S109

Strategies for Enhanced Regeneration of Hematopoietic Stem Cells

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Hematopoietic stem cell (HSC) is a rare population of stem cells that can sustain hematopoietic and immunological reconstitution, and key cellular component for regeneration of many non-hematopoietic tissues. Accordingly, the application of HSC in regenerative medicine is expanding from classical bone marrow transplantation for leukemia or blood disease to more diverse spectrum of disease such as autoimmune disease, congenital disease or many non-hematopoietic diseases. Therefore, strategy to enhance the repopulation of bone marrow, to induce their self-renewal for ex-vivo expansion, or maintenance of stem cell phenotype during gene therapeutic approach has been a major interest in these fields. Here, we present two strategies to enhance repopulation of transplanted HSCs, one increasing input amount of graft by transplanting multi-donor derived HSCs and the other, increasing the regenerative acitivty of transplanted HSCs. As a first strategy, the feasibility that two allogeneic umbilical cord blood (UCB) could be mixed transplanted into the same recipients were experimentally examined. Thus two allogenic units of UCBs were transplanted into NOD/SCID as a single or mixed graft and their donor origins were determined by donor-specific PCR-SSOP or real time quantitative short tandem repeats (STR). When two units of UCB were mixed transplanted as a total nucleated cells, cells from one donor predominated over the other regardless of HLA matching and no additive engraftment were seen from the two graft as compared to single unit transplantation control. However, depletion of lineage positivecells before grafting resulted in alleviation of one-donor predominance implicating immunological competition between the grafts. Importantly, cotransplantation of culture expanded mesenchymal stromal cells obtained from 3rd party could alleviate one-donor predominance without the need for lineage depletion of the grafts. Futhermore, MSC mediated alleviation of donor predominance was well correlated to corresponding increase in the overall engraftment from mixed UCB transplantation suggesting potential benefits in clinical transplantation. The second strategy to increase repopulation of bone marrow is to enhance the regenerative potential of transplanted HSCs. We previously showed that expression of dominant negative STAT3 (dnSTAT3) in murine fetalliver cells could selectively suppress their repopulating activity, but not with wild-type STAT3. However, constitutive activation of STAT3 in murine bone marrow cells could enhance the regenerative capacity with higher level engraftments. Serial transplantationof STAT3 activated HSC showed higher self-renewal during in-vivo reconstitution, but was limited to early physiological regenerative phase, and did not override normal HSC pool size reflecting physiological feed back regulation on these cells. While the mechanismare not clear yet, our result shows that STAT3 induced activation of HSC does not involve upregulation of HoxB4. Our results suggest that STAT3 signal may be an important parameter for the extent of in-vivo amplification of HSCs. Further studies on in-vivo self-renewal of HSC will facilitate development of more efficient cell therapeutic strategies.