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Biology of adult marrow stem cells

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Primitive bone marrow stem cells have been considered to be dormant in a hierarchy. We have developed a contrary model in which marrow stem cells are on a reversible continuum of change. We have shown, in liquid cytokine stimulated culture, reversible changes in long term engraftment, homing, global gene expression, expression of stem cell markers and transcription factors, differentiation into megakaryocytes, granulocytes, and type 11 pneumocytes tied to cell cycle phase. The cycle status of the marrow renewal stem cell was thus of importance to the validity of this model. The dogma that the long-term renewal marrow stem cell was non cycling was based on studies of highly purified stem cells, but no studies had ever been carried out on unseparated whole murine marrow cells. This seemed an oversight, since the bulk of stem cells are lost during the separation. Accordingly, we evaluated the cell cycle status of long-term multilineage repopulating murine marrow stem cells in unseparated marrow using 1.) Pyronin/Hoechst staining and FACS separation or 2.) Tritiated thymidine suicide followed by competitive engraftment into lethally irradiated mice. We found in each instance that over 50% of the repopulating cells were in S or S/G2/M phases of cell cycle. Furthermore, in vivo BrdU injections revealed that over 80% of the most primitive purified stem cells, lineage negative Sca-1+ c-kit+ Flk2- had passes through S-phase in 48 hours. These data show that primitive marrow stem cells are cycling, and thus, of necessity continually changing phenotype. They confirm the continuum model.

Biography

Dr. Peter Quesenberry is the Calabresi Professor of Oncology at The Warren Alpert Medical School of Brown University. He is an internationally renowned stem cell scientist and lists 287 publications in PubMed.