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G-CSF Alters Hematopoietic Stem Cells Function

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There is accumulating evidence that systemic signals, such as inflammatory cytokines, can affect hematopoietic stem cell (HSC) function. Granulocyte colony stimulating factor (G-CSF), the principal cytokine regulating granulopoiesis, is often induced in response to infection or inflammation. Additionally, G-CSF is the most commonly used agent for HSC mobilization prior to stem cell transplantation. Recently there has been a renewed interest in the use of “G-CSF primed bone marrow” for stem cell transplantation, so understanding the affect of G-CSF on bone marrow HSCs is clinically relevant. Because the G-CSF receptor is expressed on HSCs, and G-CSF creates biologically relevant modifications to the bone marrow microenvironment, we hypothesized that increased signaling through G-CSF may alter the repopulating and/or self-renewal properties of HSCs.

Due to G-CSF’s role as an HSC mobilizing agent, we predicted that the number of HSCs in the bone marrow would be reduced after 7 days of G-CSF treatment. Surprisingly, we observe that stem cell numbers markedly increase, regardless of their immunophenotypic identification. To assess HSC repopulating activity, we conducted competitive bone marrow transplants. Compared to untreated HSCs, we found that G-CSF treated cells have significantly impaired long-term repopulating and self-renewal activity in transplanted mice. As HSC quiescence has been positively associated with repopulating activity, we analyzed the cell cycle status over time of KLS-SLAM cells treated with G-CSF. This analysis revealed that after a brief period of enhanced cycling, HSCs become more quiescent.

To identify targets of G-CSF signaling that may mediate loss of stem cell function, we performed RNA expression profiling of sorted KSL-SLAM cells. The profiling data show that G-CSF treatment is associated with activation of inflammatory signaling in HSCs. Studies are in progress to test the hypothesis that activation of specific inflammatory signaling pathways mediates the inhibitory effect of G-CSF on HSC function.