HIGHLIGHTS

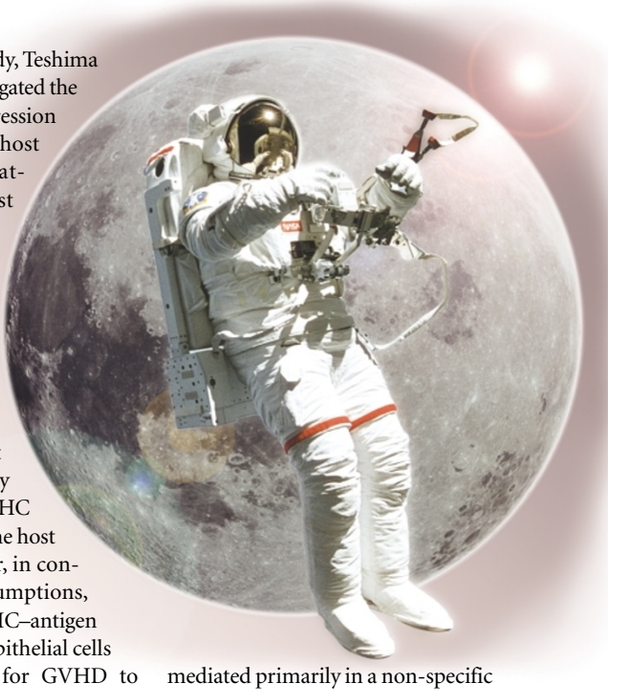
TRANSPLANTATION

A leap forward…

The mechanisms that govern organ rejection after transplantation have puzzled immunologists for some time. The current view is that antigen-specific T cells recognize and attack cells that express target antigens in the donor organ graft. But now, two papers in *Nature Medicine* highlight the previously unrecognized role of localized non-specific mechanisms in transplant settings.

It has been known for some time that transplanted kidneys secrete the complement component C3. It is also known that C3 can mediate the lysis of cells that are coated with antibody. Pratt and colleagues investigated the functional relevance of local C3 secretion using a mouse kidney-transplantation model. They found that when C3-negative donor kidneys were transplanted into C3-positive recipients, most of the kidneys survived for more than 100 days, whereas transplanted C3-positive kidneys were rejected within 12 days. When C3-positive kidneys were transplanted into C3-negative recipients, rejection also occurred swiftly, which indicates that the local production of C3 by the grafted organ is crucial for the rejection process. So, is complement-mediated injury sufficient to explain the effect of C3 on graft rejection? This seems unlikely, because anti-donor T-cell proliferative responses in recipients of C3-negative grafts were reduced, which indicates that C3 has a modulatory effect on T-cell activation.

In the second study, Teshima and colleagues investigated the requirement for expression of target antigen on host epithelium in mediating graft-versus-host disease (GVHD) after allogeneic bone-marrow transplantation. Using animals that were negative for the antigen-presenting MHC class I and II molecules, they found that GVHD developed only when there was an MHC mismatch between the host and donor. However, in contrast to previous assumptions, the expression of MHC–antigen complexes on host epithelial cells was not necessary for GVHD to develop. Rather, GVHD developed in mice in which MHC molecules were expressed only on antigen-presenting cells (APCs). So, if the epithelial cells that are under attack in GVHD do not express MHC molecules and, therefore, do not interact directly with antigen-specific T cells, what is the mechanism of tissue damage? The damage seems to be mediated by tumour-necrosis factor (TNF) and interleukin-1β (IL-1β), because neutralization of these cytokines reduced the severity of GVHD. These results indicate that the expression of MHC–antigen complexes by APCs is required to initiate T-cell activation, but that the effector phase of GVHD is mediated primarily in a non-specific manner by the release of cytokines from APCs.



These results challenge long-held assumptions that target cells must express specific antigen for graft rejection and GVHD to occur, and they have important implications for transplantation.

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References and links

ORIGINAL RESEARCH PAPER Teshima, T. *et al.* Acute graft-versus-host disease does not require alloantigen expression on host epithelium. *Nature Med.* **8**, 575–581 (2002) | Pratt, J. R., Basheer, S. A. & Sacks, S. H. Local synthesis of complement component C3 regulates acute renal transplant rejection. *Nature Med.* **8**, 582–587 (2002)

WEB SITE
Encyclopedia of Life Sciences:
http://www.els.net/transplantation