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T-CELL DEVELOPMENT

The missing link for T cells?

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Although there has been much progress in recent years in elucidating the pathway of T-cell development in the thymus, little is known about the link between extrathymic T-cell precursors and intrathymic T-cell progenitors. In this study, Harald von Boehmer and colleagues suggest a role for common lymphoid progenitors (CLPs) as the precursor cells that initially 'seed' the thymus from the blood after bone-marrow transplantation.

The most primitive early T-cell-lineage progenitors (ETPs) in the thymus are found in the double negative 1 (DN1) subset, specifically in the DN1a and DN1b fractions. These ETPs are lineage $(Lin)^-$, stem-cell antigen 1 $(SCA1)^+$ and KIT^{hi} (a phenotype known as LSK) and are therefore similar to bone-marrow LSK cells in terms of their surface markers. Bone-marrow-derived LSK cells with both myeloid and T-cell potential have been identified in the bloodstream, and this finding has led to the hypothesis that bone-marrow LSK cells contain a population of thymus-seeding T-cell precursors. However, migration of these cells into the thymus has not been shown, and whereas ETPs depend on Notch signalling in the thymus for development, bone-marrow LSK cells are not affected by a lack of such signalling. This has called into question the role of bone-marrow LSK cells in thymic immigration and has led to the investigation of alternative possibilities.

Von Boehmer and colleagues used transgenic mice with a human *CD25* reporter gene (denoted *hCD25*) under the control of regulatory elements of the gene encoding the pre-T-cell-receptor α-chain (pTα) to identify T-cell precursors inside and outside the thymus. They showed that DN1a and DN1b fractions in the thymus, which are known to contain ETPs, were both enriched for $hCD25^+$ cells and that the reporter-expressing cells therefore enter the canonical pathway of T-cell development. The authors had previously shown that a CLP subset from the bone marrow that is known as CLP2 cells $(Lin^-KIT^{-/low}B220^+)$ expresses hCD25 and can efficiently seed the thymus after intravenous transfer. They therefore set out to analyse the relationship between $hCD25^+$ CLP2 cells and ETPs.

In co-culture with OP9–DL1 cells, which mimic Notch signals found in the thymus, $hCD25^+$ CLP2 cells progressed beyond the DN1 stage of T-cell development (as indicated by expression of CD25) at a similar rate to ETPs, whereas bone-marrow LSK cells had a delay of 2–4 days. This shows that CLP2 cells are more responsive to Notch signals, and therefore to the thymic environment, than are bone-marrow LSK cells. To explain the finding that ETPs are not phenotypically similar to CLP2 cells in terms of the amount of expression of KIT and B220, the authors showed that short-term differentiation of these cells in OP9–DL1 co-cultures led to rapid changes in the expression of these markers. For example, after 6 days of culture, CLP2 cells had increased the expression of KIT to the same level as ETPs and had completely lost expression of B220 (similar to $B220^-$ ETPs). CLP2 cells were also found to reduce their expression of FLT3 (fms-related tyrosine kinase 3) to a level similar to that of ETPs faster than did LSK cells. The rapid expression of CD25 then progresses the CLP2 cells to a DN2 phenotype.

These results show that KIT and B220 are not stable markers for the differentiation of haematopoietic and lymphoid cells and that the phenotypic difference between CLP2 cells and ETPs does not exclude a role for CLP2 cells in thymic immigration. Furthermore, the rapid acquisition of a DN2 phenotype by CLP2 cells in the thymic environment could explain why it has so far been difficult to detect CLP cells as early immigrants in the steady-state thymus.

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ORIGINAL RESEARCH PAPER Krueger, A., Garbe, A. I. & von Boehmer, H. Phenotypic plasticity of T cell progenitors upon exposure to Notch ligands. *J. Exp. Med.* 17 July 2006 (doi:10.1084/jem.20060731)