HoxB4 induces definitive HSCs

Conflicting data exist for whether primitive and definitive hematopoietic progenitors share common embryonic origins. In *Cell* online, Kyba *et al.* show ectopic expression of the homeobox protein HoxB4 confers long-term hematopoietic repopulation potential onto embryonic stem (ES) cells. Hox4B conferred adult HSC potential onto both yolk sac cells and embryoid bodies that were derived from ES cells in culture on hematopoietic stroma. Even transient expression of Hox4B in primitive progenitors could induce expression of definitive hematopoietic markers—including adult β-globin and CXCR4—suggesting that these cells were poised to become definitive HSCs. *In vivo*, all hematopoietic compartments of irradiated syngeneic mice could be reconstituted with HoxB4-induced ES cells. More importantly, transplantation of ES-derived bone marrow cells could engraft secondary recipients and give rise to long-term hematopoiesis. Thus, these data show primitive embryonic progenitors can contribute to definitive hematopoiesis and offer potential strategies for gene delivery.

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Notching neighbors

Notch regulates hematopoietic cell fate choices in the cell in which it is produced. In a recent article in the *Journal of Immunology*, Kawamata *et al.* showed that Notch activation also alters the fate of neighboring cells. Irradiated mice were transplanted with a mixture of constitutively active Notch–transduced bone marrow and nontransduced bone marrow. B cell development was blocked and myeloid lineage differentiation was enhanced not only in Notch-transduced cells, but also in cells from the nontransduced compartment. Soluble factors from the medium of Notch-transduced bone marrow cultures quantitatively inhibited B cell development and promoted myeloid differentiation. In the T cell lineage there were additional abnormalities. Mice that had Notch-transduced cells and that developed T cell leukemia also showed defective differentiation of nontransduced T cells in their bone marrow. These data indicate that continuous Notch activation not only affects the cells of many lineages that carry the transgene, but can alter the development of nontransduced, neighboring hematopoietic cells.

J. Immunol. **168**, 1738–1745 (2002)

Reprogramming T or B cells

Cloning from ES cells is more effective than somatic cell cloning, which suggests that the nuclei from an embryonic cell is more easily reprogrammed than the nuclei from differentiated cells. In fact, it has been suggested that surviving clones derived from the nuclei of differentiated cells are actually derived from the nuclei of rare somatic stem cells instead. In *Nature*, Hochedlinger and Jaenisch generated monoclonal mice by nuclear transfer from mature B and T cells. Nuclei from B or T cells were transferred into enucleated oocytes to derive cloned blastocysts and subsequently ES cells, which were then injected into tetraploid blastocysts to generate mice. Mice cloned from the B cell or the T cell nucleus carried fully rearranged Ig or TCR genes, respectively, in all tissues. Thus, this study shows that a terminally differentiated cell can be reprogrammed.

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PU.1 inhibits pro-T cells

Down-regulation of PU.1, a transcription factor expressed in multipotent thymic precursors, coincides with T cell lineage commitment. In *Immunity*, Rothenberg and colleagues investigate the significance of PU.1 down-regulation for T lineage commitment by using retroviral vectors that constitutively express PU.1 in hematopoietic precursors during differentiation in fetal thymic organ culture. The forced expression of PU.1 reduced thymocyte expansion and severely blocked development at the pro-T cell stage. Transfer into conditions permissive for macrophage development could rescue PU.1-expressing cells arrested at this stage. Thus, inhibition by PU.1 depends upon both lineage and development stage. In addition, pre-Tα, RAG-1 and RAG-2 were down-regulated in PU.1-transduced cells and high PU.1 expression induced Mac-1 and Id-2 expression. Collectively, these results indicate that PU.1 down-regulation is essential for progression in the T cell lineage.

Immunity **16**, 285–296 (2002)

TACC3 link to p53

Transforming acidic coiled-coil (TACC) proteins form a conserved protein family that associate with the mitotic spindle apparatus in dividing cells; however, their function remains largely unknown. In the *EMBO Journal*, Ihle and colleagues show restricted expression of TACC3 in lymphoid organs, where it is abundant in cells of hematopoietic origin. TACC3-null mice died *in utero* at the mid-to-late gestation stage due to cell-intrinsic defects in hematopoietic stem cell (HSC) functions. TACC3-deficiency was associated with higher rates of apoptosis and increased expression of the p53 target gene $p21^{Waf1/Cip1}$. Yet, $TACC3^{-/-}$ cells did not show gross chromosomal abnormalities. Viable offspring could be produced from crosses of mice heterozygous for p53 or TACC3. $TACC3^{-/-}p53^{-/-}$ fetal liver cells could reconstitute the lymphoid compartment of Jak3-deficient mice. Thus, p53 deficiency rescued the hematopoietic defect posed by the lack of TACC3, indicating a genetic link between p53 and TACC3 function. TACC3 may couple mitotic spindle assembly to the p53-dependent sensor pathway to regulate cell cycle progression.

EMBO J. **21**, 653–664 (2002)

Cycling HSC and integrins

Engraftment of cycling HSCs occurs less successfully than their quiescent stem cell counterparts. This reversible defect is thought to reflect differences in the ability of mitotically active cells to home to supportive stromal niches in the bone marrow. In *Blood*, Giet *et al.* examine cell cycle–associated changes in adhesion and chemotactic migratory properties of human $CD34^+$ HSCs *in vitro*. Cycling HSCs adhered more tightly to fibronectin-coated wells and displayed less migration towards chemoattractants as compared to cells in G0 or G1. Fibronectin binding by the HSCs is mediated through α_4 and α_5 integrins. Neutralization experiments revealed that these integrins display nonredundant roles in HSC homing properties, which are independently modulated during transit through the cell cycle. Thus, HSC trafficking involves a balance between α_4- and α_5-mediated adhesion and migration properties.

Blood **99**, 2023–2031 (2002)