

Stem-Cell Biology and Cancer Therapy: The More Things Change...

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It has been 25 years since the accompanying review article has been published, and although much has changed, much remains the same, at least in its general form. The focus of our 1983 review of the organization of the hematopoietic stem-cell compartment has been expanded to the stem-cell compartments of other cell-renewal tissues, normal tissues not formerly considered cell-renewal tissues, and perhaps most pertinently, to tumors themselves. This work is continuing to yield important potentially clinically relevant information. Our review article focused on the hematopoietic system because it was then, as now, the most frequent dose-limiting normal tissue. The review emphasized the differences in the hematopoietic damage of different cytotoxic agents used clinically. Cyclophosphamide is different from other alkylating agents in its relative sparing of stem cells, whereas radiation, busulfan, L-PAM, and the nitrosoureas are potent stem-cell toxins. Drugs primarily affecting dividing cells (such as methotrexate, fluorouracil, and vinblastine) tend to spare the slowly dividing stem cells. This is why not all iatrogenic hematopoietic depression is the same. When caused by cycle-active agents, the more potent proliferatively inactive stem cells are more likely spared than when the cytopenia is caused by busulfan or radiation. Although bone marrow toxicity is still important, damage to other normal tissues has become increasingly important. We recognized the importance of the stroma in supporting hematopoiesis in the bone marrow and demonstrated the detrimental effects of busulfan, L-pam, the nitrosoureas, ionizing radiation, and aging on the ability of the marrow to support transplanted stem cells and the resulting hematopoiesis. Similar stromal effects should be equally critical in other normal tissues. Since the time of this review, the CNS has been shown to have stem cells present in the adult, which are important for cell renewal after injury.

The major concept important to understanding the hematopoietic stem-cell compartment is the heterogeneity of cells classified as stem cells. We believe that the model suggested in Figure 1 of the review is still valid. What is needed is much greater understanding of the founder cells. If clonal succession that allows normal hematopoiesis to be provided by only a few founder cells at a given time is true in mice, what can we say about humans? Most importantly, how is this clonal succession controlled? Is the selection of a particular stem cell for division stochastic, or are there determining causes? One may think of this as similar to radioactive decay, where

the selection of the particular nucleus to decay is considered in probabilistic terms. Is there a similar biologic uncertainty principle? Probabilistic notions may be appropriate but these may be necessary only because there is insufficient understanding of the system biology of the stem-cell compartment. The information underlying the model suggested in our review is all derived from murine studies. Most important today is to ascertain whether these concepts pertain to man and, if so, in which cell renewal systems they are present.

We know that in mice the circulating stem cells are less robust than those in the bone marrow, but this is true on average and does not mean that there aren't some early stem cells regularly circulating. More to the clinical point is the nature of stem-cell traffic in humans. Recent studies of neuronal stem cells suggest traffic within the CNS. Knowing the location, robustness, and traffic dynamics should greatly help in fashioning less toxic therapies, particularly regional therapies such as ionizing radiation. As new types of treatment of cancer emerge, new toxicities are produced. We must determine whether these are the result of damage to the stem cells of the organ at risk and, if so, whether the stem-cell organization of the hematopoietic system is a useful model for understanding this toxicity.

Twenty-five years ago there was no suggestion of tumor stem cells responsible for tumor growth and metastasis. Although appreciable cell death and terminal maturation were noted as necrosis and terminal differentiated cells, respectively, viable tumor cells were all believed to have the ability to proliferate into new tumors in situ or at a distant site. There is now some evidence for, and much discussion of, possible tumor stem cells that have properties reminiscent of those of the hematopoietic system: slow proliferation, limited differentiation markers, and both self-renewing and maturing progeny. One may wonder whether in tumors of cell renewal tissues such as the bone marrow, lymphatic tissue, skin, and GI system, the putative tumor stem cells may be stem-cell deviants. Perhaps heterogeneity of stem cells described in our review is relevant to tumors. Tumors derived from founder cells may have different prognoses than those of later stem cells. Clonal succession may be present in tumors and one can imagine that in some leukemias there are both normal and malignant stem cells. When a complete remission occurs, perhaps new stem cells are recruited to support hematopoiesis. Does chance or definable

factors determine which cells will be selected? If a leukemia stem cell is among those selected, the disease returns. Such a process would explain late tumor recurrence after an apparent destruction of all tumor cells. Although this may be a fanciful explanation, it demonstrates the importance of learning from the normal hematopoietic stem-cell compartment for both its malignancies and also as model for tumors of other cell renewal systems. Failure of a treatment may also be due to the drugs being effective primarily on the more committed progeny while the hypothesized tumor stem cells are spared. This may be due to differences in proliferative state, surface markers, or yet unknown tumor stem-cell characteristics. Tumor growth and maintenance, like the hematopoietic system, depend on a functioning stroma. Current clinical considerations of the stroma are concerned primarily with the vascular components. However, it is likely that like hematopoiesis, tumor growth requires much more from the stromal matrix in which it grows.

“The more things change the more they remain the same” is the translation of a French aphorism that appears relevant to the

current state of our knowledge of stem-cell biology. What has changed is the identification of markers, allowing significant enrichment of hematopoietic stem cells, better understanding of stem cells in the GI system, the discovery of stem cells in normal tissues not traditionally considered to be cell renewing, and the current interest in the tumor stem-cell hypothesis. Perhaps more pertinent to our 1983 review is what remains the same: stem-cell heterogeneity, stem-cell traffic, and differential drug effects. We need a far better understanding of the system biology controlling these phenomena in the hematopoietic system, and the relevance to other organs and to tumors in humans.

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