EDITORIAL

Competitive Repopulation in Unirradiated Normal Recipients

By David E. Harrison

OFTEN IN SCIENCE conventional wisdom develops from ideas that gain wide acceptance without definitive proof. Such paradigms often prove to be misleading, and block potentially important avenues of research. One such idea may be that primitive hematopoietic stem cells (hereafter called stem cells) function in close association with a supporting matrix, a microenvironmental niche. This close association is thought to bestow a competitive advantage on stem cells already in residence, so that such cells must be removed or defective before donor stem cells can be successfully transplanted.

The article by Quesenberry et al in this issue of Blood on transplantation into recipients with undamaged stem cells confirms and extends previous pioneering work. In the most impressive experiment, recipients received marrow from 2 tibias and 2 femurs daily for 5 days; after 12 months, the mean percentages of donor cells in marrow, spleen, and thymus were 48%, 32%, and 29%, respectively. Thus, a high dose of donor marrow can successfully and permanently repopulate a recipient without need for removing or damaging recipient stem cells.

These results can be analyzed as competitive repopulation, in which donor cells compete with cells in residence to repopulate the recipient. If 2 tibias and 2 femurs contain about 50 million cells, the 5 injections contain 250 million. The recipient contains about 300 million marrow cells; thus, if there is no competitive disadvantage for the donor cells, then the expected percentage of donor cells is 250 divided by 250 plus 300, or 45%. As noted above, the results actually observed are 48%, 32%, and 29%, suggesting that resident cells have little or no advantage.

The high repopulating ability observed, which was almost that of the recipient's own marrow, is surprising, because studies of previously transplanted marrow cells predict a substantial competitive disadvantage for the donor cells resulting from deleterious effects of transplantation. For example, marrow from recipients repopulated 4 months previously with 10 million marrow cells had about one-ninth the repopulating ability of fresh marrow. The damage may result from the rapid proliferation stimulated to repopulate lethally irradiated recipients. In the current experiment, there is no recipient cell loss and no abnormal stimuli.

A potential problem with these studies is the wide variability between recipients. This does not fit previous findings that variability between recipients of mixtures of distinguishable marrow cells is inversely proportional to the numbers of cells injected. It is possible that the use of male donors in female recipients stimulated immune responses against the male antigen; differing degrees of immune responses resulting by chance could have increased variabilities.

These results definitively contradict the conventional wisdom that recipient cells must be removed to leave space for donor cells in the stem cell supporting microenvironmental "niches." It is possible that stem cells need no special supporting niche. If this is true, stem cell proliferation can be stimulated in vitro once the appropriate medium is defined.

Of course, there are other possibilities. Stem cells may require niches, but they may be dynamic, so cells already occupying niches have no advantage over injected cells, or there may be a large number of empty niches available for injected cells. Finally, transplanted marrow may include the cells needed to form niches; these cells may be damaged by 5-FU, thus explaining the poorer repopulation found in that case.

These results also have direct implications for clinical procedures in which it is desirable to transplant stem cells without irradiation or drug treatment of the recipient. The most prominent example is gene transplantation using stem cells as vehicles. Such procedures apparently will not be limited by the need to remove recipient stem cells.

REFERENCES


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