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Bone Marrow–Derived Stem Cells and Radiation Response

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Abstract

The recovery of tissues and organs from ionizing irradiation is critically dependent on the repopulation of resident stem cells, defined as the subset of cells with capacity for both self-renewal and differentiation. Stem cells of both hematopoietic and epithelial origin reside in defined areas of the cellular microenvironment (recently defined as the stem cell “niche”). Experiments using serial repopulation assays in serial generations of total body irradiated mice receiving transplanted marrow and in continuous bone marrow cultures both identified specific microanatomic sites that comprise the bone marrow stem cell niche. Supportive cells of the hematopoietic microenvironment not only contribute to stem cell repopulation capacity but also to the maintenance of their quiescent or nonproliferative state, which allows the most primitive hematopoietic stem cells to stay in a noncycling state protected from both direct ionizing radiation-induced cell-cycle phase-specific killing and indirect cytokine and free radical mediated killing. Recent evidence has defined both cell contact and humoral mechanisms of protection of hematopoietic stem cells by stromal cells. There is also recent evidence for multilineage differentiation capacity of cells of the hematopoietic microenvironment termed bone marrow stromal cells (mesenchymal stem cells). Both hematopoietic stem cells and mesenchymal stem cell populations have been shown to be involved in the repair of ionizing irradiation damage of distant epithelial as well as other hematopoietic sites through their capacity to migrate through the circulation. The radiobiology of these 2 bone marrow stem cell populations is the subject of intense investigation. This review defines the status of research in the areas of stem cell quiescence, niche contact, and migratory responses to ionizing irradiation.

Nowhere are the basic principles of radiobiology more dramatically defined than in the response of bone marrow–derived stem cell populations. Hematopoietic stem cells were initially defined as that subpopulation of marrow mononuclear cells that can repopulate hematopoietic organs of lethally irradiated mice.^{1–3} These cells form discrete microscopic colonies on the surface of the recipient mouse irradiated spleen termed the colony-forming unit spleen (CFUs).^{4,5} Other cell populations within the bone marrow have been shown to form microscopic colonies in vitro in a semisolid medium^{6,7} and also display a characteristic radiation dose-response curve.⁸ There are clear cell cycle–specific chemo-therapeutic agents that define toxicity to subsets of stem cells in quiescence or the nonproliferative state, whereas other chemotherapeutic drugs are known to affect proliferating cells but spare the most primitive hematopoietic cells.⁹ After irradiation, hematopoietic stem cells show a

classic repopulation and redistribution response to irradiation, and subsets differentiate to committed progenitors.^{4,10}

There are clear microanatomic sites in the hematopoietic microenvironment in vivo in which stem cells reside. These stem cell “niches” have recently been shown to be relatively hypoxic.¹¹ The response of stem cells to irradiation has been the subject of intense investigation, particularly as related to understanding the toxicity of total body irradiation and in the discovery of new radioprotective drugs against the hematopoietic syndrome.

Two Distinct Populations of Stem Cells Reside in the Bone Marrow

There is convincing evidence that in addition to hematopoietic stem cells a second population of mesenchymal stem cells exists in the bone marrow.^{12–18} This latter population of cells also called marrow stromal cells or stromal stem cells consists of a population of adherent myofibroblast-like cells that are capable of differentiating to osteoblasts, chondrocytes, adipocytes, and fibroblasts.^{18–22} Both hematopoietic stem cells and mesenchymal stem cells migrate through the circulation and under specific conditions can show increased mobilization and transit to distant sites.^{13,14,18}

Hematopoietic stem cell mobilization from nonirradiated areas of bone marrow is followed by circulatory trafficking and allows them to home and repopulate irradiated or damaged areas.^{24,25} Shielding one limb of a total body–irradiated mouse can result in complete reconstitution and hematopoietic recovery.^{5,26,27} Mesenchymal stem cells also migrate from nonirradiated to heavily irradiated sites. Werts et al²⁸ showed repopulation of heavily irradiated mouse limbs with bone marrow stromal cells migrating through the circulation from unirradiated sites. Mesenchymal stem cells also have the capacity to contribute to the late lesion of radiation fibrosis, significantly replacing functioning pulmonary alveolar spaces with pulmonary fibrotic lesions.^{13,18,26,29}

Mobilization of both hematopoietic and mesenchymal stem cell populations can be stimulated by a variety of factors, including cytokines,³⁰ and the as-yet-unknown soluble factor involved in the radiation bystander effect.³¹ The granulocyte colony-stimulating factor and other marrow-derived cytokines have been shown to mobilize multilineage hematopoietic stem cell into the peripheral blood of humans and animal models.^{27,32–34} With respect to the lymphohematopoietic stem cells, assays that distinguish the most primitive cells from those committed progenitors include the serial transfer assay,²⁵ competitive repopulation assay,²⁴ and the R_S assay.⁴

An assay for repopulation of nonirradiated areas by mesenchymal stem cells has been shown by Prockop et al¹⁸ using an animal model system in which cell populations responsible for correcting osteoblast defects in osteogenesis imperfecta are replaced in a direct dose-response curve and then transplanted into osteogenesis imperfecta mesenchymal stem cell–deficient mice. Although the cell surface phenotype of the hematopoietic stem cell has been partially defined, cell-surface phenotypic markers for multilineage mesenchymal stem cells have been more elusive.^{16,19}

Physiology of the Hematopoietic Microenvironment

Recent studies with fluorochrome-labeled hematopoietic stem cells injected into recipient mice have shown homing and localization of stem cells into the endosteal surfaces of long bones.^{11,32,35–46} The microdissection of these cellular interactions in stem cell homing have identified myeloepithelial cells and specific subset of osteoblasts as the putative preferred targets for stem cell homing.^{38,39,46,47} Treatment of the bone marrow with parathyroid hormone, an osteoblast differentiation stimulus of stromal cells, increases stem cell homing.^{21,22,43} The mechanism of the physiological interaction between osteoblasts and stem cells remains elusive because increased osteoblast differentiation of mesenchymal stem cells at sites of bone fracture or osteogenesis has not been associated with increased hematopoiesis.¹⁸

Other experimental evidence suggests that the bone marrow endothelial cell or reticular adventitial cell may serve as the hematopoietic stem cell niche.^{27,33,46} Conditions promoting adipocyte differentiation of the mesenchymal stem cell have also been identified as those supportive of hematopoiesis in continuous bone marrow culture²⁰ although lipid accumulation in adipocytes stimulated by 17 hydroxyl corticosteroids in the low lipid content of fetal bovine serum was not associated with lipogenesis but also facilitated support of hematopoiesis by marrow stromal cells.^{6,48}

The cell-to-cell interactions required for optimal stem cell homing and return to quiescence after marrow transplantation remain a subject of intense investigation. The stem cell niche has been known to be one of relative hypoxia,¹¹ and the interaction between cells is optimized by specific receptor-counter receptor interactions in a docking mechanism that may involve complex sugars, vascular adhesion molecules, or c-Kit receptor on hematopoietic stem cell surface binding to kit-ligand (stem cell factor).^{27,32,49}

The cell cycling status, or quiescent status of bone marrow stem cells, appears to be critical for survival in the microenvironment, particularly under conditions of oxidative stress, including those that are caused by ionizing irradiation.^{24,25} Totipotent hematopoietic stem cells naturally circulate in the fetus and are detected and recoverable at high levels in umbilical cord blood.³³ After birth, stem cells can be mobilized from the hematopoietic microenvironment and reenter the circulation after treatment with granulocyte-colony stimulating factor or other cytokines (indicating that the stable stem cell niche can be perturbed by disrupting intercellular attachments).^{34,37,41,44,45,47,49,50} Given the rapid induction of cytokines in the microenvironment after ionizing radiation, it is not clear how stem cells maintain the quiescent state while cells all around them are undergoing apoptotic, autophagic, and, in the case of lymphocytes, intramitotic death.^{10,50–52}

One possible explanation for irradiation-associated stabilization of stem cells in quiescence may relate to the bystander effect.³¹ The induction of radical oxygen species in irradiated cells is associated with transport of stress-activated protein kinases from nucleus to mitochondria, increased mitochondrial membrane permeabilization, and cytochrome *c* leakage into the cytoplasm causing apoptosis.⁵³ Other cellular signaling pathways induced by ionizing irradiation include induction of a G₁ and G₂ cell cycle arrest followed by secondary proliferative response.¹⁵ Recent evidence suggests that embryonic stem cells and

potentially differentiated tissue stem cells may maintain their primitive state by an altered cyclin-dependent kinase response to ionizing irradiation.^{1,2}

The irradiation bystander effect may be mediated in part through the differential response of stem cells compared with differentiated cells when exposed to the “bystander factor.” For example, localized whole-brain irradiation has been shown to induce apoptosis in the rat spleen, indicating that some cell populations are susceptible to cytotoxic effects of humoral factors released by irradiated tissues.^{31,53} However, an antiapoptotic/quiescence stabilization response of primitive hematopoietic stem cells to the same humoral factors may be occurring. Experiments attempting to identify the “bystander factor” have included isolation of cytokines, small peptides, small macromolecules, and oxidized lipid moieties.³¹ Until the specific biochemical components of the bystander factor are identified, experiments of purified stem cell populations to test the hypothesis that such factors induce quiescence cannot be performed.

Bone Marrow Stem Cell Mobilization in the Repair of Irradiated Epithelial Tissues

There is recent evidence that bone marrow–derived cell populations contribute to both restorative tissue repair and to late fibrosis of irradiated epithelial tissues.^{54–56} Genetically marked donor bone marrow cells have been shown to share the same phenotypic markers with those cells responsible for regeneration of the irradiated lung,^{27,57} esophagus,⁵⁵ and chemical toxin–injured liver.⁵⁴ Circulatory trafficking of bone marrow–derived stem cells have been shown to be involved in the damage repair of the brain, spinal cord, skin, and other organs.⁵⁶ At present, it is not known whether bone marrow–derived cells are responsible for the early repair phase in irradiated epithelial tissues and represent true multilineage hematopoietic stem cells or alternatively are differentiated progenitors. Figures 1 and 2 outline the potential explanations of the phenomenon of marrow involvement in epithelial organ stem cell repair. It is possible that true stem cells are induced to differentiate to multilineage epithelial cells by the irradiated microenvironment of the damaged epithelial tissue, or alternatively already differentiated and committed progenitor cells may participate in a transient injury stabilization phase after irradiation. In the latter case, the resident surviving stem cells in the basal cell layer of epithelial tissues may then proliferate to restore the tissue and push out the temporary bone marrow–derived progenitors that appear to be helpful for the initial damage response.²⁰ Further studies will be required to differentiate between these possibilities.

Genetic Determinants of Stem Cell Radiosensitivity

Because assays for bone marrow–derived stem cells require in vivo transplantation, the comparison of radiosensitivity of two stem cell populations from two genetically defined mouse strains has been achieved with the competitive re-population assay.^{24,25} Using experimental conditions with one mouse strain recipient and varying ratios of each of two other donor cell populations from two different stem cell donor mouse strains, it was possible to determine that irradiation damage to the hematopoietic microenvironment of the recipient differentially affects the two engrafting cell populations.^{24,25} However, these

studies do not directly show that one donor mouse stem cell subset is more or less radiosensitive than the other because the compounding variable of the damaged hematopoietic microenvironment cannot be controlled. The critical role of cellular suppressor genes in hematopoietic stem cell transplantation, homing, quiescence, and long-term repopulation capacity has been shown in studies with p21 and p18 homologous recombinant-deficient mice.⁴³ In these experiments, hematopoietic stem cells from mice deficient in p21 or p18 were shown to have an increased competitive repopulation capacity, improved homing and survival, and superior resistance to ionizing irradiation compared with stem cells from normal litter-mates.⁴³ Recent studies showed that the irradiation-induced oxidative stress in the hematopoietic microenvironment of the bone marrow can be ameliorated by delivery of the antioxidant transgene protein manganese superoxide dismutase (Mn-SOD).⁵⁹ The data of Cheng et al⁴³ show a clear role of stem cell genotype in bone marrow stem cell transplantation capacity. They also define the critical role of the ionizing irradiation-damaged hematopoietic microenvironment in stem cell transplantation. Protecting donor hematopoietic stem cell survival by Mn-SOD transgene overexpression in cells of the hematopoietic microenvironment was effective indirectly in improving transplantation.²⁰

Stem Cells in Radiation Carcinogenesis

A dramatic and well-known late effect of ionizing irradiation is carcinogenesis. Reports of osteosarcoma in radium watch dial painters studied at Argonne National Laboratories⁶⁰ and myeloid leukemia in British patients treated for ankylosing spondylitis using orthovoltage irradiation provided the first evidence for this late effect.⁶¹ Leukemia in the epilated survivors of the Hiroshima and Nagasaki atomic bombs was also detected at increased incidence, particularly chronic myelogenous leukemia.⁶² In the modern era, secondary epithelial carcinomas have been detected in increasing numbers of cancer survivors who received fractionated megavoltage irradiation.^{63,64} Secondary breast cancer in Hodgkin disease patients and secondary lung cancer in irradiated breast cancer patients are two other prominent examples.^{57,64} Irradiation-induced soft-tissue sarcomas in the high-dose irradiated tissue volumes of patients treated for lung cancer have also been reported. How these phenomenon relate to radiation effects in marrow stem cell biology is a subject of intense investigation.

Are irradiation-induced cancers the product of malignant transformation of a slowly proliferating subset of stem cells in the irradiated field at the time of irradiation or are these tumors in fact arising from marrow origin cells that migrate into the irradiated site? Clues may be detected in understanding the biology of a related late effect of irradiation, namely radiation fibrosis. Bromodeoxyuridine-labeling studies in high-dose lung-irradiated mice chimeric for GFP+, sex-mismatched bone marrow detected significant in situ proliferation of marrow origin cells at the time of late irradiation fibrosis.⁵⁵ Similar studies in a mouse carcinogenesis model have recently been reported.⁶⁹ Alternatively, the appearance of radiation-induced carcinomas may be attributable to long-lived effects of irradiation on the in situ microenvironment.¹⁰ Recent reports have indicated that increased free radical production is detected for months after radiation of the mouse lung,^{55,57} and altered

production of both inhibitory and stimulatory growth factors has been detected in the irradiated bone marrow microenvironment for as long as months/years after radiation.¹⁰

The proliferative capacity of clonogenic mesenchymal stem cells of the hematopoietic microenvironment is significantly decreased months after leukemogenic doses of total-body irradiation in the CBA/CA mouse.¹⁴ Treatment of the hematopoietic microenvironment with the antioxidant Mn-SOD-plasmid liposome complexes has been shown to improve the efficiency of engraftment of donor hematopoietic stem cells.⁵⁸ The irradiated hematopoietic microenvironment of DBA mice has been shown to induce malignant transformation of engrafted hematopoietic cells.¹⁷ Are irradiation induced cancers attributable to migration into the irradiated site of bone marrow-derived stem cell populations? There are reports of donor origin bone marrow karyotypic markers in clinical cases of relapsed leukemia in marrow transplant recipients.^{66–67} The initial reports have been followed by other confirmations of donor cell markers in allogeneic marrow transplant recipients.^{5,23,65,68–82} However, the studies fail to rule out the possibility of cell fusion accounting for donor markers in true recipient origin initial or posttreatment recurrent tumor cells.⁶⁵

Donor bone marrow origin of epithelial cancers appearing years after successful allogeneic bone marrow transplantation is a subject of intense investigation. Donor bone marrow origin of gastric cancer in *Helicobacter pylori*-infected mice has been shown,⁶⁵ indicating that there are specific conditions of chronic inflammation wherein bone marrow origin stem cells migrating to irradiated tissue can produce donor marrow origin epithelial cancers and that these results cannot be attributable to cell fusion. Whether donor bone marrow origin of epithelial cancers occurs in human allograft transplant survivors is not known.

Ionizing irradiation effects on the bone marrow are complex and long lived. An understanding of these radiobiological effects remains a challenge for current and future scientists seeking to develop safe therapies to treat the hematopoietic syndrome without causing survival of damaged and potentially tumorigenic cells.

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Figure 1.

Bone marrow stem cells in their niche (stromal cells) are protected by maintenance in the quiescent state, resisting the cytokine proliferative response and by feedback from other proliferating cells. (A) Niche in a stable state. (B) Niche after localized radiation to that area of bone marrow. (C) Niche in the situation of total-body irradiation or distant-site large field irradiation in which a cascade of cytokines stimulates the proliferative response of both stem cells and differentiated progenitors and is associated with depletion of cellular antioxidant stores in the niche.

Figure 2.

Irradiation-induced bone marrow stem cell migration to epithelial tissues via the circulation serves as a restorative countermeasure to stimulate organ recovery. (A) Esophagus stem cells and stromal cells in a basal state. (B) Esophagus irradiation depletes basal stem cells causing proliferative response. (C) The effect of bone marrow stem cell regenerative migration (red) into the esophagus restoring the epithelial stem cell niche. (D) The effect of differentiated/committed bone marrow-derived cells (not true stem cells) moving into the irradiated esophagus restoring committed esophageal progenitor cells (red). True esophageal stem cells remain in their niche and repopulate the esophagus at a later time pushing out the marrow origin cells.