IMMUNE REGULATION

New regulatory role for NK cells

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> “…NK cells can directly regulate adaptive T-cell responses, and … it might be possible to harness this ability to eliminate autoreactive T cells in autoimmune disease and in transplantation settings.”

Studies investigating immune regulation have focused recently on the role of regulatory T-cell subsets, but the immunoregulatory role of natural killer (NK) cells is less well understood. Now, Lu and colleagues describe an inhibitory interaction between the CD94–NKG2A (natural killer, group 2, member A) receptor on NK cells and the Qa-1 molecule on activated T cells (herein referred to as the Qa-1–NKG2A interaction) and show that disruption of this interaction permits NK-cell-mediated elimination of activated autoreactive $CD4^+$ T cells in experimental autoimmune encephalitis (EAE).

Qa-1 is an MHC class 1b molecule that binds to a peptide (Qdm) derived from MHC class I leader sequences. Qa-1 is expressed on dendritic cells and on activated T and B cells. Lu and colleagues tested the idea that this interaction might function similarly to the interaction between other inhibitory NK-cell receptors and MHC class I ligands in preventing NK-cell lysis of target cells.

Qa-1-deficient $CD4^+$ T cells transferred into recombination-activating-gene-2-deficient (*Rag2*$^{-/-}$) mice, which have no B or T cells but do have NK cells, failed to undergo homeostatic proliferation. By contrast, there was expansion of Qa-1-deficient $CD4^+$ T cells that were transferred into mice deficient in both RAG2 and perforin (PRF; *Rag2*$^{-/-}$*Prf1*$^{-/-}$ mice) and which therefore lack B, T and NK cells. Similar results were observed for antigen-induced T-cell expansion using the OTII transgenic system (in which T cells express a T-cell receptor (TCR) that recognizes a peptide from ovalbumin). Using this system, the authors also showed that Qa-1 expression is essential for the development of $CD4^+$ memory T cells. Restoration of Qa-1 expression by OTII cells (using a lentiviral expression vector) in *Rag2*$^{-/-}$ hosts resulted in T-cell proliferation to a similar level as that observed in *Rag2*$^{-/-}$*Prf1*$^{-/-}$ mice.

Next, the authors analysed the Qa-1–NKG2A interaction using $CD4^+$ T cells from transgenic mice expressing the 2D2 TCR that is specific for a peptide from myelin oligodendrocyte glycoprotein (MOG). Transfer of Qa-1-deficient 2D2 $CD4^+$ T cells into *Rag2*$^{-/-}$ hosts, together with MOG peptide, complete Freund’s adjuvant and pertussis toxin, resulted in little or no disease, compared with the EAE that developed when Qa-1-sufficient cells were transferred.

The authors then developed knock-in mice in which Qa-1 is expressed as a mutant form (R72A) that cannot interact with CD94–NKG2A. Consistent with results from the Qa-1-deficient mice, the T cells that expressed mutant Qa-1 were susceptible to lysis by NK cells. Similarly, in the MOG-induced EAE system, antibody blockade of the Qa-1–NKG2A interaction virtually eliminated EAE as a result of NK-cell-mediated lysis of autoreactive T cells.

This study reveals that as well as being able to modulate dendritic cell function, NK cells can directly regulate adaptive T-cell responses, and that it might be possible to harness this ability to eliminate autoreactive T cells in autoimmune disease and in transplantation settings.

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