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NATURAL KILLER CELLS

Adaptive control of NK cells

Forkhead box P3 (FOXP3)$^+$ regulatory T (T_{Reg}) cells maintain peripheral self-tolerance by suppressing the responsiveness of other immune cells, including natural killer (NK) cells. Three recent studies have discovered a mechanism by which T_{Reg} cells regulate NK cells.

In the first study by Gasteiger *et al.*, the authors found that NK cell reactivity to strong activating signals, as well as their tolerance to self ligands, was not affected by the absence of T_{Reg} cells. However, NK cell-mediated targeting of MHC class I-deficient cells (which lack NK cell inhibitory receptors; also known as the 'missing-self response') was greatly enhanced in the absence of T_{Reg} cells. Interleukin-2 (IL-2) neutralization reversed this enhanced missing-self response, as did the depletion of CD4$^+$ T cells, which readily produce IL-2 in T_{Reg} cell-deficient mice. These data suggest that T_{Reg} cells specifically suppress NK cell reactivity to missing-self targets by limiting the availability of CD4$^+$ T cell-derived IL-2.

Of note, IL-2, which was shown to increase the adhesiveness of NK cells to missing-self targets, also enhanced NK cell adhesion to, and NK cell-mediated killing of, 'weak' targets — that is, cells that are normally inefficiently killed by NK cells.

In the second study by this group, the minor CD127$^+$ NK cell splenic population was shown to increase in the absence of T_{Reg} cells. This expanded population comprised mainly immature NK cells that gave rise to mature CD11b$^+$ NK cells following their transfer to lymphopenic hosts. CD127$^+$ NK cells were the only NK cells that expressed CD25 (the high-affinity receptor for IL-2). The expression of CD25 by these cells was upregulated in response to the pro-inflammatory cytokine IL-12, levels of which are increased following T_{Reg} cell depletion. The expansion of the CD127$^+$ NK cell population in the absence of T_{Reg} cells depended on the presence of CD4$^+$ T cells and on IL-2, which suggests that T_{Reg} cells control the homeostasis of this immature NK cell population by restricting T cell-derived IL-2 availability. Interestingly, immature CD127$^+$ NK cells also accumulated in tumour-bearing and chronically infected mice.

In a third study, Sitrin *et al.* showed that following acute T_{Reg} cell depletion in BDC2.5/NOD mice (a model of type 1 diabetes), pancreas-infiltrating NK cells were activated and had enhanced IL-2-induced gene expression. IL-2 neutralization in T_{Reg} cell-depleted BDC2.5/NOD mice reduced NK cell accumulation and their production of interferon-γ (IFNγ), which the group had previously shown to promote disease in this model. Correspondingly, supplementation of T_{Reg} cell-sufficient BDC2.5/NOD mice with IL-2 induced pancreatic NK cell proliferation and IFNγ production. The main source of IL-2 in this model was found to be CD4$^+$ T cells in the pancreas.

Taken together, these studies suggest that T_{Reg} cells control the activity of NK cells by limiting their exposure to T cell-derived IL-2. These findings have important implications for the therapeutic manipulation of NK cells and for IL-2-based immunotherapies.

Olive Leavy

> “T_{Reg} cells control the activity of NK cells by limiting their exposure to T cell-derived IL-2”

ORIGINAL RESEARCH PAPERS Gasteiger, G. *et al.* IL-2-dependent tuning of NK cell sensitivity for target cells is controlled by regulatory T cells. *J. Exp. Med.* 6 May 2013 (doi:10.1084/jem.20122462) | Gasteiger, G. *et al.* IL-2-dependent adaptive control of NK cell homeostasis. *J. Exp. Med.* 6 May 2013 (doi:10.1084/jem.20122571) | Sitrin, J. *et al.* Regulatory T cells control NK cells in an insulitic lesion by depriving them of IL-2. *J. Exp. Med.* 6 May 2013 (doi:10.1084/jem.20122248)