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NATURAL KILLER CELLS

Maturation and function of NK cells

> NK cell responsiveness may be therapeutically boosted by blocking NKp46

Natural killer (NK) cells are cytokine-producing cytotoxic innate lymphocytes that have essential roles in immunity to pathogens and tumours. Two papers, published in *Immunity* and *Science*, provide new insights into the molecular pathways involved in the maturation and functional regulation of these cells.

The precise hierarchy of the transcription factors that control NK cell maturation is not known. Gordon *et al.* found that NK cell development was greatly impaired in the absence of the T-box transcription factors T-bet (encoded by *Tbx21*) and eomesodermin (EOMES). But what are the individual contributions of these factors? Adult *Tbx21*$^{-/-}$ mice lacked a subset of immature NK cells that expresses the death receptor TRAIL and that is predominantly found in the liver in wild-type mice. Furthermore, when hepatic NK cells in which *Tbx21* had been conditionally deleted *ex vivo* were transferred to immunodeficient mice, only mature TRAIL^{-} NK cells could be recovered. These data suggest that T-bet stabilizes immature TRAIL^{+} NK cells.

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Mature NK cells are characterized by a loss of TRAIL expression, upregulation of CD49b expression (cells expressing this marker are known as DX5^{+} NK cells) and the expression of a full complement of LY49 receptors. NK cells from mice in which haematopoietic cells lacked expression of EOMES had an immature phenotype (TRAIL^{+}DX5^{-}). Furthermore, EOMES-sufficient, but not EOMES-deficient, immature NK cells gave rise to mature NK cells expressing LY49 receptors following transfer into immunodeficient mice. These data suggest that EOMES is essential for immature TRAIL^{+} NK cells to become mature DX5^{+} NK cells. Of note, the maintenance of certain maturation markers, but not of LY49 receptor expression, on mature NK cells was shown to depend on EOMES expression.

Finally, fetal and hepatic NK cell development to the immature NK cell stage requires T-bet expression but does not proceed further owing to restricted EOMES expression. By contrast, EOMES expression is induced in the spleen and bone marrow, allowing for the development of mature NK cells at these sites in adult mice. These data indicate that T-bet and EOMES control distinct checkpoints in NK cell maturation.

In a second study, Narni-Mancinelli *et al.* describe the importance of the NK cell 'activating' receptor NKp46 (encoded by *Ncr1*) in downregulating NK cell responses by silencing the expression of the transcription factor Helios. While screening mice with *N*-ethyl-*N*-nitrosourea (ENU)-induced mutations, the authors identified a mouse pedigree in which the NK cells were hyperresponsive to a broad range of stimuli, and they termed these mice *Noé* mice. Although NK cell numbers were normal, mouse cytomegalovirus (MCMV)-infected *Noé* mice had more interferon-γ-producing and degranulating NK cells than wild-type mice, and *Noé* mice were more resistant to infection. This NK cell hyperresponsiveness was due to a point mutation in *Ncr1* at residue 32 (W32R). This mutation results in defective cell-surface expression of NKp46 and increased expression of Helios. Silencing of Helios expression in NK cells from *Ncr1*$^{W32R/W32R}$ mice restored their reactivity to that of wild-type NK cells.

Although *Ncr1*$^{W32R/W32R}$ mice clear pathogens more quickly than wild-type mice, the frequencies of antigen-specific effector CD4^{+} and CD8^{+} T cells were found to be lower. Furthermore, during a secondary challenge, the memory CD8^{+} T cell response was significantly decreased and the pathogen load was much higher in *Ncr1*$^{W32R/W32R}$ mice compared with in controls. Therefore, enhanced NK cell reactivity during T cell priming negatively affects the development of fully protective memory T cells.

Finally, the authors showed that NK cells from wild-type mice treated with blocking NKp46-specific antibodies had an increased responsiveness to tumour cells *in vitro* compared with NK cells from untreated mice. Therefore, NK cell responsiveness may be therapeutically boosted by blocking NKp46, thereby removing the brake on Helios expression.

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ORIGINAL RESEARCH PAPERS Gordon, S. M. *et al.* The transcription factors T-bet and Eomes control key checkpoints of natural killer cell maturation. *Immunity* **36**, 55–67 (2012) | Narni-Mancinelli, E. *et al.* Tuning of natural killer cell reactivity by NKp46 and Helios calibrates T cell responses. *Science* **335**, 344–348 (2012)
FURTHER READING Sun, J. C. & Lanier, L. L. NK cell development, homeostasis and function: parallels with CD8^{+} T cells. *Nature Rev. Immunol.* **11**, 645–657 (2011)