Endometrial Regenerative Cells and Exosomes Thereof for Treatment of Radiation Exposure

4

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In 2007, we discovered a novel subset of mesenchymal stem cells (MSCs) derived from the endometrium, termed "endometrial regenerative cells (ERC)." In comparison to other MSC types (e.g., bone marrow and adipose), ERC possess (a) more rapid proliferative rate, (b) higher levels of growth factor production (VEGF, GM-CSF, PDGF), and (c) higher angiogenic activity. We are currently running two clinical trials for these cells in patients with critical limb ischemia and heart failure.

The main cause of morbidity and mortality in patients suffering from acute radiation syndrome (ARS) is hematopoietic toxicity. Although ARS treatment is not part of routine medicine, our commercial interest lies in the ability to rapidly obtain FDA approval using the "Animal Efficacy Rule," which allows for developers of therapies used in disaster settings circumvention of Phase II and III trials if human clinical safety is established and efficacy is demonstrated in a relevant animal model.

Recent studies have demonstrated that BM-MSC are capable of preventing lethality subsequent to radiation exposure; however, these cells have performed poorly in late-phase trials. Given that ERC are substantially more economical to manufacture in large numbers and produce more hematopoietically relevant factors as compared to other MSC sources, we discuss the possibility of utilizing ERC as a cellular therapy for treatment of radiation exposure.

Exosomes are nanoparticles generated by a variety of cell types, implicated in cell-to-cell communication. MSC-BM exosomes have been shown to be a major mediator of MSC paracrine therapeutic effects. Our data demonstrate that ERC-generated exosomes stimulate BM mononuclear cell proliferation. We propose that administration of ERC-derived exosomes will increase postirradiation survival and hematopoietic recovery.

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Need for Effective Means of Treating Radiation Injuries

Protection against accidental or terrorist radiation exposure is attracting an increasing attention from military and civilian groups [1]. The possibility of nuclear war remains a reality: currently, there are approximately 30,000 nuclear warheads deployed around the world, 100 "suitcase bombs" unaccounted for, and attempts of terrorists to acquire a nuclear weapon, a "dirty bomb," or to attack a nuclear power plant or waste site. A Nuclear Regulatory Commission study stated that breaching a cask of spent fuel could release lethal radiation over an area many times larger than that affected by a 10 kt nuclear weapon [2]. Acute radiation syndrome (ARS), which is the main cause of morbidity and mortality associated with ionizing radiation exposure, is characterized by the triad of dysfunctions in the (a) neurovascular, (b) hematopoietic, and (c) gastrointestinal systems [3]. Intermediate-dose ARS, which is similar to that received by firefighters at the Fukushima Daiichi Nuclear Power Plant (3–7 Gy total body irradiation), is generally treated with hematopoietic growth factor support, whereas high-dose ARS (7–10 Gy) is treated experimentally with hematopoietic stem cell transplant [4]. Of the three systems that ARS targets, by far the most work has been performed in hematopoietic recovery with specific guidelines in place for administration of growth factors such as G-CSF and GM-CSF postexposure [3]. However, in addition to high cost, these factors are immunogenic and induce sites effects including bone pain. To date, with exception of potassium iodine, there is only one drug that has been FDA approved for postradiation exposure, amifostine, which acts as a DNA protectant and antioxidant [5]. Unfortunately, its administration is associated with a variety of adverse

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effects including hypotension in >60 % of patients, and its radioprotectant effects are limited in cases of myeloablative radiation [6]. Thus, alternative approaches are needed to support hematopoietic recovery in patients that receive intermediate or high doses of irradiation.

Mesenchymal Stem Cells (MSCs) Support Hematopoiesis

MSCs are known to contribute to the bone marrow hematopoietic microenvironment. Given that this microenvironment is disrupted by radiation damage [7, 8], studies were conducted to demonstrate that human MSC can accelerate hematopoietic reconstitution and/or recovery in animal models [9, 10]. Therapeutic activities of MSC are believed to occur by differentiating into cells of mesenchymal origin [11] and also through an indirect "chaperone" effect. This includes production of trophic/angiogenic factors, as well as anti-inflammatory/antioxidant properties [12, 13]. One interesting aspect of MSC is that production of growth factors such as IGF-1, VEGF, and HGF-1 seems to be upregulated by conditions associated with injury such as hypoxia [14] and inflammatory conditions [15, 16]. Supporting the possible use of MSC in treatment of radiation injuries are findings that MSC specifically home to areas of radiation exposure [17]. In preclinical studies, it has been demonstrated that human MSC administration enhances engraftment of human CD34 cells postradiation [10]. Accordingly, clinical implications of using MSC administration to enhance hematopoiesis were examined.

The original clinical use of expanded autologous MSC in 1995 demonstrated feasibility and safety of intravenous administration of these cells in 15 patients suffering from various hematological malignancies to prevent cytopenia [18]. In a subsequent study from the same group in 2000, the use of MSC to accelerate hematopoietic reconstitution was performed in a group of 28 breast cancer patients who received high-dose chemotherapy [19]. Donor MSCs were demonstrated to neutrophil and thrombocytic reconstitution in a post bone marrow transplant setting in a 46-patient trial [20]. In a similar study, Ball et al. reported on the use of purified donor-specific MSC (1–5 million/kg) being injected alongside with isolated CD34 from HLA-mismatched relatives in 14 pediatric leukemia patients. They showed that in contrast to traditional graft failure rates of 15 % in 47 historical controls, all patients given MSCs showed sustained hematopoietic engraftment without any adverse reaction [21]. The use of "third-party" MSC to enhance hematopoietic recovery was performed by Baron et al. in 20 patients who received non-myeloablative hematopoietic stem cell transplant, whose outcomes were compared to a historic control of 16 patients receiving a similar transplant protocol without MSC. Accelerated hematopoietic reconstitution and significant difference in 1-year survival (80 % vs 44 %) was noted [22]. These findings established a foundation for MSC-based therapies to be investigated clinically as augmenters of hematopoietic reconstitution and/or prevention of GVHD, with Phase II/III trials ongoing or having been completed [23].

MSC and Radiation Injury

In addition to preclinical and clinical data supporting the use of MSC in acceleration of hematopoietic reconstitution, several animal studies have formally studied ARS protection by MSC. Yang et al. demonstrated that a onetime infusion of either virally immortalized or primary mouse BM-MSC (one million cells per mouse i.v.) 24 h subsequent to 700 cGy X-radiation exposure led to a 53 % survival in mice receiving immortalized and 60 % survival for the group receiving primary MSC at 7 weeks post irradiation. All mice that were treated with vehicle control died [24]. Lange et al. obtained similar results in that administration of one million cloned or primary BM-MSC into lethally irradiated (9.5 Gy from cesium-137 source) 8 h after radiation resulted in 7-week survival of 66 % of treated animals, whereas 100 % of control animals died within 3 weeks. Although administered cells were localized primarily in the lung, microarray detection of gene expression in the bone marrow was noted, particularly, upregulation of genes associated with cell cycle and protection from oxidative stress, such as Cdkn1a and BRPK, as well as anti-inflammatory and detoxification genes Thbs2 and Gstm5. Survival was associated with reconstitution of endogenous hematopoiesis [25]. Similar results were reported by another group, in which it was demonstrated that BM-MSC infusion after sublethal irradiation (5.5 Gy) was associated with enhanced survival of BALB/c mice, as well as stimulation of bone marrow cell entry into cell cycle and reduction of apoptosis [26].

Non-hematopoietic Benefits of MSC Transplantation Following Irradiation

Although bone marrow failure is the major cause of morbidity and mortality, in "real-life" situations, ARS will be accompanied by GI failure, neurological consequences, pulmonary fibrosis, and possibility of multiorgan failure. Protection of the GI tract and 100 % 3-week survival subsequent to 10.4 Gy whole-body radiation exposure were demonstrated in mice treated with BM cells cultured in an MSC-differentiation media, whereas 100 % mortality occurred in controls [27]. MSCs have been demonstrated to be neuroprotective in models of stroke [28], intracerebral hemorrhage [29], as well as having the ability to stimulate endogenous neurogenesis [30]. Although to date studies on MSC prevention of radiation-induced neural damage have

not been performed, given that radiation inhibits endogenous neurogenesis [31], this is an appealing possibility. MSCs have been demonstrated to inhibit pulmonary fibrosis through anti-inflammatory mechanisms in several models [32]. Furthermore, multiorgan failure, whether induced by radiation or sepsis, presents with similar qualities. Inhibition of sepsis associated multiorgan failure has been demonstrated by BM-MSC and appears to function through an IL-10 and PGE-2-dependent pathway [33].

ERC as a Clinically Relevant MSC Population

Endometrial regenerative cells (ERC) were discovered by us in 2007 as a menstrual-blood-derived MSC population that possesses a higher proliferative rate (19–22 h), increased growth/angiogenic factor production, and longer passage ability as compared to BM-MSC [34]. These properties, as well as enhanced antifibrotic activities, were confirmed by two independent groups a year after [35, 36]. Currently, we are conducting a Phase I study in critical limb ischemia (NCT01558908) in the USA and a Phase II double-blind placebo-controlled cardiac study Ex-USA. To date, intrathecal [37], intramuscular [38], and intravenous administration [39] of the cells in pilot compassionate-use cases has revealed clinical safety of cell administration. This is relevant not only because of potential benefit based on enhanced antifibrotic and growth factor production properties of ERC but also due to low cost of isolation and mass production ($500 per clinical dose of 100 million cells).

The unique features of ERC made us examine their activity in an immunocompetent model of critical limb ischemia [40]. Subsequent to our publication, other groups have used these cells for treatment of stroke [41], Parkinson's disease [42], and diabetes [43, 44]. We successfully took the ERC from discovery to GMP manufacture and FDA approval for clinical trials. Clinical production, delivery, and potency assays for ERC are covered in our patent application #61/566460. The use of ERC for treatment of vascular conditions is covered in our patent application # 20090291061, the use for treatment of diabetes was in-licensed to us from Hugh Taylor of Yale University #61/510,812, and the use in traumatic brain injury and Duchenne muscular dystrophy is covered by our patent applications, #61/618974 and #61/164,810, respectively.

Exosomes as Mediators of Paracrine MSC Activity

Exosomes are nanoparticles (40–100 nm) in size that possess highly defined homogeneous characteristics [45]. Exosomes are used by various cells for intercellular communication and have been identified in T cells [46, 47], B cells [48, 49], dendritic cells [50, 51], tumor cells [52, 53], neurons [54, 55], oligodendrocytes [56], and placental cells [57]. Recent studies have demonstrated that stem cell-derived exosomes are responsible, at least in part, for paracrine angiogenic and cardioprotective activity of cell therapy products such as MSC or CD34+ cells [58, 59], given that exosomes can be produced en masse in a bioreactor setting and that safety and distribution of exosomes are conceptually superior to administration of live cells.

Commercial Significance

Development of novel radioprotectants in the area of cell therapy has attracted significant defense interest. Osiris received a $4.2 million upfront grant for large animal studies along with a procurement order of $224.7 million (http://investor.osiris.com/releasedetail.cfm?releaseid=284617), while Cellarant last year received a $153 million award for development and stockpiling of their hematopoietic progenitor cells from the Biomedical Advanced Research and Development Authority (BARDA) for use in radiation sickness (http://www.cellerant.com/pr_090110.html). The "Animal Efficacy" Rule developed by the US Food and Drug Administration (FDA) in 2002 eliminates the requirement for Phase II and Phase III clinical trials for therapies against ARS, since it would be unethical to conduct efficacy studies in humans. In such cases, approval is based upon efficacy studies in representative animal species and only extended Phase I safety, human volunteers. We believe that based on the clinical safety data that will emerge from ongoing trials, we can apply for registration based on animal efficacy experiments, the protocol for which, including dose escalation study and route of administration, will be finalized in Phase II of this project.

Experimental Data

Previous studies demonstrated that the postradiation acceleration of hematopoietic recovery subsequent to BM-MSC administration is mediated by paracrine factors given that the majority of administered BM-MSC are sequestered in the lung [24]. Growth-promoting activities of various stem cells such as CD34 hematopoietic stem/progenitor cells and MSC have been reported to be mediated by exosomes in cardiac infarct recovery model and in hind limb ischemia models [58, 59].

We recently demonstrated that ERC are capable to produce high levels of exosomes. Furthermore, ERC-derived exosomes stimulate proliferation of bone marrow hematopoietic progenitors. Specifically, exosomes were prepared from the supernatant of day 4 ERC or BM-MSC (Cambrex) cultures by differential centrifugation. Conditioned media was subjected to three successive centrifugations at 300 g (5 min),

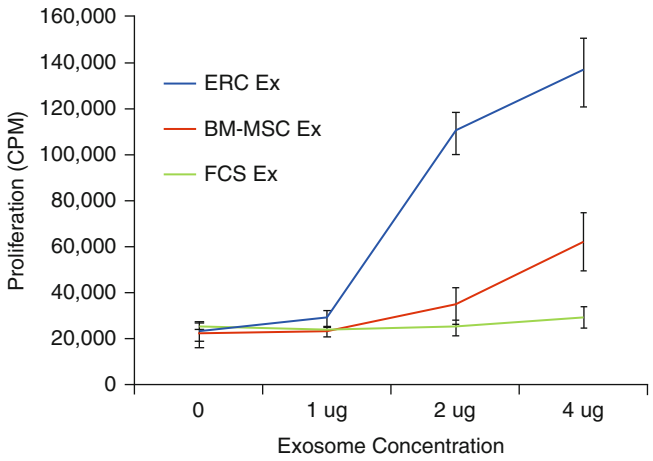

Fig. 4.1 Stimulation of bone marrow mononuclear by ERC and BM-MSC exosomes

1,200 g (20 min), and 10,000 g (30 min) to eliminate cells and debris, followed by centrifugation for 1 h at 100,000 g. To remove excess serum proteins, the exosome pellet was washed with a large volume of PBS, centrifuged at 100,000 g for 1 h, and resuspended in 120 µl of PBS for further studies. The exosomes were quantified by a micro-Bradford protein assay (Bio-Rad). Each batch was standardized by protein content. As a control, we used exosomes isolated from fetal calf serum (FCS Ex). To evaluate stimulatory properties of exosomes on hematopoietic stem/progenitor cell proliferation, mouse bone marrow cells were extracted from femurs and tibia of 6–8-week-old female C57BL/6 mice (Jackson Laboratories, Bar Harbour, Maine). Bone marrow mononuclear cells were plated at a concentration of 100,000 cells per well in a volume of 100 ml of complete DMEM media. On day 2, 1 uCi of [3H]thymidine was added to each well 16 h before harvest. Radioactive labeling of proliferating cells was measured on a microplate beta counter (Wallac). Data in Fig. 4.1 demonstrate that human ERC exosomes (ERC Ex) possess a higher stimulatory ability compared to BM-derived exosomes (MB-MSC Ex), which in turn was higher than fetal calf serum-derived exosomes (FCS Ex).

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