

activity, however, was shown to be markedly reduced in immature B cells. Immunoprecipitation studies showed directly that Id2 and E2A form heterodimers in immature B cells, which indicates that Id2 might be responsible for the inhibition of E2A function.

This study shows, for the first time, a role for Id2 in the regulation of B-cell maturation in the spleen. In this process, it seems that Id2 has two functions — it allows commitment to the marginal-zone B-cell lineage and controls the differentiation of follicular B cells. But, the genes that are regulated by Id2 at this stage of development have not been identified yet.

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References and links

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FURTHER READING Engel, I. & Murre, C. The function of E- and Id proteins in lymphocyte development. *Nature Rev. Immunol.* **1**, 193–199 (2001)

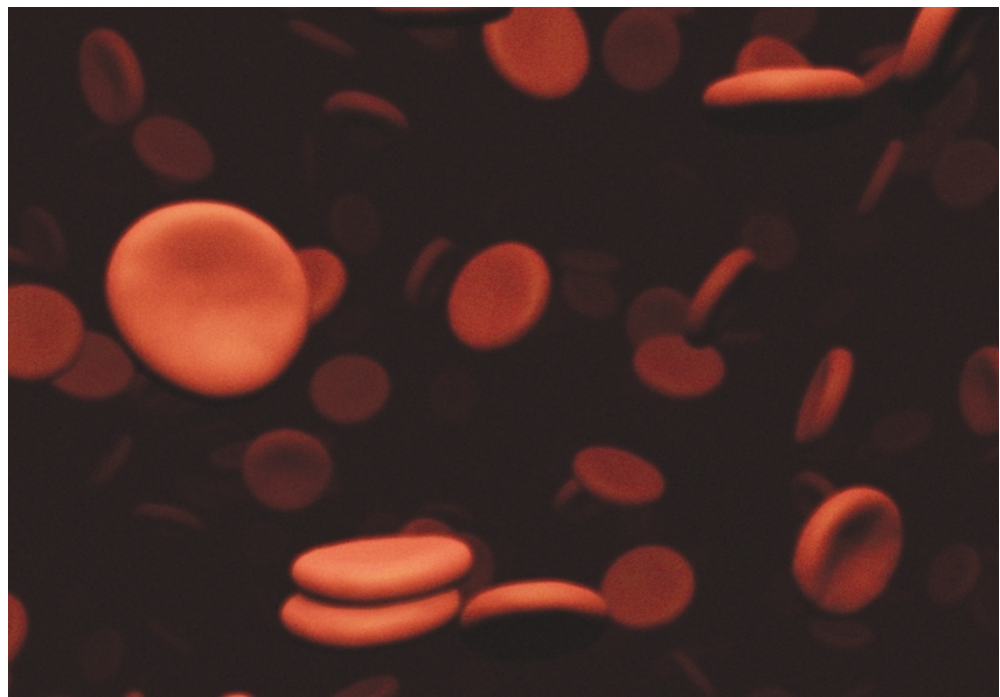
Interaction of NFAT with the nuclear factor AP1 is essential for the transcription of effector cytokine genes during T-cell activation, but is this interaction involved in the induction of anergy? Activation of AP1 was not detected in ionomycin-treated T cells. Furthermore, the transduction of T cells with a constitutively active NFAT1 that cannot interact with AP1 was sufficient to render the T cells anergic and to induce the expression of several anergy-associated genes.

On the basis of their results, the authors propose a new model of T-cell anergy (see figure). Importantly, this model predicts that blockade of the NFAT–AP1 interaction should prevent T-cell activation and induce a long-lasting state of tolerance. This is a key goal of organ transplantation that current regimes of immunosuppression fail to achieve.

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WEB SITE
 Anjana Rao's lab: <http://www.hms.harvard.edu/dms/bbs/fac/rao.html>



HAEMATOPOIESIS

The origin of HSCs

Despite intensive investigation, the origin of the first haematopoietic stem cells (HSCs) that develop during mammalian embryogenesis is unclear. Two recent studies published in *Immunity* provide clues as to the cellular origin of these HSCs and their location within the embryonic tissues from which they emerge.

HSCs give rise to all haematopoietic lineages and are also capable of self-renewal. In adult animals, HSCs reside in the bone marrow, but during mouse embryonic development, HSCs are found first in the dorsal aorta within the aorta–gonads–mesonephros (AGM) region and in the vitelline and umbilical arteries before the bone marrow forms.

The transcription factor Runx1 and its heterodimeric protein partner core-binding factor- β (CBF β) are essential for the formation and/or function of HSCs, because the homozygous deletion of either of the genes that encode these proteins results in a total block in definitive haematopoiesis. In addition, Runx1 is expressed in all sites from which HSCs emerge. These previous studies had indicated that the expression of Runx1 marks the first HSCs in the embryo but, until now, this had not been shown directly.

North and colleagues used adoptive-transfer assays to determine whether Runx1 is expressed in embryonic HSCs. They isolated Runx1⁺ and Runx1⁻ cells from the AGM region, vitelline and umbilical arteries, and livers of mouse embryos and then carried out transplantation assays. For each of the haematopoietic tissues tested, all HSCs were found in the Runx1⁺ population and no

HSCs were found in the Runx1⁻ population.

Further experiments showed that most HSCs in wild-type embryos express endothelial cell-surface markers and CD45 (a leukocyte marker that is expressed by all haematopoietic cells except erythrocytes). By contrast, HSCs in Runx1^{+/-} embryos are heterogeneous, and include cells that express CD45, as well as CD45⁻ endothelial cells and mesenchymal cells. These studies, therefore, show that all HSCs in mouse embryos express Runx1, and that Runx1 affects the distribution of HSCs into different cell populations in a dose-dependent manner.

In the second study, De Bruijn *et al.* investigated the spatial localization of HSCs within the mouse embryo, using the Sca1 surface glycoprotein (a well-known marker of HSCs) and a green fluorescent protein (GFP) marker gene (expressed under the control of Ly-6A gene regulatory sequences, which encode Sca1). First, they established that the Ly-6A–GFP transgene is expressed by all functional HSCs in the AGM of embryonic day 11 mice; then, they carried out immunohistochemical staining to investigate where these cells reside. In the AGM, GFP⁺ cells were specifically localized to the single layer of CD31⁺ endothelial cells that lines the wall of the dorsal aorta, but were not found in the underlying mesenchyme. The authors concluded that HSCs are generated within the layer of endothelial cells that lines the wall of the dorsal aorta, and by additional flow-cytometric analysis, they showed that these cells have both endothelial and haematopoietic cell-surface characteristics. The authors hope that, on the basis of these findings, future studies might allow the immediate precursors of HSCs to be identified.

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References and links

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