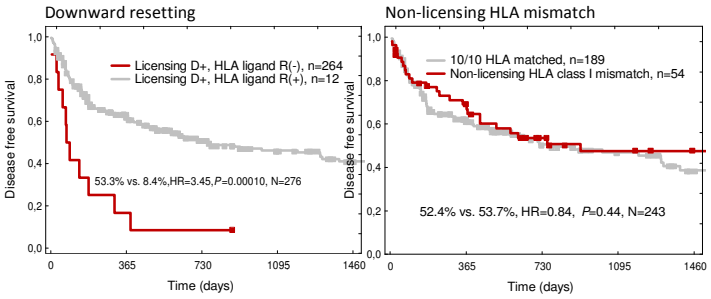
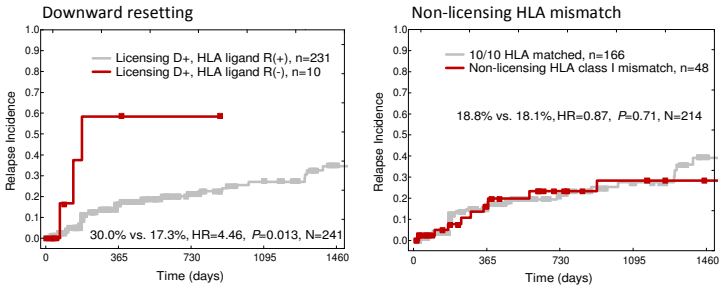


Figure 2. *Relapse Incidence*



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Biography

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