The NK cell inhibitory receptor repertoire is shaped by MHC-dependent and independent effects

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***Short Abstract* — Natural Killer (NK) cells play an important role in many pathological conditions and treatments. Understanding the effects of the Major Histocompatibility Complex (MHC) on the NK cell repertoire is required for the prediction of their function in these situations. Here, we perform a statistical analysis on data describing NK cell repertoires in mice and humans from different MHC backgrounds, in order to characterize and quantify the effects of MHC-dependent and independent effects of MHC on the repertoire.**

***Keywords* — Natural Killer Cells. Lymphocyte Repertoires.**

I. Background

Natural killer (NK) cells specificity for target cells is determined by a range of stimulatory and inhibitory cell surface receptors. Inhibitory receptors for MHC class I are expressed in a variegated fashion and are responsible for self-nonself discrimination in NK cells [1]. There is an ongoing debate regarding whether NK receptor expression is random and independent, or is affected by the MHC class I [2-4]. Our aim was to quantify the effects of MHC-dependent and independent processes that shape the NK repertoire.

We used statistical tools and information theory-based tools in order to characterize and quantify the deviations of the observed repertoire from the 'product rule', which describes random association of independent events. If tolerance is achieved by regulating the expression of different combinations of receptors, then the expression pattern of the inhibitory receptors would not comply with the product rule, but rather differ between hosts with a different MHC background and be similar between hosts with a similar MHC background. Furthermore, combinations of self-MHC receptors should exhibit different deviation patterns than combinations of non-self MHC.

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II. Methods

A. Data

We used multicolor flow cytometry to examine NK cell repertoires in MHC-sufficient mice and humans and MHC-deficient mice. Repertoires consisted of the numbers of cells expressing each possible combination of the five inhibitory receptors examined.

B. Model

A Jensen-Shannon distance-based algorithm was used in order to measure the distance between individuals within the same MHC background and between different MHC backgrounds. Student's t-test was used to compare the observed repertoire and the expected repertoire, assuming receptor expression follows the product rule.

III. Results and Conclusions

The inhibitory receptor repertoire in MHC-deficient mice deviates significantly from the 'product rule'. These deviations appear to be random and could be due to epigenetic modifications in the receptor genes or variations of promoter activities. MHC-sufficient mice displayed additional MHC class I allele specific repertoire changes, on top of those dictated by MHC-independent effects. Human repertoires showed large inter-individual deviations from each other, but as a group also deviated from the 'product rule'. Due to the large variation between individuals, no certain conclusions regarding potential MHC-effects in humans could be derived.

References

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