Hematopoietic Stem Cell Fate Regulation and Cancer

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Hematopoietic transcription factors are key regulators of cell growth and differentiation. To identify novel transcription factors that regulate hematopoietic cell fate, we performed microarray analysis and found that inhibitor of DNA binding 1 (Id1) is expressed in myeloid progenitor but not in more primitive progenitors. Id1 is high in myeloid cells but decreased in erythroid, B and T cells. Id1 is not expressed in hematopoietic stem cells (HSC) and common lymphoid progenitors (CLP), but is expressed in common myeloid progenitor cells (CMP) and increased in granulocyte/monocyte progenitors (GMP). Id1 is up-regulated by IL-3, GM-CSF (myeloid) but not by growth factor (HGF) that promote lymphoid, erythroid and megakaryocyte development. Therefore, Id1 may play an important role in myeloid development. To define the functional role of Id1 in hematopoietic development, we infected hematopoietic bone marrow stem cells with retroviral vectors that express Id1 (5FU-Id1, GFP+) and plated cells in colony assays or transplanted them into irradiated recipients *in vivo*. 5FU-Id1 cells were hyperproliferative and showed increased colony forming activity in response to HGF. We found that cell lines could be readily derived by plating 5FU-Id1 cells in multiple HGF. These 5FU-Id1 clones had blast cell morphology, normal chromosomes by karyotyping, expressed cell surface markers and genes present in CMP/GMP progenitors and show a strong proliferative response to myeloid HGF, moderate response to erythroid HGF, and less response to B-cell HGF. Finally, these cell lines show a significant decrease in cell cycle inhibitors: p15, p16, p19, p21 and p27, which may account for the immortalization of the cells. Overexpress of Id1 *in vivo*, Id1 greatly increases myeloid cells and cause leukemia but greatly decreased B cells. In addition, anemia was observed in these mice suggesting that Id1 may affect erythroid differentiation *in vivo*. Id1-GFP$^+$ bone marrow cells from transplant recipient were injected into SCID mice and resulted in lethal death of the mice. Taken together, we propose that Id1 may instruct stem cells toward a myeloid cell fate versus B-lymphoid and erythroid cell fates. Id1 significant impairs B cell development, which is crucial for immune system. Id1 may play a crucial role in CMP/GMP stem cell self-renewal and can act as an oncogene to immortalize hematopoietic progenitor cells.