NATURAL KILLER CELLS

When killers come good

DOI:
10.1038/nri1922

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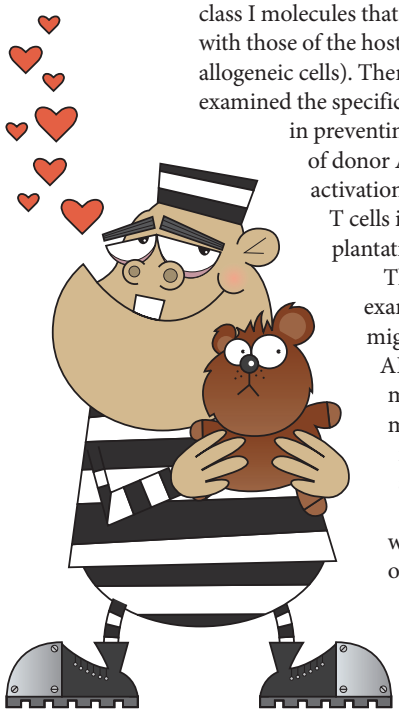
> the ability of NK cells to recognize and kill allogeneic APCs regulates the activation of alloreactive T cells in skin-transplantation



The precise mechanism by which natural killer (NK) cells can promote the induction of tolerance to certain allografts has now been solved. Recent research published in *The Journal of Experimental Medicine* shows, in a skin-transplantation model, that host NK cells kill graft-derived antigen-presenting cells (APCs), thereby preventing these APCs from migrating to lymphoid and non-lymphoid sites in the host, where they directly activate alloreactive T cells.

Transplant rejection involves the priming of alloreactive host T cells in secondary lymphoid organs, mainly by graft-derived APCs. Therefore, the ability of these donor APCs to survive and migrate in the host might be crucial to the induction of the rejection response. NK cells recognize and kill foreign cells displaying MHC class I molecules that are mismatched with those of the host (known as allogeneic cells). Therefore, Yu *et al.* examined the specific role of NK cells in preventing the migration of donor APCs and the activation of alloreactive T cells in a skin-transplantation model.

The authors examined the migration of donor APCs in two mouse strains: mice deficient in recombination-activating gene (RAG) protein, which are devoid of T and B cells; and mice deficient in both RAG protein and the common cytokine-receptor γ-chain (γ_c), which additionally lack NK cells. Following transplantation of skin allografts from DBA/2 mice, donor cells (including dendritic cells, DCs) were found in the spleens of RAG- and γ_c-deficient mice but were absent from the spleens of RAG-deficient mice. The authors then directly transferred purified DCs from DBA/2 mice to these two mouse strains. They found high numbers of allogeneic DCs in the spleens, livers and lungs of mice deficient in both proteins but not mice deficient in RAG protein alone, indicating that NK cells have a crucial role in preventing the survival and dissemination of donor DCs in host mice.

To determine whether these allogeneic DCs could stimulate the activation of T cells in the absence of NK cells, allogeneic DCs from DBA/2 mice were transferred to both strains of mice, and T cells that were genetically similar to those of the host mice were transferred 2 weeks later. Transferred T cells that were recovered 3 days later from the spleen, liver and lungs of RAG- and γ_c-deficient mice had undergone multiple rounds of cell division and readily produced interferon-γ, whereas T cells that were recovered from RAG-deficient mice had not undergone cell division. These data indicate that, in the absence of NK cells, allogeneic DCs can induce the activation of alloreactive T cells at multiple sites in host mice.

So the ability of NK cells to recognize and kill allogeneic APCs regulates the activation of alloreactive T cells in skin-transplantation models, highlighting that NK cells are potential therapeutic targets for the induction of tolerance to transplants.

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ORIGINAL RESEARCH PAPER Yu, G. *et al.* NK cells promote transplant tolerance by killing donor antigen-presenting cells. *J. Exp. Med.* 24 July 2006 (doi:10.1084/jem.20060603)