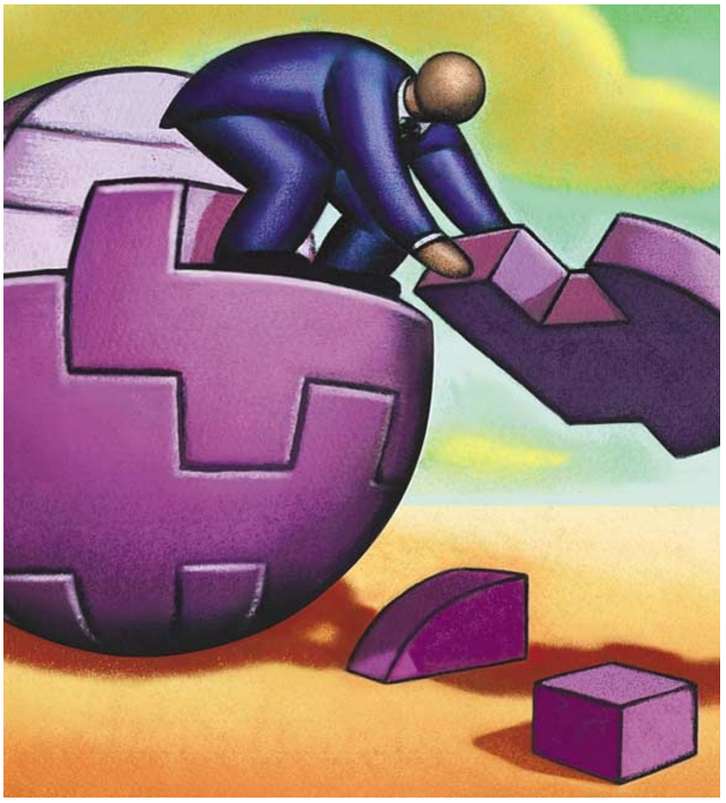
SIGNALLING

Build your own B cell



Our map of antigen-receptor signalling pathways is based largely on studies in which the function of signalling molecules was disrupted. This knockout approach allows the ordering of components in a pathway, but it can tell us little about feedback mechanisms that might exist. This led Rolli and colleagues at the University of Freiburg to devise an alternative approach — the reconstruction of B-cell receptor (BCR) signalling pathways in *Drosophila* cells. The new system has produced some surprising results, which are reported in *Molecular Cell*.

Interference from endogenous signalling pathways is a potential problem when expressing receptors and signalling components in another vertebrate cell type. To minimize this, Rolli *et al*. used *Drosophila* Schneider S2 cells. These cells are used commonly for large-scale protein production, so it was probable that they would be able to 'cope' with the co-transfection of several foreign genes. Expression vectors containing a copper-sulphate-inducible promoter were used to express the BCR and various signalling components in S2 cells.

According to present models, BCR signal transduction is initiated by phosphorylation of the two tyrosine residues in the ITAMs (immunoreceptor tyrosine-based activation motifs) of Igα/β (the paired signalling subunits of the BCR) by the membrane-associated SRC-family protein tyrosine kinase (PTK) LYN. This is thought to allow recruitment of the cytosolic PTK SYK and activation of downstream effector enzymes. But, by transfecting S2 cells with the BCR and various combinations of wild-type or mutated forms of Igα/β, LYN and SYK, the authors found that LYN tends to phosphorylate only the first tyrosine of the ITAM, whereas SYK can phosphorylate both tyrosines. Therefore, SYK can phosphorylate the BCR independent of LYN, and it is a more probable candidate for the first step in BCR signal transduction.

Further experiments showed that the SRC-homology 2 (SH2) domains of SYK, which bind to phosphorylated ITAMs, are required to optimize the activity of its catalytic domain. This implies that SYK can regulate its own activity, because its product — phosphorylated ITAMs — induces the further activation and recruitment of SYK. This positive-feedback loop has the potential to

HIV

Immunological burn-out

The failure to control HIV-1 infection results in immunodeficiency and destruction of the immune system in infected individuals. In addition to infecting and killing $CD4^+$ T cells directly, HIV-1 causes chronic immune activation, which has been proposed to contribute to the immunodeficiency. Now, Rene van Lier's group have shown that persistent immune activation — in this study induced by chronic co-stimulation through CD27–CD70 interactions — can indeed result in lethal immunodeficiency.

Members of the tumour-necrosis factor receptor family, which includes CD27, are involved in the regulation of diverse immunological processes, including immune-cell proliferation and survival. CD70, the ligand for CD27, is expressed by activated lymphocytes after antigenic stimulation. Here, the authors used *Cd70*-transgenic mice, in which B cells chronically express CD70, as a model to assess the effects of persistent immune activation on the immune system.

***Cd70*-transgenic mice had increased numbers of effector T cells in their spleens and peripheral lymph nodes, owing to increased T-cell proliferation. With time, the number of naive T cells in the secondary lymphoid organs decreased, as did naive T-cell production, but effector-memory T cells accumulated. Further experiments showed that this excessive production of effector-memory T cells was dependent on CD27–CD70 interactions and on the presence of foreign antigens, but was independent of interferon-γ.**

How do these changes in T-cell populations affect the health of the *Cd70*-transgenic mice? By 20 weeks of age, most of the mice suffered from *Pneumocystis carinii* pneumonia — an opportunistic infection that is commonly seen in situations of severe T-cell immunodeficiency — which resulted in their premature death at around 28 weeks of age.

This study shows that persistent immune activation, as has been proposed to occur during chronic HIV-1 infection, is sufficient to cause lethal immunodeficiency. As activated T cells from HIV-1-infected individuals have been shown to express increased levels of CD70, the authors suggest that CD27–CD70 interactions could be targeted to avoid the negative effects of persistent immune activation.

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References and links

ORIGINAL RESEARCH PAPER Tesselaar, K. *et al.* Lethal T-cell immunodeficiency induced by chronic costimulation via CD27–CD70 interactions. *Nature Immunol.* 9 December 2002 (DOI: 10.1038/ni869)