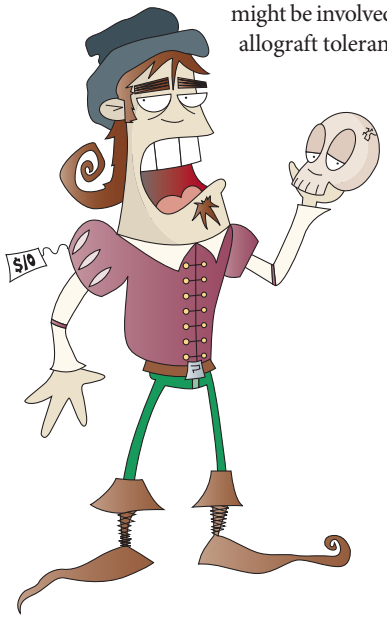
TRANSPLANTATION

New role for NK cells in allograft tolerance

One of the main mechanisms thought to be responsible for the induction of allograft tolerance is the generation of MHC-class-II-restricted $CD4^+$ regulatory T cells, but a study published in *Nature Medicine* has uncovered an unexpected role in tolerance induction for MHC-class-I-dependent responses that involve natural killer (NK) cells. This is in contrast to previous studies that show a role for NK cells in inflammation and graft injury.

The authors used a mouse model of tolerance to islet allografts induced by monoclonal antibody specific for CD40 ligand (CD40L). Surprisingly, they showed that, although antibody treatment was ineffective at prolonging graft survival in MHC-class-I-deficient mice, the requirement for MHC class I molecules did not depend on $CD8^+$ T cells, because mice that were depleted of $CD8^+$ T cells could accept islet allografts long-term in the presence of CD40L-specific monoclonal antibody. Therefore, the authors proposed that innate NK and NKT cells, which also require host expression of MHC class I molecules, might be involved in allograft tolerance.



Mice that were depleted of $NK1.1^+$ cells before transplantation did not have prolonged graft survival in the presence of CD40L-specific antibody, which confirms a role in tolerance induction for NK and/or NKT cells, both of which express NK1.1 in the mouse strain that was used. CD1-deficient recipients, which do not have NKT cells but are NK-cell replete, had long-term survival of islet allografts with CD40L-specific antibody treatment, showing that NK cells are sufficient for MHC-class-I-dependent tolerance induction in this model.

Experiments using F_1 (self × donor) allografts showed that the direct activation of NK cells by the absence of host MHC class I molecules on the graft (that is, by 'missing self') is not required for the tolerance that is induced by CD40L-specific antibody. Instead, NK cells modulate the host T-cell response to donor antigen-presenting cells (APCs) in the presence of CD40L-specific antibody, as shown when mice were immunized in the footpad with allogeneic APCs; mice that received CD40L-specific antibody had a marked reduction in the T-cell response in the draining lymph node, but this reduction was abrogated by NK-cell depletion. Using perforin-deficient mice reconstituted with perforin-competent NK cells, the authors showed that perforin production by NK cells is required for tolerance induction.

This result has implications for the design of tolerance-inducing protocols, which should promote the graft-protective role of NK cells while inhibiting the graft-destructive role.

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References and links

ORIGINAL RESEARCH PAPER Beilke, J. N., Kuhl, N. R., Van Kaer, L. & Gill, R. G. NK cells promote islet allograft tolerance via a perforin-dependent mechanism. *Nature Med.* **11**, 1059–1065 (2005)

IN BRIEF

NATURAL KILLER CELLS

Cytolytic granule polarization and degranulation controlled by different receptors in resting NK cells.

Bryceson, Y. T. *et al*. *J. Exp. Med.* **202**, 1001–1012 (2005)

Bryceson *et al*. developed a system using *Drosophila melanogaster* Schneider cell 2 (SC2) cells transfected with individual ligands for natural killer (NK)-cell activating receptors to investigate the role of the receptors in target-cell lysis mediated by resting human NK cells. Expression of the lymphocyte function-associated antigen 1 (LFA1) ligand intercellular adhesion molecule 1 (ICAM1) by SC2 cells induced polarization of NK-cell granules, but it did not induce degranulation or cytotoxicity. By contrast, ligation of CD16 at the surface of NK cells (through expression of IgG by the SC2 cells) induced degranulation, but not polarization of NK-cell granules or target-cell lysis. Resting human NK cells did mediate target-cell lysis when both LFA1 and CD16 were engaged, indicating that granule polarization and degranulation are uncoupled in these cells.

ANTIBODIES

Engineering the Fc region of immunoglobulin G to modulate *in vivo* antibody levels.

Vaccaro, C. *et al*. *Nature Biotechnol.* **23**, 1283–1288 (2005)

The authors of this paper took a novel approach to antibody engineering and generated a human IgG1 variant with a mutated Fc region. The mutant was designed to reduce endogenous levels of IgG by exploiting the activity of the Fc receptor FcRn, which regulates IgG concentrations. The mutant IgG1 bound FcRn with higher affinity and with less pH dependence than did wild-type IgG. Because binding to FcRn protects IgG molecules from degradation and, instead, recycles them, preferential binding to FcRn by the mutant IgG1 resulted in increased degradation of endogenous IgG1. The authors propose that this could be a useful reagent for clearing pathogenic autoantibodies in autoimmune diseases such as systemic lupus erythematosus.

TUMOUR IMMUNOLOGY

Tumor-associated $CD8^+$ T cell tolerance induced by bone marrow-derived immature myeloid cells.

Kusmartsev, S. *et al*. *J. Immunol.* **175**, 4583–4592 (2005)

This study shows that the immature myeloid cells (iMCs) that accumulate in large numbers in the spleen, lymph nodes and tumour tissues of tumour-bearing mice can take up and present tumour antigens to $CD8^+$ T cells *in vivo* to induce antigen-specific tolerance. In a model of adoptive transfer of transgenic T cells to tumour-free mice, the addition of iMCs isolated from tumour-bearing mice inhibited the T-cell response to specific antigen in an MHC-class-I-dependent manner. Furthermore, iMCs from mice that were injected with ovalbumin (OVA)-expressing tumour cells displayed an OVA-derived epitope on their surface and inhibited OVA-specific T-cell responses. T-cell tolerance is an important mechanism of tumour escape, and in this model, the number of iMCs correlated directly with the size of the tumour. Therefore, targeting iMCs could be a useful strategy to improve the efficacy of cancer vaccines.