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ADULT MESENCHYMAL STEM CELLS AND RADIATION INJURY

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Abstract

Recent understanding in the cellular and molecular signaling activations on adult mesenchymal stem cells have provided new insights into their potential clinical applications, particularly for tissue repair and regeneration. This review focuses on these advances, specifically in the context of self-renewal for tissue repair and recovery after radiation injury. Thus far, MSCs have been extensively characterized and shown mitigation and therapy on acute radiation syndrome and cognitive dysfunction. Use of MSCs for treating radiation injury alone or in combination with additional trauma is foreseeable.

Keywords

stem cell; survival; repair; radiation; wound; bacteria; therapy

INTRODUCTION

Mesenchymal stromal cells (MSCs), also referred to as mesenchymal stem cells, have been attracting attention for different applications, including tissue engineering and regeneration on cell-based therapies (Kolf et al. 2007). They have been isolated from bone marrow and fat tissues. MSCs are characterized by fibroblast-like morphology, high proliferation rate, attachment to cell culture dishes and form colonies, and the capacity to differentiate into different mesenchymal lineages. They have been applied clinically to control autoimmune and graft-versus-host diseases (Chamberlain et al. 2007; Le Blanc et al. 2008; Tian et al. 2008; Djouad et al. 2009). In pre-clinical studies, MSC have been shown to provide protection against radiation-induced liver injury (Francois et al. 2013), promote healing in irradiated murine skin wounds (Hao et al. 2009; Kiang and Gorbunov, 2014), improve survival in irradiated mice (Hu et al. 2010), mitigate the gastrointestinal syndrome in mice (Saha et al. 2011), and restore the intestinal mucosal barrier in irradiated mice (Garg et al. 2014). Abdel-Mageed et al. (2009) reported that superoxide dismutase (SOD) gene-transfected MSCs improved survival in irradiated mice. However, other reports showed that MSCs alone did not improve survival in irradiated mice (Abdel-Mageed et al. 2009; Kiang and Gorbunov, 2014).

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MSC CHARACTERIZATION

MSC Negative Markers

Friedenstein and colleagues identified MSCs as colony-forming unit-fibroblasts (CFU-Fs) in 1970, and Pittenger and colleagues described in detail the tri-lineage potential of MSCs in 1999. Our understanding of these cells has greatly moved forward since then. MSCs are multi-potent, adherent, and can be isolated from many adult tissue types. To ensure the isolated cells are MSCs, there is a consensus (Kolf et al. 2007) that MSCs do not express glycophorin-A (an erythroid linerage marker), cluster of differentiation (CD) 11b (an immune cell marker), CD31 (an endothelial and hematopoietic cell maker), CD34 (a primitive hematopoietic stem cell marker), CD45 (a marker of all hematopoietic cells), and CD117 (a hematopoietic stem/progenitor cell marker).

CD11b, CD34, CD45, and CD117 are certain MSC negative markers in both human MSCs and murine MSCs, while CD34 surface marker is certainly negative in human MSCs. In contrast, CD34 has also been found to be positive in murine MSCs (Kolf et al., 2007). Because of this uncertainty of markers in murine MSCs, multiple negative and positive surface markers are used for MSCs verification.

MSC Positive Markers

To ensure that isolated cells are MSCs, MSC positive markers are available. There are Stro-1, CD13, CD29, CD44, CD73, CD105, and CD106/vascular cell adhesion molecule-1 (VCAM-1) in human MSCs and murine MSCs. However, stem cells antigen-1 (Sca-1), CD10, CD90/thymocyte antigen 1 (Thy-1), and CD309/ fetal liver kinase 1 (Flk-1) are variable in both human MSCs and murine MSCs (Kolf et al., 2007). Therefore, it is important to characterize MSCs with more than one positive markers and negative markers. Stro-1 is the best-known MSC marker by far, because Stro-1 negative cells do not form colonies (Simmons et al. 1991). However, its expression in MSCs is gradually lost during culture expansion (Gronthos et al. 2003), with yet unidentified mechanism(s). It is unclear whether the loss of stro-1 marker will result in the loss of colony capability. Nevertheless, MSCs are always identified with Stro-1 in conjunction with other MSC positive and negative marker proteins.

Abdel-Mageed et al. (2009) identified MSCs with positive expression of CD13, CD29, CD44, CD105 and Sca-1 and negative expression of Thy-1.2, CD117/c-kit, CD11b, CD19, CD31, CD34, CD45, CD73, and CD135, while Francois et al. (2013) identified MSCs with positive expression of CD105 and CD73 and negative expression of CD45. Saha et al. (2011) identified MSCs with positive expression of CD29 and CD105 and negative expression of CD11b and CD133. Felka et al. (2014) identified MSCs with positive marker proteins CD73, CD90, CD105, and CD146, and negative marker proteins CD11b, CD14, CD34, and CD45.

The markers reported in the above publications to characterize MSCs are varied. But most of them showed at least 2 positive markers along with 2 negative markers to ensure MSCs. It should be even more credible by including CFU-Fs. In our laboratory, MSCs are identified with positive expression of Strol-1, Sca-1, CD44, and CD105 and negative expression of

CD3 and CD34. MSCs are indeed further confirmed with colony formation (Kiang and Gorbunov, 2014). The combination we used to verify isolated MSCs and their expansion warrants correct identity of these cells.

MSC Self-Renewal and Maintenance

MSCs maintain their capability of self-renewal without differentiation. They express the embryonic stem cell gene markers octamer-binding transcription factor-4 (oct-4), sex determining region Y-box-2 (sox-2), and reduced expression protein-1 (rex-1, Izadpanah et al. 2006) that are involved in maintaining the repression of differentiation genes (Boyer et al. 2006). Additionally, the presence of leukemia inhibitory factor (LIF, Jiang et al. 2002; Metcalf 2003), fibroblast growth factor (FGF, Tsutsurri et al. 2001; Zaragosi et al. 2006), and mammalian homologues of drosophila wingless (Wnts, Kleber and Sommer, 2004; Boland et al. 2004) is detected. Hepatocyte growth factor (HGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and/or cytokines support MSC stemness in an MSC niche (Kolf et al. 2007). Beta-catenin, an extracellular matrix protein for anchoring cells in place is thought to be involved in Wnt regulation of MSC self-renewal (Bienz 2002). It takes 32–35 h (De Luca et al. 2013; Kiang and Gorbunov, 2014) to double MSC numbers.

The molecular mechanisms underlying MSC differentiation remain unclear. As for tissue repair and regeneration, MSC differentiation needs to be induced clinically by administration of transforming growth factor-beta (TGF-beta), bone morphogenetic protein (BMF), growth and differentiation factor (GDF, Chen et al., 2004), and Wnt ligands (Hartmann, 2006) for chondrogenesis, tenogenesis, and osteogenesis, peroxisome proliferator-activated receptor gamma (PPARgamma) for adipogenesis (Nuttal and Gimble 2004), and Notch 1 for myogenesis (Dezawa et al. 2005), respectively. The differentiation signal must find its way to the MSC niche for initiation of differentiation (Kolf et al. 2007).

MSCs AND THERAPY

MSCs and Radiation-induced damage in intestinal mucosal barrier

Radiation is known to induce intestinal damage. Garg and colleagues (2014) reported that male CD2F1 mice were subjected to a dose of 8 Gy total body irradiation (Cs-137 irradiator, 1.35 Gy min^{-1}). Within 4–6 h after irradiation these mice received an intravenous injection of 2×10^7 bone marrow cells (BMCs) supplemented with 1×10^7 spleen cells. The transplantation accelerated peripheral blood counts, enhanced the recovery of intestinal immune cell populations in jejunum mucosa, reduced intestinal permeability, reduced interleukin-1 α (IL-1α) increases, restored IL-6, IL-10, and IL-12 concentrations, and modulated the expression of Claudin-2 and -4 (tight junction proteins). Since whole bone marrow preparation was injected, whether MSCs were responsible for mitigation of intestinal mucosal barrier damage remains unclear and needs to be further studied. Whole bone marrow transplantation also showed the significant survival improvement in female B6D2F1 mice after irradiation (Ledney and Elliott, 2010).

Saha and colleagues (2011) reported that male C57BL/6 mice were irradiated at 10 Gy (total body irradiation) or 16–20 Gy (abdominal irradiation) with a 320 KvP, Phillips MGC-40

orthovoltage irradiator (0.72 Gy min^{-1}). These mice were then intravenously injected with 2×10^6 MSCs per mouse at 24 and 72 h after irradiation. All MSC administered mice survived from 10 Gy or 16–20 Gy for more than 25 days whereas irradiated mice administered with either the enriched myeloid fraction or the non-myeloid factions failed to improve survival. MSCs induced crypt interstitial stem cell (ISC) regeneration, restitution of the ISC niche, and xylose absorption. R-Spondin1, keratinocyte growth factor (KGF), PDGF, FGF2, and anti-inflammatory cytokines such as granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) were elevated in serum, while inflammatory cytokines (IL-6, IL-10, IL-12, and IL-17) declined.

MSCs and radiation-induced liver injury

Radiation induces liver injury that can be detected by elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Francois and colleagues (2013) reported that NOD/SCID mice were irradiated with Cs-137 at 3.2 Gy (1.85 Gy min^{-1}) and then intravenously administered with 5×10^6 human MSCs in 0.1 mL 1× phosphate buffered saline. They indicated that MSC administration alone did not produce liver toxicity. MSC transplantation restored plasma urea, reduced plasma AST and ALT, and decreased the oxidative stress indicated by malondialdehyde (MDA) formation.

It has been reported that stromal cell-derived factor 1 (SDF1) secreted by cells within injured tissues and its receptor C-X-C chemokine receptor type 4 (CXCR4) were necessary for the MSC migrating to damaged tissues. Livers of MSC administered mice displayed high levels of SDF1 and CXCR4 with reduction of mir-27b after irradiation. The latter is known to down-regulate SDF1. It took 15 days for MSCs to differentiate into the hepatocyte phenotype as indicated by measuring liver specific genes such as cytokeratin 18 (CK18), CK19, and alpha-fetoprotein (AFP, Francois et al. 2013). Mir-27a has been shown to regulate genes for nuclear factor-keppa B (NF-keppaB) expression and hypoxia inducible factor-1alpha (HIF-1alpha) expression (Kiang et al., 2015).

MSCs and radiation-induced delay in wound healing

It is evident that radiation delays skin wound healing (Hao et al. 2009, Kiang et al. 2012). Hao et al. (2009) report that male Sprague-Dawley rats were exposed to 6 Gy of ^{60}Co gamma-ray (0.31 Gy min^{-1}) followed by a full-thickness excisional skin-wound (2% total body surface area). Then 1×10^7 recombinant adenovirus Adv-hPDGF-A/hBD2-GFP-infected MSCs (T-MSCs) or non-transfected MSCs (N-MSCs) were injected into the wound bed and margin of the excisional wound. These authors indicated that wounds in non-irradiated rats and irradiated rats took 17–18 days and 27–28 days, respectively, to heal. T-MSC administration and N-MSC administration was associated with a shorter healing time of 21 days and 24–25 days, respectively. MSCs promoted the deposition and remodeling of collagen in wounds. Significantly less bacterial colony formation was found in the cultured under-scar samples from the T-MSC administered wound bed. In our laboratory, when female B6D2F1 mice were exposed to 9.25 Gy of ^{60}Co gamma-ray (0.4 Gy min^{-1}) followed by a full-thickness excisional skin-wound (15 % total body surface area), MSCs (3×10^6) were intravenously injected 24 h after irradiation. Their wounds were fully closed by day 21 after irradiation, whereas wounds in vehicle-treated irradiated mice were not fully healed yet

at this time. Our results are in agreement with observations reported by other laboratories (Hao et al. 2009). Wound healing is always a big issue after irradiation. The effectiveness of MSCs administration seems very promising for future clinical uses to shorten the healing process, improve patients' hospitalization time and life quality, and reduce medical costs.

The benefit of MSCs can be a crucial factor in large animals as in small animals. Riccobono et al. (2012) reported that minipigs were locally irradiated at a dose of 50 Gy (^{60}Co gamma-ray) and wound healing was measured. These authors found that autologous adipocyte-derived MSCs improved cutaneous radiation syndrome wound healing, whereas allogeneic adipocyte-derived stem cells did not. In small animals, MSCs collected from different individuals seem not to be an issue (Nemeth et al. 2009).

MSCs and radiation-induced cognitive dysfunction

Radiotherapy frequently leads to progressive and long-lasting declines in cognition that can severely impact quality of life (Aayomi, 1997; Butler et al., 2006; Meyers and Brown, 2006). Recent publications have demonstrated that administration of MSCs restores neuronal plasticity after irradiation. Acharya and the colleagues (2015) reported that radiation on brain resulted in cognate dysfunction. When total 4×10^5 human neural stem cells (hNSC) were injected into 4 different sites of hippocampus 1 month after 10 Gy at 2.07 Gy/min to the brain of immunodeficient male athymic nude rats, the hNSC transplantation promoted the long-term recovery of host hippocampal neurons and ameliorated cognitive dysfunction. The results are stunning and provide insights to further advance research in neuronal injury due to irradiation.

MSCs and radiation as well as bacterial challenge

MSCs normally have relative high amounts of constitutively expressed HSP70 and NF-keppaB-p65, and a detectable amount of NAD^+-dependent deacetylase sirtuin-3 (Sirt3). Significant increases in heat shock protein 70kDa (HSP70), NF-keppaB-p65, Sirt3, and matrix metalloproteinase-3 (MMP3) were found, when MSCs were exposed to 12 Gy but not 8 Gy. Sirt3 is a mitochondrial stress-response protein. Increases in Sirt3 expression suggest that radiation induces stress to mitochondria. Caspase-3, a marker for caspase-dependent apoptosis, was not detected in irradiated MSCs, suggesting that no apoptosis takes place in MSCs after irradiation. Radiation induced significant increases in light chain 3 (LC3) expression, a marker of autophagy, detected by Western blotting and LC3-containing autophagy vacuoles displayed by immunofluorescent staining, suggesting presence of up-regulation of autophagy defense machinery.

It has been demonstrated that radiation induces systemic bacterial infection (Kiang et al. 2010; Fukumoto et al. 2013). In bone marrow, the immune homeostasis and defense response to blood pathogens are mediated by the marrow-blood barrier, which consists of endothelial, reticuloendothelial and mesenchymal stromal cell lineages (Balduino et al. 2005; Greenberger and Epperly, 2009; Krebsbach et al. 1999; Owen and Friedenstein, 1988). When MSCs were exposed to radiation or in combination with Gram-negative *E. coli* challenge (5×10^7 bacteria/ml), increases in lysosomal-associated membrane protein 1 (Lamp1), small ubiquitin-related modifier 1 (SUMO1), collagen III, MMP3, MMP13, and

p62/SQSM1 were observed 24 h after radiation or combined with *E. coli* challenge. MSCs performed extensive phagocytosis and inactivated bacteria in autolysosomes (Gorbunov et al. 2013). When MSCs were challenged with Gram-positive *S. epidermidis* (5×10^7 bacteria/ml) for 3 h, the cells displayed remarkable resistance to the bacterial challenge and sustained confluence over the period of observation. Similar observations to that with *E. coli* challenge were found as well (Gorbunov et al. 2015). These results suggest that MSCs can contribute to the innate defense response to radiation injury.

MSCs and mitochondrial remodeling

Radiation results in bacterial infection (Kiang et al. 2010). Radiation or bacterial challenge of MSCs results in alteration of the mitochondrial network. Transmission electron microscopy and immunofluorescence microscopy showed that the normal mitochondrial network is a combination of round and elongated organelles containing discrete cristae at high densities. Mitochondrial fusion and fission take place when necessary.

Using electron transmission microscopy, the bacterial challenge resulted in extensive mitochondrial swelling and cristae fragmentation 5 h post-challenge. The entire mitochondrial body almost became reticular by 24 h post-challenge. This structure re-arrangement and fragmentation were triggered by increased expression of immunity-related GTPase family M (IRGM) and inducible nitric oxide synthase (iNOS). Bacterial challenge induced dynamin-related protein 1 (Drp1, a marker of mitochondrial fission) translocation from cytosol to mitochondria, leading to activation of PTEN induced putative kinase 1-parkin RBR E3 ubiquitin protein ligase (PINK1-PARK2) to initiate mitophagy to degrade fragmented mitochondria (Gorbunov et al. 2015). Using Western blotting, proteins of mitofusin-1 (Mfn1, a marker of mitochondrial fusion), PINK1, and PARK2 in MSCs were significantly elevated 24 h after the bacterial challenge. The HSP70 basal level was not affected and no caspase-3 was detected in these cells (Gorbunov et al. 2015). These results suggest that mitophagy but not caspase-dependent apoptosis in MSCs occurs after the bacterial challenge. It is warranted that caspase-independent apoptosis caused by molecular pathways involving with apoptosis-inducible factor (AIF) or by senescence signals of protein 16 (p16) and beta-galactosidase (beta-gal) in MSCs after bacterial challenge shall be explored. MSCs exposed to ionizing irradiation alone also show mitochondrial fission and subsequent fusion as well as mitophagy (Gorbunov et al. 2015).

MSCs and signal transduction

Radiation activates protein kinase B (AKT), c-Jun N-terminal kinases (JNK), and p38 mitogen-activated protein kinases (p38 MAPK) (Kunwar et al. 2012). Felka et al. (2014) reported that NO activated proto-oncogene serine/threonine-protein kinase [c-Raf, part of the extracellular-signal-regulated kinases (ERK) pathway], JNK, p38 MAPK, p53, and a nuclear factor E2-related factor (NRF2)-associated stress response, which may have detrimental consequences for bone remodeling or bone regeneration. Therefore, one can postulate that priming MSCs to elevate pro-survival signaling molecules may enhance MSCs' multi-functionality as a therapy. MSCs exposed to ionizing radiation results in decreases in AKT and ERK activation and increases in JNK activation (Kiang, Ho, and Smith, unpublished data).

PERSPECTIVE

MSCs have been extensively characterized. They also have been demonstrated to mitigate acute hematopoietic syndrome, gastrointestinal syndrome, and cutaneous syndrome caused by exposure to high doses of ionizing irradiation. Therefore, MSCs as an effective therapy for radiation patients/victims are promising. MSCs can be easily harvested from bone marrow and fat tissues. They can be cultured, grown, and expanded in the laboratory for mass production. Therefore, meeting commercial needs for health maintenance or tissue repair and regeneration can be envisioned and accomplished.

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