HIV

Quality control

Quality not quantity. That's the message of a study by Migueles *et al.* into the control of HIV replication by CD8$^+$ T cells. They show that although the frequency of HIV-specific CD8$^+$ T cells is similar in all patients, the T cells of long-term non-progressors (LTNPs) limit viral replication by means of their higher proliferative capacity coupled to increased perforin expression.

To determine the frequency of HIV-specific CD8$^+$ T cells in HIV$^+$ patients, peripheral-blood mononuclear cells were stimulated with HIV-infected autologous primary CD4$^+$ T cells. No difference in the number of activated CD8$^+$ T cells — as measured by the detection of intracellular interferon-γ — was found between LTNPs and progressors (individuals with progressive HIV infection). Therefore, it seems that there is no quantitative difference between individuals that might account for their different clinical outcomes.

By contrast, the ability of these T cells to proliferate in response to HIV-infected targets was shown to differ markedly. A greater proportion of HIV-specific CD8$^+$ T cells underwent a greater number of cell divisions in LTNPs compared with progressors. Furthermore, in two individual patients, the degree of proliferation correlated strongly with the extent to which viral replication was inhibited in the absence of therapy.

Perforin is essential for the granule-exocytosis pathway of cell killing, but expression of this protein is tightly regulated. The expression of perforin by HIV-specific CD8$^+$ T cells was shown to parallel cell division. These data indicate that qualitative factors (ability to proliferate and expression of perforin) determine the extent to which HIV replication is controlled.

This study has important implications for vaccine design, given that many of the HIV vaccines that are in development aim to elicit a CD8$^+$ T-cell response, rather than an antibody response. Attention must be paid to the quality, and not just the quantity, of HIV-specific T cells that are induced.

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References and links

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FURTHER READING Lieberman, J., Shankar, P., Manjunath, N. & Anderson, J. Dressed to kill? A review of why antiviral CD8 T lymphocytes fail to prevent progressive immunodeficiency in HIV-1 infection. *Blood* **98**, 1667–1677 (2001)

B-CELL SIGNALLING

Directing B-cell destiny

New-Delhi immunologists have discovered a new B-cell signalling pathway. Akanksha Chaturvedi and co-workers, reporting in *Nature Immunology*, show that the glycosyl-phosphatidylinositol (GPI)-linked form of immunoglobulin D initiates cyclic-AMP-dependent signalling that promotes the differentiation of resting B cells to germinal-centre (GC) B cells.

B cells that are activated by antigen in the T-cell areas of lymphoid tissues have two possible fates. They can either differentiate locally to antibody-secreting plasmablasts or migrate to a B-cell follicle to proliferate and form a GC. It is not clear how this cell-fate decision is regulated, but the authors speculate that the tuning of B-cell-receptor signalling might be important.

To determine which signalling pathways promote the differentiation of resting B cells to GC B cells, the authors activated mouse B cells with a surrogate antigen, anti-IgD Fab, and treated them with inhibitors of various signalling pathways. The cells were then assessed for phenotypical changes that are associated with GC B cells and for their ability to form GCs when injected into an antigen-primed mouse.

Surprisingly, the inhibition of protein kinase A (PKA), which is a cAMP-dependent signalling molecule, resulted in a failure to induce the expression of GC markers, such as GL7 and PNA-R, and the ability of these B cells to form GCs was impaired. This result was unexpected, because cAMP-dependent signalling had not been implicated in B-cell activation previously. Cross-linking of IgD resulted in a tenfold increase in the level of intracellular cAMP (cAMPi), which further supports the idea that this is a new pathway of B-cell signalling.

Membrane-lipid microdomains known as rafts have been implicated in the control of B-cell activation — so, does the IgD–cAMPi pathway involve rafts? Disruption of rafts in anti-IgD antibody-stimulated B cells had no effect on the classical Ca^{2+} flux, but the cAMPi response was markedly impaired. This indicates that, unlike Ca^{2+} signalling, IgD-induced cAMPi signalling is initiated in rafts.

GPI-linked proteins are enriched in rafts, so the authors wondered if the GPI-linked form of IgD might be involved. Resting B cells were treated with PI-PLC, an enzyme that cleaves GPI-linked proteins from the cell surface. Whereas the amount of IgD in the non-raft membrane fraction was not affected by treatment with PI-PLC, the amount of IgD in rafts was decreased by approximately 60%. Strikingly, IgD-dependent cAMPi responses were wiped out in PI-PLC-treated cells.

Finally, to show that optimal GC responses require GPI-linked IgD, resting B cells were treated with PI-PLC then activated with anti-IgD Fab. The upregulation of expression of GC phenotypic markers was inhibited and the B cells had a reduced capacity to form GCs. So, the GPI-linked form of IgD, first described ten years ago, finally has a function.

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References and links

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WEB SITE

Kanury Rao's lab: http://www.icgeb.trieste.it/RESEARCH/ND/Rao.htm