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RADIATION BIOLOGY AND STEM CELLS (P WILSON & C PORADA, SECTION EDITORS)

Use of MSCs and MSC-Educated Macrophages to Mitigate Hematopoietic Acute Radiation Syndrome

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Abstract

Purpose of Review Innovative and minimally toxic treatment approaches are sorely needed for the prevention and treatment of hematopoietic acute radiation syndrome (H-ARS). Cell therapies have been increasingly studied for their potential use as countermeasures for accidental and intentional ionizing radiation exposures which can lead to fatal ARS. Mesenchymal stem/stromal cells (MSCs) are used in cell therapy that have shown promising results in preclinical studies of ARS and are being developed in clinical trials specifically for H-ARS. MSCs, MSC-educated macrophages (MEMs), and MSC-exosome–educated macrophages (EEMs) all have the potential to be used as adoptive cell therapies for H-ARS. Here, we review how MSCs have been reported to mitigate inflammation from radiation injury while also stimulating hematopoiesis during ARS.

Recent Findings We discuss emerging work with immune cell subsets educated by MSCs, including MEMs and EEMs, in promoting hematopoiesis in xenogeneic models of ARS. We also discuss the first placental-derived MSC product to enter phase I trials, PLX-R18, and the challenges faced by bringing MSC and other cell therapies into the clinic for treating ARS.

Summary Although MSCs, MEMs, and EEMs are potential cell therapy candidates in promoting hematopoietic HRS, challenges persist in translational clinical development of these products to the clinic. Whether any of these cellular therapies will be sufficient as stand-alone therapies to mitigate H-ARS or if they will be a bridging therapy that insures survival until a curative allogeneic hematopoietic stem cell transplant can be performed are the key questions that will have to be answered.

Keywords Mesenchymal Stromal/Stem Cells · MSC-educated Macrophages · MSC-exosome–educated Macrophages · Hematopoietic Acute Radiation Syndrome · Cell Therapy · Radiation Medical Countermeasure

Introduction

Ionizing radiation (IR) injury of healthy visceral tissues or organs is an important public health issue that can arise from accidental nuclear or radiological emergencies and terrorist-related improvised nuclear devices, as well as during medical applications such as total body irradiation prior to bone marrow transplantation (BMT) or infusion of medical radioisotopes for cancer treatment. The impact of charged particle-induced radiation injury from solar energetic particle (SEP) and galactic cosmic ray (GCR) exposures is also gaining attention with increased efforts by the National Aeronautics and Space Administration (NASA) to send astronauts back to the Moon and onward to Mars.

IR injuries can be classified into acute and chronic radiation syndromes. The US Centers for Disease Control and Prevention (CDC) defines acute radiation syndrome (ARS) as acute illness caused by IR exposure when (1) the radiation dose is high [greater $\geq \sim 0.7$ Gray (Gy)]; (2) the dose is external to the body; (3) the involvement of penetrating ionizing radiations such as high energy X-rays, gamma rays, and neutrons; and (4) the involvement of the entire body receiving the dose. Chronic radiation syndrome is caused by lower radiation

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doses (< 1 Gy) administered over repeated exposures and is discussed extensively elsewhere [1–3]. IR-induced ARS is a significant problem due to its acute toxicity and mortality; thus, urgent treatment options are needed in acutely exposed individuals as early as possible after exposure.

The classical disease pathophysiology of ARS includes three major complications: hematopoietic, gastrointestinal (GI), and cardiovascular (CV)/central nervous system (CNS) ARS [4]. GI, CV, and CNS ARS result from high-dose IR exposures in a short time frame with the likely outcome of mortality without clinical intervention. However, hematopoietic ARS (H-ARS) is characterized by the loss of peripheral blood cells due to damage to bone marrow (BM)–derived hematopoietic stem cells, leading to suppression of BM function [5]. The secondary neutropenia that results, puts the patient at high risk for life-threatening infections. Although allogeneic BMT can be curative for IR-induced BM failure, identifying a suitable matched unrelated donor takes weeks to months. Thus, first-line therapies involve supportive care measures like administration of hematopoietic growth factors to stimulate BM production of leukocytes and help protect patients against infection and transfusion of red blood cells and platelets for treating anemia and preventing bleeding until an allogeneic BMT can be performed (or the patient's own BM recovers).

Current Food and Drug Administration (FDA)-approved growth factors such as Neupogen® and Neulasta®, both formulations of filgrastim (recombinant G-CSF), can improve neutrophil recovery but are not curative for H-ARS. Thus, medical countermeasures are sorely needed that can either protect, or even reverse, BM damage associated with H-ARS. Cellular therapies are being increasingly explored due to their favorable toxicity profiles and potential ability to not only modulate the host BM niche but also repair/rejuvenate cells and tissues injured by IR [6•, 7–9]. Developing cellular therapies as a radiation medical countermeasure (MCM) first requires a detailed understanding of the pathophysiology of H-ARS.

Detrimental Changes in the Bone Marrow After Ionizing Radiation Injury

IR causes cellular damage through both direct and indirect mechanisms. Direct IR effects are mediated by ionizations and excitations induced along particle tracks and if this occurs within cells (and more importantly within cell nuclei) it can induce chemical changes of both DNA and/or proteins requiring subsequent repair or removal. Indirect effects are mediated by charged particle-induced water radiolysis and involve the production and local diffusion of multiple free radical species which can similarly alter the chemistries of nearby DNA and proteins [10]. Collectively, both direct and indirect IR effects can generate DNA damage that if "mis-repaired" or left unrepaired can generate lethal chromosomal aberrations and subsequent mitotic cell death or the activation of programmed cell death pathways (e.g., apoptosis), depending upon cell lineage. It is also well known that immature stem and progenitor cells undergoing rapid cell division are more radiosensitive than mature non-dividing cells [11]. Since the BM is always in a state of active hematopoiesis throughout our lifetime, hematopoietic cells are significantly sensitive targets to IR with exposures causing hypocellularity and increase in BM fat content [12–14].

Hematopoietic stem cells (HSCs) respond to IR through well-defined DNA damage response (DDR) mechanisms [15]. If the level of IR-induced DNA damage is sufficient, HSCs undergo apoptosis that is mediated primarily by TP53 and its various downstream effector proteins including Puma. Indeed, it has been shown that HSCs from Puma knockout mice display reduced sensitivity to IR-induced apoptosis [16, 17]. IR can also affect HSC differentiation by causing telomere dysfunction and skewing toward lymphoid lineages through the G-CSF/Stat3/BATF pathway [18]. IR also induces senescence of HSCs through other mechanisms including reactive oxygen/nitrogen species (ROS/RNS) [19, 20]. Altogether, IR affects the stemness of HSCs by forcing them to undergo apoptosis, senescence, and biased differentiation.

Mesenchymal stromal cells (MSCs) are non-hematopoietic stromal/stem cells which are present in the BM niche that support hematopoiesis and bone regeneration [21, 22]. Several studies have shown that MSCs are less sensitive to radiation than HSCs in the setting of BMT. MSCs derived from BMT recipients are not donor in origin, and thus are always recipient-derived in patients who undergo myeloablative irradiation and chemotherapy for transplant conditioning [23–25]. Thus, MSCs survive post-irradiation in BMT recipients, resulting from their greater radioresistance. It has also been demonstrated that although IR affects the proliferation and differentiation capacities of BM MSCs, such effects are transient and MSCs regain their activity after a recovery period [26–29].

MSCs' reduced sensitivity to IR has been explained by multiple mechanisms. MSCs possess high anti-oxidant capacity, low levels of proapoptotic proteins, and strongly induce DDR pathways which collectively make them survive from radiation injury [30]. IR-induced oxidative stress often leads to DNA damage–associated cell death, and MSCs exhibit increased oxidative stress resistance compared to other cell phenotypes which further explains MSCs' resistance to IR injury [29]. Therefore, the natural radio-resistant ability of BM MSCs may be utilized to mitigate BM failure and enhance hematopoiesis and an ideal IR MCM strategy. Moreover, the use of macrophages after co-cultivation with MSCs to produce MSC-educated macrophages (MEMs) or the direct use of MSC-

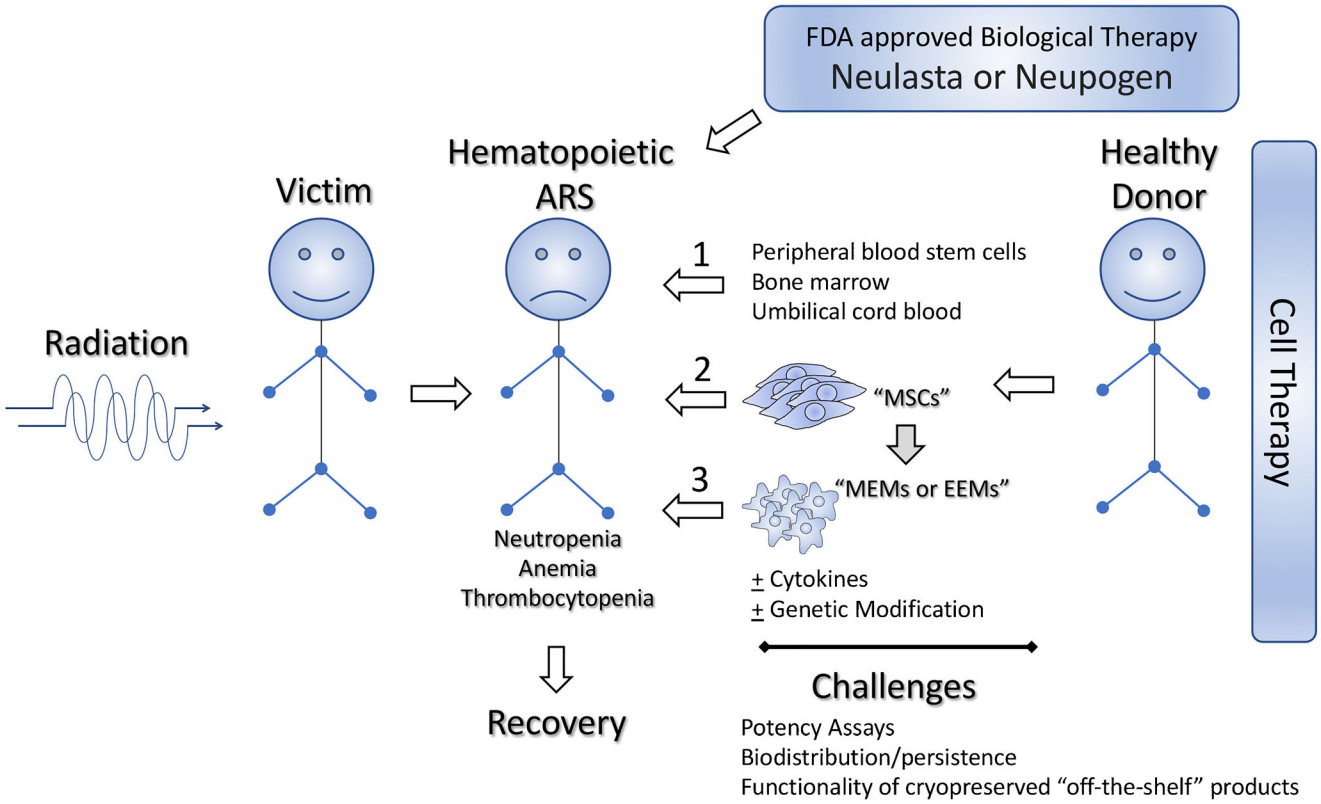

Fig. 1 Paradigm of potential of cell therapy candidates to mitigate acute hematopoietic radiation syndrome. Potential cell therapy candidates: mesenchymal stem/stromal cells (MSCs), MSC-educated macrophages (MEMs), exosome-educated macrophages (EEMs) that mitigate H-ARS are shown along with the challenges in bringing forward their clinical cell therapy application

derived products such as secreted extracellular vesicles and exosomes are considered promising cell therapy candidates for H-ARS (Fig. 1).

Mechanisms Underlying MSC-Mediated Mitigation of H-ARS

MSCs are the leading cell therapy candidate for mitigation of many degenerative and inflammatory disorders, but to date, no MSC products are FDA-approved in the USA for any indication. However, MSCs are approved for clinical use by regulatory authorities in Europe, Canada, Australia, Japan, and South Korea to treat disorders such as complex perianal fistula from non-active/mildly active luminal Crohn's disease and steroid-refractory graft-versus-host disease [31, 32]. Therapeutic MSCs can be isolated from BM, adipose tissue, umbilical cord, cord blood, placenta, and dental tissue [33]. The International Society for Cell Therapy has provided guidance to define MSCs that are in vitro culture expanded [34–36]. MSCs must be adherent; express the surface markers for CD105, CD73, and CD90; and lack expression of CD45, CD34, CD14 or CD11b, CD79-alpha or CD19, and HLA-DR and should be able to differentiate to osteoblasts, adipocytes, and chondroblasts in vitro [37]. Accumulating evidence from preclinical studies demonstrate that infusion of MSCs can protect animals from lethal IR injury [38–48]. Several studies have demonstrated that infusion of MSCs protect animals from radiation toxicity by ameliorating damage to the GI tract, CNS, and lungs [38–48]. However, the potential of MSCs to mitigate H-ARS is emerging as another promising indication.

BM-derived MSCs endogenously express many genes that support hematopoiesis. In addition, expression of hematopoietic genes remains intact and is not downregulated even in the presence of inflammatory cytokines such as IFNγ [49]. Cord blood HSCs co-cultured with BM MSCs in vitro prior to transplantation into patients show faster kinetics of immune reconstitution of neutrophil and platelets compared to cord blood HSCs alone. This accelerated engraftment is believed to be due to MSC-mediated skewing of cord blood HSCs toward progenitor populations committed to megakaryocyte and myeloid lineages [50]. Since IR skews HSC differentiation into a lymphoid commitment [18], this characteristic to use MSCs to promote myeloid lineages should be a beneficial attribute as an MCM for H-ARS. In vitro analysis has

demonstrated that MSCs can support the expansion of irradiated CD34+ HSCs in the presence of SCF, FLT3 ligand, TPO, and IL3 [51]. Another study demonstrated that MSCs can rescue CD34+ HSCs from radiation-induced apoptosis and support hematopoietic reconstitution after co-culture [52••]. Altogether, these experimental data suggest that MSCs can support hematopoiesis in patients with H-ARS.

Preclinical in vivo studies also suggest that MSCs can enhance hematopoiesis post-irradiation. While in vivo studies often establish "proof of concept" evidence, not many of the published studies provide mechanistic underpinnings of MSC-mediated mitigation of H-ARS. Infusion of umbilical cord MSCs modulates the expression of FLT3L, a growth factor that stimulates the proliferation and differentiation of hematopoietic multipotent progenitors in the BM of irradiated animals and confers radioprotection [53]. Administration of MSC-like stromal cells from placenta confers protection of lethally irradiated animals by increasing the number of CD45+/SCA1+ hematopoietic progenitor cells in the BM and the plasma levels of hematopoietic cytokines such as G-CSF, GRO, MCP-1, IL-6, and lL-8 [53, 54]. In addition to hematopoiesis, BM-derived MSC infusion provokes a radioprotective mechanism by dampening inflammatory events, enhancing detoxification and cell cycling, and reducing oxidative stress, which collectively promote hematopoiesis in animals subjected to lethal irradiation [55]. Genetic engineering of MSCs is a promising strategy to enhance their potency and functionality, as gene-modified MSCs (e.g., superoxide dismutase-expressing umbilical cord MSCs) were shown to be superior to naïve MSCs in enhancing hematopoietic recovery and conferring protection of sublethally irradiated animals [56]. Another approach is the utilization of MSCs in conjunction with HSC to promote hematopoietic recovery and stem cell engraftment. Co-transplantation of MSCs and HSCs enhances the engraftment of CD34+ HSCs in a non-human primate model of HSC transplantation [57]. Similarly, co-transplantation of human MSC progenitors and CD34+ HSCs into pre-immune fetal sheep results in early appearance of human donor cells in circulation and boosts cell levels in BM at later time points after transplantation [58]. Based on these promising experimental results, some clinical trials have also evaluated the use of MSCs in promoting hematopoietic engraftment. While these trials showed that this approach is safe, they were not large enough to statistically demonstrate MSC's efficacy in promoting hematopoietic engraftment [59]. However, a large phase III clinical trial, testing MSCs following hematopoietic cell transplantation in steroid-resistant acute graft-versus-host disease model did show anti-Graft-versus-Host Disease (GvHD) efficacy [60••]. Since MSCs can promote hematopoiesis and mitigate inflammation and injury in GVHD, it stands to reason that their use in combination with HSC transplantation could be a useful approach to rescue H-ARS.

Using MSC or MSC-Derived Exosomes to Educate Macrophages for Treatment of Hematopoietic ARS

One of the major limitations that may prevent random donor allogeneic MSCs from becoming a durable countermeasure for H-ARS is that MSCs persists short term after intravenous infusion in vivo. It is now becoming increasingly appreciated that biologic effects seen after MSC infusion may represent in vivo education of cell subsets like macrophages that have the capacity to replicate and persist in the BM for extended periods of time [61]. One strategy that has been developed to recapitulate this observed phenomenon is by using MSC co-cultures to educate human macrophages ex vivo. Infusion of these so-called MSC-educated macrophages (MEMs) into immunodeficient mice with lethal ARS [62••] was shown to protect against radiation-induced lethality compared to infusion of MSCs themselves (Fig. 1). MEMs showed a phenotype of alternatively activated macrophages which is distinct from that of classical macrophages isolated from peripheral blood and BM. These anti-inflammatory MEMs are characterized by high expression of IL-10, transforming growth factor-β1 (TGF-β1), and programmed death ligands (PDL) 1 and 2 [62••]. TGF-β1 plays a significant role in wound-healing by promoting re-epithelialization, fibroblast proliferation, and angiogenesis, while IL-6 plays an immune-orchestrating role, and IL-10, PDL1, and PDL2 provide substantial immune suppression. All of these pathways work together on MEMs to enable their ability to be radioprotective [62••].

One methodology to shorten the biomanufacturing time and utilize an "off the shelf" approach to generate MEMs is to use exosomes from lipopolysaccharide (LPS)-stimulated MSCs to induce macrophages to become educated macrophages (EEMs) that are radioprotective in vivo [63•]. LPS-EEMs show improved survival and clinical scores for ARS compared to PBS controls, MSCs, uneducated macrophages, and EEMs [63•]. Moreover, mice treated with LPS-EEMs show improved hematopoiesis in multiple BM sites as well as the spleen histologically, leading to improved complete blood cell counts in peripheral blood weeks after irradiation. LPS-EEMs exhibit increased gene expression of *STAT3*, and protein expression of IL-10, IL-15, and FLT3L, which collectively can prevent inflammation, stimulate various immune cell subsets, and promote hematopoietic growth. They showed increased phagocytosis important for the elimination of neutrophils during the healing process and tissue remodeling. In summary, the potential of using MSCs, or derivatives of MSCs like extracellular vesicles, as a means of generating radioprotective cell subsets like macrophages ex vivo, remains an emerging area of research for treating lethal H-ARS.

Current MSC Therapies in Clinical Development

PLX-R18 (Pluristem Therapeutics, Inc) is a placenta-derived, MSC product grown in a current good manufacturing practice (cGMP) 3-dimensional bioreactor that has been granted orphan drug designation by the FDA for the treatment of H-ARS. Preclinical xenogeneic studies in mice showed improved survival when the first dose of PLX-R18 was administered intramuscularly within 48 h of (7.7 Gy) IR exposure, with lower but still significant improvement 72 h post-exposure, followed by a second dose 5 days later [54]. The mechanism of action is thought to be from secretion of cytokines and growth factors that stimulate hematopoiesis, combined with inhibition of T cell responses as well as inhibition of monocyte differentiation into mature dendritic cells [64]. An open-label phase I study will evaluate the safety of cryopreserved PLX-R18 thawed for the post-exposure prevention or treatment of H-ARS (NCT03797040), and the safety data combined with the prior preclinical data should inform a biologics license application for FDA approval using the Animal Rule [65]. Each subject will receive 2 administrations of PLX-R18 at 4 million cells/kg, 4 days apart, up to a maximum of 400 million cells through intramuscular route of administration. The first administration will preferably be given within 48 h of suspected exposure. The inclusion criteria include subjects exposed, or suspected to have been exposed, to ionizing radiation of ≥ 1 Gy and is at risk of developing H-ARS, as assessed by the treating physician, based on Radiation Emergency Medical Management guidelines.

Challenges of Developing Cell Therapies for Hematopoietic ARS

Despite cell therapies like MSCs being a promising platform for the treatment of H-ARS, there are challenges to achieve sustainable and consistent efficacy. Some of the key factors that confound their widespread application include the source of cells, challenges associated with accurate potency analysis of cell therapy products, delivery issues, biomarker identification of responder and non-responder populations of therapy, and reliability of preclinical animal model studies for accurately predicting human response [66, 67••, 68].

Although autologous personalized cell therapy is ideal for IR injury, from a feasibility point-of-view, pre-expanded/activated, allogeneic cell therapy products are highly preferred. Practically, it is feasible to isolate, expand, and cryopreserve cell therapy products in a bank, and then whenever needed, aliquots/doses can be thawed and infused into the patients, and thus bypass lengthy cell manufacturing time required in the setting of autologous cell therapy. This is particularly important in treating H-ARS, since the timing of the therapy is crucial to rescue patients from BM failure as early as possible post-exposure. Although an "off-the-shelf" cell therapy approach is feasible and perhaps more clinically relevant, the ultimate clinical efficacy of such an approach is yet to be confirmed.

There are two factors that need to be addressed for off-the-shelf cell therapy approaches. The first of these is the tissue source from which the MSCs are derived, e.g., BM, adipose tissue, umbilical cord, placenta, etc. [33], since the biology of MSCs, and cells educated by MSCs, could vary based on the source of the cells and choice of the donors from whom these cells are derived. Importantly, in the situation where multiple dosing regimens are needed for efficacy, it is necessary to define if the cells can be derived from a single donor, or if multiple donors will be required for longitudinal administration. Second, the effect of cryopreservation-thawing on the allogeneic cell therapy product needs to be examined to determine whether these processes may impact upon therapeutic efficacy after infusion. Large-scale cryobanking of cellular products, and their infusion into the patients immediately post-thaw, is an attractive option from a clinical perspective. However, an important yet controversial question is whether pre-freeze functionality of cell products like MSCs are equivalent to their freeze/thawed counterparts. Mixed data is emerging on the efficacy of immediately thawed MSCs [69–82]. Although freeze-thawing optimization and cell manufacturing technologies may overcome this issue, an important salvage consideration needs to be the culture recovery of cryopreserved cells prior to infusion. Culture recovery is a process where cryopreserved cells can be thawed and cultured in the incubator for a period of 24–48 h to regain their fitness prior to infusion to preserve viability and hopefully their biologic functionality [76••, 82, 83].

Several BMT studies have demonstrated that biodistribution of intravenously infused MSCs is unique as they do not home to BM, unlike HSCs [23, 84–86]. It is also demonstrated that MSCs show highly efficient homing to the BM but lose homing ability following culture [87]. In contrast, allogeneic BMT in patients with osteogenesis imperfecta had shown that MSCs were detected in the BM, which suggests that physiology of marrow niche and disease status may play an important role in the homing of MSCs [88]. Importantly, infused MSCs were not detected in the bone marrow of non-human primates that were subjected to lethal IR [89]. Hence, the enhancement of hematopoiesis as seen in the animal model studies could be due to the peripheral modulation of hematopoietic cytokines and growth factors, and thus understanding which of these molecules are stimulated post-infusion is important toward development of potency assays during cGMP production and/or biomarker measurements post-infusion. Dosing and biodistribution of products are also important parameters to consider whenever cellular therapies are infused intravenously. For example, a large number of

MSCs can be trapped in the lungs post-intravenous infusion, and current clinical trials use up to 10^7 cells/kg body weight in the settings of intravenous infusion [90, 91]. Although preclinical animal model studies have demonstrated the efficacy of infusing cells intravenously, intramuscularly, and intraperitoneally [53, 54], and clinical trial with PLX-R18 (NCT03797040) deliver cells intramuscularly innovative approaches are still needed to overcome challenges involved with optimizing dosing by maximizing persistence of cell therapies like MSCs post-infusion.

The US FDA and European Medicines Agency (EMA) classify in vitro culture-expanded cells as more than minimally manipulated cellular and gene therapy products, which apply to MSCs and macrophages [92, 93]. Potency assays are necessary to inform advanced clinical trials and also marketing approval to use these cell therapy products. However, development of potency assays for MSCs, MEMs, and EEMs is challenging due to their largely undefined mechanisms of action in humans that predict the recovery of hematopoiesis post-IR injury. Although animal studies provide insight about the potential toxicities and mechanism of action in mitigating H-ARS, discrepancies between animal vs human-derived MSC populations and their biological properties suggest that animal model studies cannot be entirely translated into human clinical studies [66]. MSCs derived from monkey and pig share similarities with human whereas mouse, rat, rabbit, and hamster MSCs are not equivalent to human [94]. Hence, caution must be exercised in translating animal studies into clinical potency assay development of MSCs. An ideal approach would be the identification of biomarkers in responders versus non-responders, which could then be used as a measure of potency of the products before infusion. In addition, developing a potency assay that only measures a single cytokine or growth factor from MSCs may not recapitulate the entire mechanism of action and potency of MSCs, especially since the cells are both anti-inflammatory and promote wound healing. Hence, a combination approach analyzing components of the secretome, selective transcriptome, and phosphorylation status of critical molecules could collectively be used to predict hematopoietic-repairing potential as a surrogate measure of potency [95, 96]. Nonetheless, animal studies remain crucial for informing potential toxicities and for fulfilling the Animal Rule, which is a critical pathway for cell therapies to achieve FDA approval for H-ARS.

Conclusion

MSCs have been successfully developed as a cellular therapy for treating inflammatory disorders and promoting wound healing. In the case of H-ARS, MSCs are also emerging as off-the-shelf cell products with enormous potential, and early clinical testing is underway. Major questions still remain on whether MSCs, or cells educated by MSCs/MSC-exosomes like MEMs and EEMs, can be used as a primary therapy for the prevention or treatment of H-ARS, or whether cellular therapies will have to be combined with currently used approaches like allogeneic hematopoietic stem cell transplantation or FDA-approved growth factors like filgrastim/G-CSF. Increasing support from federal grants as well as continued guidance from regulatory agencies like the FDA and EMA will ensure cellular therapies continue to be developed for this challenging condition.

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Compliance with Ethical Standards

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