Leukemia Supplements (2014) **3**, S18

www.nature.com/leusup

SPECIAL REPORT

Adult marrow hematopoiesis: a continuum of change

PJ Quesenberry, L Goldberg, M Dooner, M Pereira and J Aliotta

Leukemia Supplements (2014) **3,** S18; doi:10.1038/leusup.2014.10

Keywords: extracellular vesicles; stem cells heterogeneity; cycling stem cell

Adult marrow hematopoiesis has been felt to represent a classical hierarchical system with a primitive stem cell progressively differentiating into hematopoietic cells. Colony-forming unit spleen was the initial stem cell and there followed definition of a wide variety of progenitors with different lineage potentials. Purification studies indicated that the critical stem cells were lineage negative and Sca-1+c-kit+CD150+.[1] Our studies over the past decade indicate that the phenotype of the stem cell changes reversibly with cell cycle transit. Characteristics showing such changes include long-term multilineage engraftment into irradiated mice, differentiation, homing to marrow, expression of adherence proteins and global gene expression, progenitor phenotype and uptake of extracellular vesicles. It was demonstrated that most stem cells are discarded during the separation. The final purified stem cell is in fact dormant, but the vast majority of stem cells that are discarded (over 90%) are in active cell cycle.[2] In these studies it was shown that cells in S/G2/M accounted for over 50% of long-term engraftment of whole unseparated marrow and that the classical purified lineage-negative Sca-1-c-kit+CD150+ stem cell rapidly progressed through the cell cycle so that after 48 h exposure to *in vivo* bromodeoxyuridine up to 80% of the 'dormant' cells incorporated bromodeoxyuridine. These data indicated that most mature marrow stem cells were discarded with the purification and that these cells were virtually all proliferating. Studies on the different fractions of a purification indicated that the vast majority of adult marrow stem cells were present in the lineage-positive and lineage-negative populations and that these cells were cycling. Thus, the true marrow stem cells rapidly transited the cell cycle and were continually changing phenotype; they could not be 'purified' by assessing a set number of epitopic markers. The bulk of studies on murine marrow stem cells has been carried out on 'purified stem cells' and thus have been addressing an irrelevant population of cells. These studies need to be readdressed. Further heterogeneity of adult marrow stem cells is introduced by considerations of interactions of these cells with extracellular vesicles.[3] Studies on lineage-negative Sca-1 + progenitor/stem cells traversing the cell cycle under cytokine stimulation in liquid culture indicated that vesicle uptake varied with both the cell cycle state of the target cell and the nature of treatment of the originator lung cells (irradiation or no irradiation). Thus the adult marrow stem cell continually alters phenotype with cell cycle transit and this is further impacted upon by interactions with vesicles from a variety of cell types. The cell phenotype induced by vesicle exposure appears to be a stable epigenetic change induced by an RNase-sensitive agent that is not messenger RNA, presumably a non-coding RNA species. These observations suggest unique strategies for determination of cell fate and restoration of damaged cells. These data also suggest that while cell populations may be stable at the tissue or population level they are not stable at the individual cell level.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

LG received grant support from the Rhode Island Foundation. The symposium and publication of this supplement were sponsored by the Division of Hematology/Oncology at the Warren Alpert Medical School of Brown University and NIH Center of Biomedical Research Excellence (COBRE) for Stem Cells Biology at Rhode Island Hospital.

REFERENCES

1 Oguro H, Ding L, Morrison SJ. SLAM family markers resolve functionally distinct subpopulations of hematopoietic stem cells and multipotent progenitors. *Cell Stem Cell* 2013; **13**: 102–116.
2 Goldberg LR, Dooner MS, Johnson KW, Papa EF, Pereira MG, Del Tatto M *et al.* The murine long-term multi-lineage renewal marrow stem cell is a cycling cell. *Leukemia* 2014; **28**: 813–822.
3 Aliotta JM, Lee D, Puente N, Faradyan S, Sears EH, Amaral A *et al.* Progenitor/stem cell fate determination: interactive dynamics of cell cycle and microvesicles. *Stem Cells Dev* 2012; **21**: 1627–1638.

Division of Hematology/Oncology, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI, USA. Correspondence: Professor PJ Quesenberry, Division of Hematology/Oncology, Warren Alpert Medical School of Brown University, Rhode Island Hospital, George 3, 593 Eddy Street, Providence, RI 02903, USA.
E-mail: pquesenberry@lifespan.org