ANTIBODY RESPONSES

Behaviour of secretory IgA explained

Structural studies of human FcαRI (CD89), the IgA-specific receptor, help to explain some of the mysteries that surround the behaviour of secretory IgA.

IgA — the main antibody isotype at mucosal surfaces — occurs in three distinct forms: monomeric IgA and dimeric IgA, which are present in the serum, and secretory IgA (SIgA), which is present in mucosal secretions. SIgA is a covalent complex of dimeric IgA and the ectodomain of the polymeric immunoglobulin receptor (pIgR), to which dimeric IgA binds before it transcytoses through the epithelial layer and is released into mucosal secretions as SIgA.

IgA-mediated responses, including phagocytosis and antibody-dependent cell-mediated cytotoxicity, are induced through FcαRI. Monomeric and dimeric IgA can bind to FcαRI, causing receptor clustering and downstream signalling that activates phagocytosis and other immune responses. SIgA, however, requires the presence of an integrin co-receptor for signalling through FcαRI, and even then, cannot trigger phagocytosis. Work by Herr *et al.*, published in *Nature*, now helps to explain why this might be so.

The authors have shown previously that, in solution, two FcαRI molecules bind to each dimer of Fcα (the Fc region of IgA). This is confirmed in the latest study by determination of the crystal structure. First, the structure of FcαRI alone was resolved, indicating the presence of two immunoglobulin-like domains, which are oriented at right angles to each other. Next, the FcαRI–Fcα complex was examined. Fcα is a dimer of IgA heavy chains, which both contain two immunoglobulin constant domains, Cα2 and Cα3. The FcαRI–Fcα complex was shown to consist of two FcαRI molecules and a single Fcα dimer, with one receptor binding to each of the Cα2–Cα3 junctions.

Further analysis of the interaction interface between Fcα and FcαRI indicated more details about the FcαRI-binding site. The pIgR ectodomain of SIgA seems to interact with residues of IgA that are required for binding to the FcαRI-binding site, so possibly explaining why SIgA needs an integrin co-receptor to bind and activate FcαRI.

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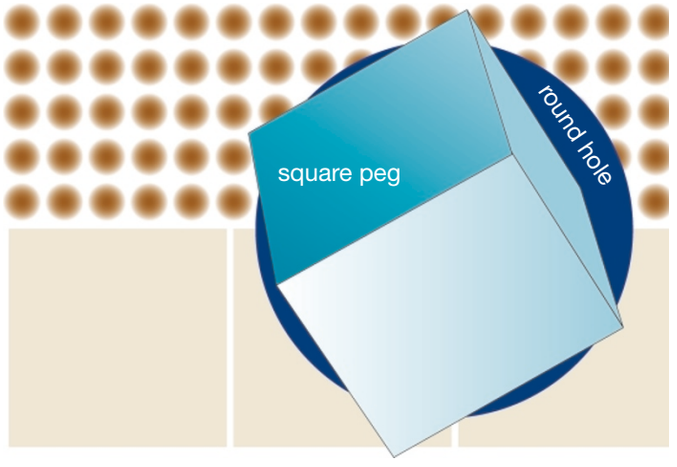
References and links

ORIGINAL RESEARCH PAPER Herr, A. B. *et al.* Insights into IgA-mediated immune responses from the crystal structures of human FcαRI and its complex with IgA1-Fc. *Nature* 21 May 2003 (DOI: 10.1038/nature01685)

FURTHER READING Herr, A. B. *et al.* Bivalent binding of IgA1 to FcαRI suggests a mechanism for cytokine activation of IgA phagocytosis. *J. Mol. Biol.* **327**, 645–657 (2003)



IN BRIEF

HAEMATOPOIESIS

Hematopoietic stem cells engraft in mice with absolute efficiency.

Benveniste, P. *et al. Nature Immunol.* 25 May 2003 (DOI: 10.1038/ni940)

Haematopoietic stem cells (HSCs) are unique in that they can self renew, are pluripotent and can differentiate into blood cells of all lineages. Transfer of mouse HSCs to irradiated mice can restore haematopoiesis in the recipient but, until now, this process was thought to be inefficient. Using two independent experimental approaches, Benveniste *et al.* show, in contrast to previous studies, that when single purified HSCs are injected into recipient mice, nearly all of these result in successful engraftment. However, only a minority of these cells established grafts that were long lasting, indicating that it is the ability to retain self-renewal capabilities rather than inefficient initial engraftment that reduced the success of previous attempts to engraft mice in this way.

GENE THERAPY

Transcription start regions in the human genome are favored targets for MLV integration.

Wu, X. *et al. Science* **300**, 1749–1751 (2003)

Retroviruses, including mouse leukaemia virus (MLV), are efficient gene-delivery vehicles that have been used in many gene-therapy trials. It was believed that retroviruses integrated randomly into the genome, but recent developments indicate that this might not be so. Here, a high-throughput method was used to clone the genomic regions that are adjacent to the integration sites. 903 MLV and 379 HIV-1 pro-viral integrations in the human genome were mapped in this study. MLV preferentially integrated near the transcription-start site of active genes, and HIV-1 showed a preference for transcribed regions. This work provides an insight into the mechanisms of pro-virus integration and shows that these differ between retroviruses, which could have important implications for gene-therapy trials.

LYMPHOCYTE MIGRATION

Microangiectasias: structural regulators of lymphocyte transmigration.

Secomb, T. W. *et al. Proc. Natl Acad. Sci. USA* **100**, 7231–7234 (2003)

Lymphocyte migration is thought to occur as a result of a multi-step adhesion cascade. According to this model, localized expression of adhesion molecules by endothelial cells allows lymphocytes to overcome the flow shear forces. Shear stresses in normal vessels are ~20 dyn/cm^2, but lymphocyte adhesion usually occurs at wall shear stresses of ~1dyn/cm^2. Furthermore, blood flow during inflammation is likely to increase the shear stresses rather than decrease them. Now, Secomb and colleagues present data to support the idea that lymphocyte migration actually occurs in specialized vascular regions. They detected focal structural dilations — microangiectasias — in the vessels, in which shear forces are reduced sufficiently to allow lymphocyte–endothelial cell interactions to occur.