Neutralizing antibodies revisited

Although early work on developing an HIV-1 vaccine investigated the role of neutralizing antibodies, most of the recent work has focused on vaccines that stimulate cytotoxic T cells. Now, as reported in the *Proceedings of*

HIV



the National Academy of Sciences, Maxime Moulard and colleagues have isolated a neutralizing antibody that recognizes an epitope on a complex between HIV-1 envelope glycoprotein 120, CD4 and CC-chemokine receptor 5 (gp120–CD4–CCR5). This antibody is broadly cross-reactive with HIV-1 isolates from various clades, which has implications for vaccine development.

HIV-1 enters host cells by forming a complex between gp120, the CD4 receptor and a chemokine co-receptor, which might be CCR5 or CXC-chemokine receptor 4 (CXCR4), depending on the HIV-1 isolate. Binding of gp120 causes conformational changes in the HIV-1 envelope protein and initiates the cell-fusion process, but the precise mechanism of HIV-1 entry is not fully understood. Working on the theory that intermediate conformations of the envelope protein might contain epitopes that are conserved between different HIV-1 isolates — which could be effective vaccine targets— Moulard and colleagues used a phage-display

T-CELL SIGNALLING

SOCS and the TCR

There are numerous similarities between T-cell receptor (TCR)-mediated and cytokinereceptor-mediated signalling — both involve receptor-subunit clustering and the activation of tyrosine kinases. Cytokine signalling is regulated by the suppressor of cytokine signalling (SOCS) family, but whether SOCS proteins are also involved in TCR signalling remains unclear. Recent work from Banerjee and colleagues published in *The Journal of Immunology* implicates SOCS3 in the negative regulation of TCR signalling.

Initial experiments showed that the level of Socs3 mRNA in mouse primary CD4⁺ T cells increases after TCR ligation. The authors then used T-cell lines and primary T cells to investigate the effects of Socs3 on TCR signalling. The overexpression of Socs3 inhibited the activity of the interleukin-2 (IL-2) promoter in these cells after TCR ligation.

Further co-transfection experiments in Jurkat cells indicated that SOCS3 might suppress the transcriptional activation of the IL-2 promoter that is mediated by nuclear factor of activated T cells (NFAT). Normally, TCR engagement results in the rapid calcineurindependent translocation of NFAT transcription factors from the cytoplasm to the nucleus. The active maintenance of dephosphorylated NFAT in the nucleus is crucial to control the expression of genes such as that encoding IL-2, which is required for the proliferation and activation of effector T cells.

The overexpression of SOCS3 in Jurkat cells resulted in the inhibition of NFAT activity and reduced production of IL-2. NFAT dephosphorylation was less efficient in these cells, which implies that SOCS3 limits the activity of NFATp by inhibiting its dephosphorylation. Finally, Banerjee *et al.* showed that there is an interaction between SOCS3 and the catalytic subunit of calcineurin, the phosphatase that is responsible for the dephosphorylation of NFAT.

The authors are aware that these results are based on the overexpression of SOCS3 in T cells and, therefore, that further experiments are necessary to prove that SOCS3 regulates the activation of NFATp *in vivo*. The embryonic lethality of *Socs3^{-/-}* mice precludes these studies at present, but the generation of chimeric mice in which only T cells are deficient for Socs3 will help to clarify this issue.

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References and links
ORIGINAL RESEARCH PAPER Baneriee, A. et al., Suppressor

original RESEARCH PAPER Banerjee, A. *et al.* Suppressor of cytokine signaling 3 inhibits activation of NFATp. *J. Immunol.* **168**, 4277–4281 (2002) approach to identify neutralizing antibodies specific for these epitopes.

Using purified gp120-CD4-CCR5 complexes as the selecting antigen, the group identified a human antibody Fab (fragment of antigen binding), X5, from a phage-display library that was generated from a seropositive donor. X5 bound to envelope proteins from primary isolates of various clades with high affinity (nM range). The binding of X5 to gp120 was significantly enhanced by CD4, which indicates that the gp120 epitope is exposed to a greater extent after gp120-CD4 interaction. X5 was able to inhibit the infection of blood cells by different HIV-1 primary isolates with a potency that was comparable to that of a previously identified neutralizing antibody.

So, the identification of X5 implies that conserved conformational epitopes can be recognized by potent, broadly neutralizing antibodies, and this might be an important area for further study.

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References and links
ORIGINAL RESEARCH PAPER Moulard, M. et al. Broadly
cross-reactive HIV-1-neutralizing human monoclonal Fab
selected for binding to gp120-CD4-CCR5 complexes.
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