NK Cell Activation through KIR-HLA Interactions Decreases Leukemia Relapse after Transplant

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Hematopoietic stem-cell transplantation (HSCT) is used to treat patients with a number of cancers and hematological diseases, including acute myeloid leukemia (AML). AML is a cancer of white blood cells of the myeloid lineage, which accumulate in the bone marrow as immature blasts and disrupt normal blood cell development. One potential problem with HSCT is the possibility of donor cells detecting recipient cells as foreign and inducing graft-versus-host disease (GVHD). To prevent this, unrelated HSCT donors are matched to recipients based on ten alleles for the human leukocyte antigen (HLA).

Natural killer (NK) cells are part of the innate immune system that mediates recognition of self antigens and that targets cells expressing non-self antigens for destruction. NK cells recognize HLA present on all cells through activator and inhibitor cell surface receptors, including killer-cell immunoglobulin-like receptors (KIRs). All KIRs are randomly expressed on NK cells, which are educated to self-HLA when they mature. KIRs vary genetically between people, and the balance of KIR activating and inhibiting signals regulates NK cell function. Donor NK cells mediate an antileukemic effect in HSCT recipients when inhibitory KIRs are mismatched for HLA type in transplants, since these cells will recognize the recipient leukemia cells as foreign. The mismatched donor NK cells can decrease the rate of relapse; however, the mismatched transplant also has an increased risk of GVHD.

Activating KIRs can also mediate NK cell antileukemic effects by targeting cells with matched HLA between donor and recipient, with decreased risk of GVHD. In collaboration with researchers from Memorial Sloan Kettering, Drs. Ted Gooley, Effie Petersdorf, and Mari Malkki from the Clinical Research Division asked if the presence of the specific activating receptor *KIR2DS1* in donors affected outcomes in AML patients receiving HSCT. KIR2DS1 is the only activating receptor that can either activate or tolerize NK cell function depending on the HLA interaction. In a retrospective study, clinical data and DNA genotyping was assessed for 1277 AML patients who received HSCT from unrelated donors matched for *HLA-A*, *B*, *C*, *DR* and *DQ* or with a single mismatch to minimize the contribution of inhibitor KIRs. Results indicated that patients who received HSCT from *KIR2DS1*-postive donors had a significantly lower rate of relapse than *KIR2DS1*-negative donors, 26.5 percent

versus 32.5 percent respectively (95% CI, 0.61 to 0.96; P=0.02).

KIR2DS1 recognizes HLA-C1 and HLA-C2 alleles. Previous published data showed that homozygous *HLA-C2* tolerizes NK cell activation by KIR2DS1, decreasing NK cell function. In accordance, the antileukemic effect of *KIR2DS1*-positive donors was only mediated if those donors also had *HLA-C1/C1* homozygous or *HLA-C1/C2* heterozygous alleles, 24.9 percent relapse, versus donor*HLA-C2/C2* homozygous alleles, 37.3 percent relapse (95% CI, 0.28 to 0.75; P=0.002). Recipients with *HLA-C2/C2* had increased relapse rates, regardless of *KIR2DS1* status, most likely due to causes independent of *KIR2DS1*.

Activating KIR receptors are diverse within the population, and most people have multiple activating KIRs. Donors positive for*KIR2DS1* are mostly positive for *KIR3DS1* as well, yet *KIR3DS1*-positive status had no effect on AML relapse. However, *KIR3DS1*-positive donor cells decreased mortality, 60.1% versus 66.9% for *KIR3DS1*-negative donor cells in agreement with a previous study. This suggests that activating KIRs could provide different mechanisms for improved HSCT outcomes. By assessing the presence of KIR and HLA interactions of transplant donor and recipients, whether inhibitory or activating, patient outcomes after HSCT may be improved. Future prospective trials will need to be organized to address this question. Importantly, NK cell protective effect is most effective in myeloid leukemias, no protection from relapse was observed by *KIR2DS1*-positive donors in 427 transplant patients with acute lymphoblastic leukemia (ALL).

Venstrom JM, Pittari G, Gooley TA, Chewning JH, Spellman S, Haagenson M, Gallagher MM, Malkki M, Petersdorf E, Dupont B, Hsu KC. 2012. HLA-C-dependent prevention of leukemia relapse by donor activating KIR2DS1. *New England Journal of Medicine*367(9): 805-16.

Also see. Velardi, A. 2008. Role of KIRs and KIR ligands in hematopoietic transplantation. *Current Opinion in Immunology* 20 (5): 581–587.

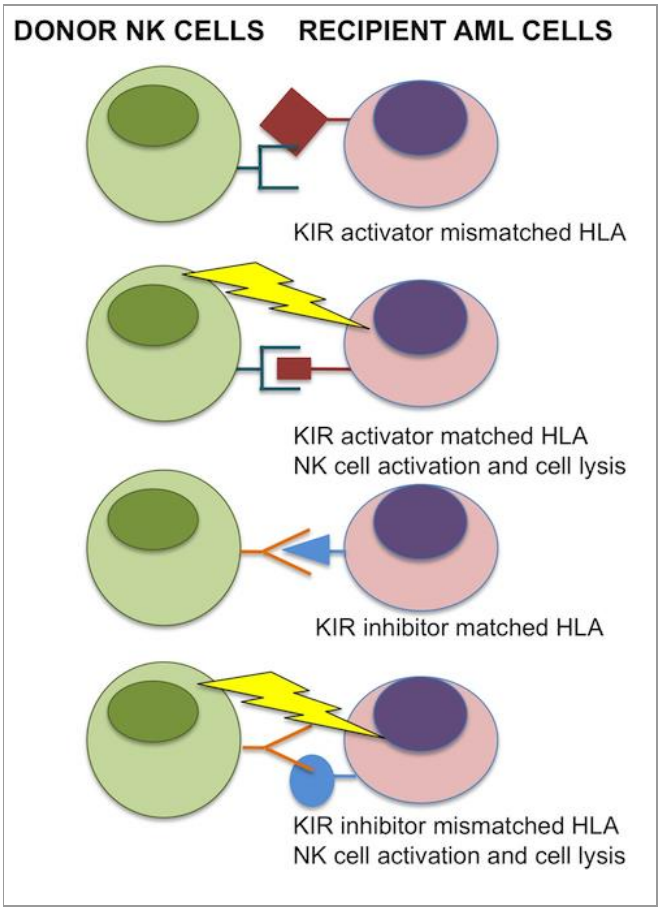

Image adapted from Velardi A., 2008.

NK cell function is regulated by KIR interactions with matched HLA class I alleles. In the case for inhibitor KIRs, binding with matching HLA prevents donor NK cell activation to self. If HLA is mismatched in transplant recipient leukemic cells, NK cells are relieved from inhibition and induce cell lysis. For activating KIRs, donor NK cells that bind the matched HLA are activated and induce cell lysis of transplant recipient AML cells. KIR2DS1 is an activating NK cell receptor that decreases the relapse rate in AML transplant recipients with HLA-C1/C1 or HLA-C1/C2 alleles.