HAEMATOPOIESIS

When do thymic precursors commit?

A recent report in *The Journal of Experimental Medicine* sheds light on two longstanding and much debated questions in thymopoiesis research. What are the first haematopoietic precursors that seed the thymus? And when do thymic precursors commit to the T-cell lineage? By studying the clonal differentiation potential of the most immature precursors in the thymus, Claudia Benz and Conrad Bleul identify, on a single-cell level, the first multipotent precursor in the thymus and indicate that, for some progenitor cells, commitment to the T-cell fate occurs after arrival in the thymus.

Populations of precursors in the thymus can produce T cells, B cells and dendritic cells (DCs), but it is still unclear whether these cell types are derived from a single multipotent progenitor or from distinct pre-committed precursor cells. To address this, the authors generated mice in which T-lineage cells were tagged by expression of enhanced green fluorescent protein (EGFP) from the CC-chemokine receptor 9 (*CCR9*) locus, which is expressed at sites of T-cell development. In these mice, they identified $Lin^{-}CD25^{-}CD117^{+}EGFP^{+}$ thymic precursor populations in the bone marrow, blood and thymus, and these contained T-lineage precursors that could give rise to all of the stages of T-cell development when cultured under appropriate conditions. This indicates that the $Lin^{-}CD25^{-}CD117^{+}EGFP^{+}$ precursors are likely to be thymus-repopulating cells that travel from the bone marrow to the thymus through the blood. By taking advantage of the different levels of EGFP expression among early thymic progenitors, they showed that the most immature precursors had the highest levels of EGFP expression in the thymus and had a differentiation potential that closely resembled that of the precursors in the blood. In addition to T cells, these $EGFP^{hi}$ thymic precursors could give rise to B cells, natural killer cells, DCs and myeloid cells. By contrast, the $EGFP^{low}$ population did not give rise to B cells, indicating that the $EGFP^{hi}$ population marks the branching point of the T- and B-cell lineages. Moreover, by single-cell cloning, they confirmed that a single $EGFP^{hi}$ cell could give rise to all of the haematopoietic lineages that are known to develop in the thymus, indicating that these thymic precursors enter the thymus as multipotent progenitors and commit to the T-cell lineage in the thymus and not before.

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References and links

ORIGINAL RESEARCH PAPER Benz, C. & Bleul, C. C. A multipotent precursor in the thymus maps to the branching point of the T versus B lineage decision. *J. Exp. Med.* **202**, 21–31 (2005)

HIV

Another string to HIV's bow

HIV has a plethora of mechanisms that allow it to evade immune control, and now another can be added to the list. In a report in *The Journal of Clinical Investigation*, Yechiel Shai and colleagues show that the fusion peptide (FP) in the amino terminus of the HIV envelope glycoprotein gp41 targets T-cell receptor (TCR) molecules and interferes with antigen-specific T-cell activation.

Previously, these authors observed that the 33-amino-acid FP, which has a central role in the fusion of HIV virions with host-cell membranes, is inserted at specific membrane microdomains of T cells. By confocal fluorescence microscopy, they now show that these microdomains also contain TCR, CD3 and CD4 molecules. Fluorescence resonance energy transfer (FRET) analysis and immunoprecipitation experiments confirmed the colocalization of FP with TCR molecules. To test whether this colocalization interfered with T-cell activation, the authors first assessed the *in vitro* T-cell responses of lymph-node cells from rats immunized with *Mycobacterium tuberculosis*. Culture with FP inhibited the proliferation of T cells, as well as the secretion of interferon-γ and interleukin-10 that is usually triggered in response to mycobacterial antigens. By contrast, a mutant FP, which contained a single amino-acid substitution (Val2Glu) and did not co-immunoprecipitate with TCR molecules, had less of an inhibitory effect on T-cell activation than did FP. Consistent with direct interference of the TCR, FP did not inhibit T-cell activation triggered by stimulation with PMA (phorbol 12-myristate 13-acetate) and ionomycin or with CD3-specific antibody, both of which by-pass the TCR.

The immunosuppressive role of FP was then studied *in vivo*, using a rat model in which arthritis was induced by immunization with *M. tuberculosis* in oil. Rats that received FP mixed with the mycobacteria and oil at the time of arthritis induction had milder arthritis than those that received the Val2Glu-mutant peptide, as shown by reduced ankle swelling and lower arthritis clinical scores. Moreover, delayed-type hypersensitivity responses to PPD (tuberculin purified protein derivative) — a measure of T-cell activity — were reduced further in the rats treated with FP than in those treated with the Val2Glu-mutant peptide.

This study identifies a function for the HIV gp41 fusion domain in immunosuppression, which the authors suggest might be important at the point of virus transfer from the surface of dendritic cells (DCs) to T cells, by decreasing DC death following T-cell activation and therefore increasing viral infection of additional T cells.

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References and links

ORIGINAL RESEARCH PAPER Quintana, F. J., Gerber, D., Kent, S. C., Cohen, I. R. & Shai, Y. HIV-1 fusion peptide targets the TCR and inhibits antigen-specific T cell activation. *J. Clin. Invest.* 7 Jul 2005 (doi:10.1172/JCI23956)