Do educated natural killer cells make the grade in treating acute myeloid leukemia?

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The functions of natural killer (NK) cells are regulated by a complex array of inhibitory and activating killer cell immunoglobulin-like receptors (KIR). Under physiological conditions, recognition of self-HLA class I ligands on normal cells by inhibitory KIR blocks spontaneous killing by NK cells.[1] In contrast, acute myeloid leukemia (AML) blasts lacking surface HLA class I become highly sensitive to lysis consequent to NK release from KIR-mediated inhibition. The precise threshold for NK activation is further regulated by additional input signals from a panoply of activation receptors, including activating KIR.[1]

KIR2DS1 is an activating NK receptor with low affinity for HLA-C2 molecules (HLA-C molecules that share a common lysine^{80}) but no affinity for HLA-C1 (that share a common asparagine^{80}).[2] Since *HLA* and *KIR* genes segregate independently, individuals inheriting *KIR2DS1* may be further grouped according to the levels of activating HLA-C2 ligand that NK cells encounter *in vivo*. This is significant because KIR2DS1-expressing NK clones derived from *C2/C2* donors are less able to generate cytokines or kill when compared to similar clones derived from donors that are either *C1/C2* or *C1/C1 (C1/X)*.[3] These findings are consistent with a model in which physiological expression of HLA-C2 on normal cells educates or 'tunes' NK cells bearing the KIR2DS1. Although the mechanisms underlying this form of tolerance induction are not known, education via activating KIR may be required to prevent inappropriate NK triggering in the steady state.

These findings are of potential clinical relevance, since the education model predicts that following allogeneic stem cell transplantation, KIR2DS1$^+$ NK cells from *C2/C2* donors will be less effective in killing AML cells than those derived from *C1/X* donors. Hsu and colleagues have now explored this concept in an important study of 1,277 patients receiving mostly T-replete HLA-identical or single allele mismatched unrelated allografts for AML, where both HLA and KIR genotyping data were available.[4] In their analysis, protection against relapse was significantly enhanced following transplants from *KIR2DS1* positive compared to negative donors, especially under conditions of mismatching at the HLA-C locus.[4] Importantly, this benefit was restricted to *KIR2DS1* positive donors that were homozygous or heterozygous for *C1 (C1/X)*. When donors were *C2/C2*, the rate of relapse was similarly high in *KIR2DS1* positive and negative donors, in keeping with the concept that NK cells educated via an activating KIR become hypo-functional.

Should we now adjust donor selection policies to take account of this effect? Even within a very large study, it is difficult to control for the extensive heterogeneity within the *KIR2DS1* positive group. NK functions will also be influenced by co-inheritance of variable numbers of other *KIR* genes that individually or in composite have the potential to influence transplant outcomes.[5,6] Rigorous dissection of this heterogeneity and of its impact are still required before changes to donor selection policies can be recommended. Such studies will also need to link KIR/HLA genotyping data to biological readouts of KIR expression on NK clones after transplantation and determine actual rather than predicted NK function. This may also provide the opportunity to discover whether KIR2DS1-mediated education occurs exclusively within the donor or will also occur upon interactions with recipient cells following transplantation. The relative contribution of bone marrow-derived (donor) and non-hematopoietic (recipient) cells to NK education will be of relevance here, as will the functional plasticity of mature *versus* developing NK cells.

References

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