

 NATURAL KILLER CELLS

A virtual pick and mix

The diversity of the natural killer (NK) cell repertoire is determined by the array of germline-encoded activating and inhibitory receptors that they express. Using mass cytometry (also known as CyTOF) to analyse human NK cell receptor expression, Horowitz *et al.* describe an unprecedented level of NK cell diversity and confirm previous suggestions that inhibitory receptor expression is mainly determined by genetics, whereas activating receptor expression is mainly influenced by environmental determinants.

Human peripheral blood NK cells from a cohort of 5 sets of monozygotic twins and 12 unrelated healthy individuals of defined HLA and killer cell immunoglobulin-like receptor (KIR) genotypes were used in this

study. The diversity of the NK cell repertoire in this cohort was analysed by mass cytometry, using a panel of 36 monoclonal antibodies that were specific for lineage markers and NK cell receptors. Classification of the cells as positive or negative for the expression of each of the 28 NK cell receptors facilitated the assessment of 268,435,456 receptor combinations and revealed a vast heterogeneity of NK cell phenotypes. No single phenotype accounted for more than 7% of the total NK cells, and only 14 of the 28 receptors analysed were expressed by NK cells in the 50 most frequent phenotype populations. As a result of the abundance of low-frequency phenotypes, the authors also used a clustering algorithm to further analyse the data.

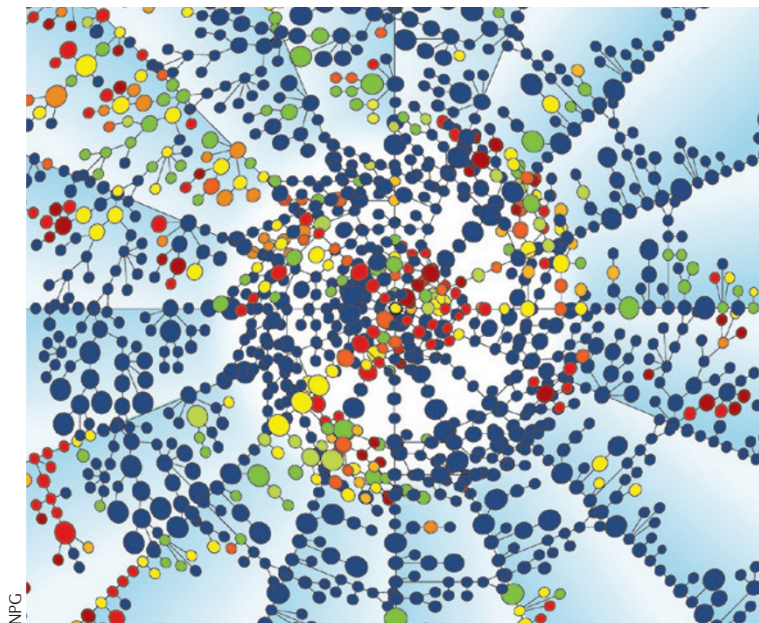
Both analytical algorithms revealed that the distribution of inhibitory NK cell receptor expression was more similar for monozygotic twins than for unrelated individuals, which suggests that host genetics determine the inhibitory receptor repertoire. By contrast, the level and frequency of activating receptor expression on NK cells was more diverse, even between twins, which suggests that environmental factors influence activating receptor expression.

Further analyses revealed that the human NK cell repertoire is anchored by a less mature NKG2A⁺CD94⁺ NK cell population and a more mature CD16⁺CD57⁺ NK cell population, with the stochastic expression of additional NK cell receptors creating enormous phenotypic diversity. Quantification of this diversity predicted between 6,000 and 30,000 distinct NK cell phenotypes within an individual and an estimated 108,000 to 125,000 NK cell phenotypes on a population level.

These data reveal a vast phenotypic diversity of NK cells and suggest a mechanism by which NK cells could maintain self tolerance through the strict genetic control of inhibitory receptor expression, while maintaining flexibility to respond to infections and cancers through the environmental control of activating receptor expression.

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ORIGINAL RESEARCH PAPER Horowitz, A. *et al.* Genetic and environmental determinants of human NK cell diversity revealed by mass cytometry. *Sci. Transl. Med.* <http://dx.doi.org/10.1126/scitranslmed.3006702> (2013)