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Formation of the Inhibitory KIR Repertoire in Human Natural Killer Cells

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ABSTRACT

Natural killer (NK) cells are lymphocytes of the innate immune system that are able to secrete cytokines and detect virus infected and transformed cells. Contrary to T cells, NK cells recognize targets that lack expression of MHC class I molecules at the cell surface, a phenomenon referred to as "missing self" recognition. The process is dependent on a NK cell receptor family termed killer cell immunoglobulin-like receptors (KIRs) and their interaction with MHC class I. However, although we have gained insights into the molecular specificity of NK cell responses, several fundamental questions relating to the generation of human NK cell repertoires remain elusive. Some studies imply that there is a minor effect of HLA on KIR expression frequencies, but it is unclear to what extent this leads to a bias for expression of self-KIRs in the total repertoire. In this thesis we sought to investigate how inhibitory KIR repertoires are formed and whether selection is required to preserve self tolerance and maximize the ability of NK cells to detect abnormal expression of MHC class I.

Here, we have used a unique platform for multi-parameter flow cytometry and performed a detailed evaluation of complete inhibitory KIR repertoires in healthy donors. We compared observed experimental data with theoretical data obtained under random sequential KIR acquisition in the presence and absence of selection. We found that co-expression of multiple KIRs was more frequent than expected by the product rule and that the probability of KIR acquisition increased with cellular expression of other KIRs. Presence or absence of self MHC class I molecules did not influence the total KIR repertoire, neither with respect to the number of receptors expressed nor the type (self versus non-self) of KIR. In parallel with the acquisition of KIRs we also noticed a gradual downregulation of NKG2A and appearance of CD57. Hence, we propose that the expression patterns of the receptors define different stages in a differentiation process of the $CD56^{dim}$ NK cell population. Our data provide new insights into the formation of human KIR repertoires and revisit prevailing models of NK cell selection.

The combination of *KIR* and *HLA* genes influence outcomes of human diseases and treatment thereof. In hematopoietic stem cell transplantation (HSCT), it is sometimes necessary to search for unrelated partially HLA-mismatched donors. In such situations, a potential beneficial role for NK cell alloreactivity may occur based on missing KIR ligands in the recipient. Prediction of NK cell alloreactivity in allogeneic HSCT is currently determined by *HLA* and *KIR* genotyping. However in this thesis we demonstrate that although a particular donor is mismatched to the recipient on a genetic level, the frequency of alloreactive NK cells may range from 0 to 62%. The results demonstrate a vast variability of the functional and alloreactive NK cell repertoire and have implications for donor selection in HSCT and adoptive NK cell-based immunotherapy.

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