DONOR *KIR3DL1* AND *HLA-B* SUBTYPE COMBINATIONS PREDICT ACUTE MYELOGENOUS LEUKEMIA CONTROL AFTER HLA-COMPATIBLE HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Diverse interactions between subtypes of the natural killer (NK) receptor KIR3DL1 and HLA-B vary NK reactivity and HIV control. We hypothesized that these interactions could impact outcomes in allogeneic hematopoietic cell transplantation (HCT), where donor NK reactivity controls leukemic relapse. In 1328 patients with acute myelogenous (AML) undergoing HCT, subtype combinations of donor *KIR3DL1* and *HLA-B* predictive of weak or non-interaction were associated with lower relapse and overall mortality compared to strongly interacting pairs (relapse: HR=0.72, 95% CI: 0.57-0.90, p=0.004; mortality: HR=0.84, 95% CI: 0.72-0.98, p=0.030). Notably, these outcomes are especially prominent among recipients exhibiting HLA-$C1^+$ and $C2^+$ (relapse: HR 0.52, 95% CI: 0.37-0.73, p<0.001; mortality: HR 0.72, 95% CI: 0.57-0.91, p=0.006), and additive to the known beneficial combination of *KIR2DS1* + *HLA-C1* (relapse: HR=0.60, 95% CI 0.44-0.82, p=0.001; mortality: HR 0.77, 95% CI=0.63-0.95, p=0.01 compared with donor-patient pairs lacking beneficial KIR3DL1 and KIR2DS1 configurations).

HLA expression by AML cell lines and primary blasts is variable, upregulated by a pro-inflammatory environment, and capable of inhibiting NK cells. We find that NK cytotoxicity against KIR ligand-matched target cells corresponds with the predicted capacity of KIR3DL1:HLA-B subtype combinations for relapse control following HCT, suggesting that the NK cells' sensitivity to inhibition interferes with its anti-leukemic activity. Indeed, the intracellular retention of common KIR3DL1-null variants precludes inhibition of NK cells by HLA-B, but not their responsiveness against AML cells, demonstrating that inhibitory sensitivity and NK alloreactivity can be dissociated. Collectively, these findings reveal that sensitivity to inhibition by HLA present on leukemia cells is titrated by allele subtype combinations and a critical factor determining NK alloreactivity in HCT. Consideration of *KIR3DL1* and *HLA-B* subtypes in stem cell donor selection is highly feasible and may facilitate better disease control by minimizing NK inhibition in patients with AML undergoing allogeneic HCT.