

Role of STAT3 for Hematopoietic Stem Cells

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Abstract

Self-renewal of hematopoietic stem cells (HSCs) is a major factor determining the yield of ex-vivo manipulation of HSC or regeneration of bone marrow after transplantation. Despite the many interests, molecular mechanisms regulating the self-renewing process of HSC remains largely uncertain. Based upon previous finding that activating gp-130 signal enhance self-renewal of HSC, we speculated that STAT3, one of down stream molecule of gp-130, could be a effector molecule. In the expression analysis, higher level of STAT3 transcripts were detected in primitive human bone marrow cells (CD34⁺CD38⁻) cells compared to their in-vitro differentiated products or uncultured CD34⁺CD38⁺ cells. Similar quantitative difference was also observed in protein level of STAT3 in 5-FU treated murine bone marrow cells. To test the effect of STAT3 activity in various stages of hematopoiesis, murine fetal liver cells (TER119 depleted) were transduced with retrovirus (MSCV-IRES-GFP) encoding either wild type (wt) or dominant negative form (dn) of STAT3. Profound suppression of lympho-myeloid repopulation was observed in the cells transduced with dn form of STAT3, but no changes in further down stage of hematopoietic activities as defined by spleen colony formation (CFU-S) or in-vitro colony formation (CFC). Similar results were observed using murine bone marrow cells stimulated with 5-FU, suggesting that HSCs of more broad spectrum requires STAT3 activity for their repopulating activities. In contrast, overexpression of wild type STAT3 did not affect any of those hematopoietic activities. However, when similar study was performed using another mutant form of STAT3 (STAT3-C) that can dimerize without being phosphorylated, significant increases in the repopulating activities of transduced cells were observed. Our study suggests that the STAT3 plays a direct regulatory role for gp-130 mediated induction of self-renewal in HSCs.
