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Stromal Progenitor Cells in Mitigation of Non-Hematopoietic Radiation Injuries

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Abstract

Purpose of review—Therapeutic exposure to high doses of radiation can severely impair organ function due to ablation of stem cells. Normal tissue injury is a dose-limiting toxicity for radiation therapy (RT). Although advances in the delivery of high precision conformal RT has increased normal tissue sparing, mitigating and therapeutic strategies that could alleviate early and chronic radiation effects are urgently needed in order to deliver curative doses of RT, especially in abdominal, pelvic and thoracic malignancies. Radiation-induced gastrointestinal injury is also a major cause of lethality from accidental or intentional exposure to whole body irradiation in the case of nuclear accidents or terrorism. This review examines the therapeutic options for mitigation of non-hematopoietic radiation injuries.

Recent findings—We have developed stem cell based therapies for the mitigation of acute radiation syndrome (ARS) and radiation-induced gastrointestinal syndrome (RIGS). This is a promising option because of the robustness of standardized isolation and transplantation of stromal cells protocols, and their ability to support and replace radiation-damaged stem cells and stem cell niche. Stromal progenitor cells (SPC) represent a unique multipotent and heterogeneous cell population with regenerative, immunosuppressive, anti-inflammatory, and wound healing properties. SPC are also known to secrete various key cytokines and growth factors such as platelet derived growth factors (PDGF), keratinocyte growth factor (KGF), R-spondins (Rspo), and may consequently exert their regenerative effects via paracrine function. Additionally, secretory vesicles such as exosomes or microparticles can potentially be a cell-free alternative replacing the cell transplant in some cases.

Summary—This review highlights the beneficial effects of SPC on tissue regeneration with their ability to (a) target the irradiated tissues, (b) recruit host stromal cells, (c) regenerate endothelium

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Compliance with Ethics Guidelines

Conflict of Interest

Shilpa Kulkarni, Timothy Wang and Chandan Guha declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

and epithelium, (d) and secrete regenerative and immunomodulatory paracrine signals to control inflammation, ulceration, wound healing and fibrosis.

Keywords

Stromal Progenitor Cells; Growth factors; Radiation Induced Gastrointestinal Diseases; Intestinal Stem Cells; Epithelial Regeneration; Vascularization; Exosomes; Inflammation

INTRODUCTION

Currently 50% of all cancer patients receive some form of radiation therapy (RT), including curative and palliative therapy with about 40% patients receiving curative treatment, making it one of the most efficient and popular treatment modalities against cancer (1). However despite the obvious benefits of curing neoplastic diseases and extending survival significantly, RT tends to lead to acute and chronic effects in normal tissue (2). Most RT studies indicate that treatment modalities associated with better tumor control and survival more often lead to normal tissue toxicity; therefore, adjuvant mitigators of normal tissue injury are needed for improving local tumor control and overall survival with RT (3). Radiation injury occurring within days after exposure is classified as “acute injury” and often associated with direct damage to the stem cell and its niche, including the stroma and microvasculature. Late injury, which manifests months to years after exposure, is due to persistent oxidative and inflammatory signaling, aberrant stem cell regeneration, damage to the vascular stroma and scarring. Among various pharmacological approaches used, cell transplantation is one of the most effective strategies in treating radiation injury (4–6).

Bone marrow transplantation (BMT) has been an attractive treatment option for various pathologies including radiation injury. Traditionally, BMT is used for bone marrow injury that involves loss of hematopoietic stem cells. Although bone marrow derived stromal progenitor cells (SPC) were initially assumed to contribute only to the HSC niche, it has become increasingly evident that the stromal progenitors derived from bone marrow (BM-SPC) or adipose tissue (Ad-SPC) contribute to extramedullary regeneration and repair, including recovery from radiation-induced gastrointestinal, pulmonary, and renal injury (7–9). This review briefly covers the beneficial role of SPCs or BM derived stromal cells in mitigating radiation injury, especially that pertaining to radiation-induced gastrointestinal syndrome (RIGS). The progression of radiation toxicity over time and the manifestation of acute and consequential delayed injuries from acute exposure, along with the mechanisms involved, are depicted in Figure 1. The figure also describes the beneficial role of SPC or MSC at various stages of acute and delayed injury of the GI tract.

RIGS and stromal injury

Radiation-induced gastrointestinal syndrome (RIGS) results from a combination of direct cytotoxic effects on intestinal crypt and endothelial cells and subsequent loss of the mucosal barrier, resulting in microbial infection, septic shock and systemic inflammatory response syndrome (SIRS) (10). The intestine is also a model for an “early responding” tissue that is frequently targeted by DNA damaging agents, such as ionizing radiation (IR), resulting in RIGS. It is due in part to ISC depletion and signaling defects of IR-damaged ISC niche, thus

providing an ideal model system to study intestinal stem cell (ISC) growth and differentiation in response to radiation-induced intestinal injury.

The mammalian intestinal mucosa is a rapidly proliferating tissue and is a model for tissue parenchymal cells originating via hierarchical cell proliferation and differentiation from stem cells, in this case the ISC located in the intestinal crypt. The intestinal crypts are surrounded by a variety of supporting cells, including mesenchymal-derived cells, microvascular endothelial cells, macrophages and lymphocytes. These stromal cells provide the niche and supply critical growth factor/signals for ISC regeneration; thus, acute injury to the stroma is also highly detrimental to the ISC function. While IR induces apoptosis of ISCs, crypt endothelial cells and enterocytes within hours in a dose dependent manner, stromal components play critical role in preserving the ISC function. For instance, recruitment of host myelomonocytic cells and mesenchymal stem cell to irradiated GI region has been shown to improve GI regenerative capacity and maintain function when the stroma is damaged by irradiation (5, 11).

Intestinal Stem Cells homeostasis and radiation sensitivity

ISCs proliferate and migrate either toward the villus while differentiating into enterocytes, goblet, and enteroendocrine cells, or toward the crypt base while differentiating into Paneth cells. The severe gastrointestinal side effects of radiotherapy (RT) have been attributed to radiation-induced death of ISCs. The early mitotic arrest and cell death occurring in these stem cells, coupled with continued migration of differentiated daughter cells toward the extrusion zone at the villus apex, results in cellular depletion of the crypt while attempting to maintain the villus mass (12). Shrinkage of the villus commences after crypt depletion is completed, leading to involution of the mucosa and formation of frank ulcers with consequential metabolite and electrolyte imbalance, diarrhea and sepsis secondary to the entry of microbial agents in the systemic circulation. Within 3–4 day post-RT, epithelial regeneration proceeds from a few surviving cells out of a larger clonogenic population, seen as microcolonies of 10 or more crypt cells (12). By day 7 post-RT, the process of crypt budding provides new crypts with their own stem cells. Thus, after a cytotoxic insult induced by RT or drugs, ISCs and their immediate progeny are capable of dividing to regenerate an entire functional intestinal epithelium.

Differential sensitivity of critical tissue elements of the GI tract to radiation-induced cell death is observed in a dose dependent fashion. ISCs are heterogeneous, and comprise both active cycling stem cells as well as quiescent reserve stem cells that mediate regeneration after injury (13). The relative radiosensitivity and growth requirements of various intestinal stem cell pools are poorly understood. However, genetic inducible fate mapping studies have demonstrated that small intestinal epithelial cells are replaced from at least two principal stem cell pools: active, recycling, crypt based columnar cells (CBCs) expressing Lgr5, and more quiescent cells situated at position +4 above the crypt base which are often Hopx- and Bmi1-expressing (14–17)(18). Yan et al (17) reported that in mice exposed to 12 Gy whole body irradiation (WBI) and treated with BMT, Bmi1-ISC were able to regenerate intestinal epithelium whereas, Lgr5-ISC were depleted up to 7 days post-WBI, thus demonstrating that Lgr5+ cells are largely dispensable while other ISC populations including Bmi1+ cells

are capable of intestinal epithelial regeneration. This could be possibly due to interconversion between active and quiescent stem cell populations following intestinal injury, which could not be demonstrated by the lineage tracing models used in this study. Alternatively, Lgr5+ cells may not be of major importance in regenerative conditions.

Using a similar Cre-dependent lineage tracing model, Asfaha et al (19) demonstrated that Krt19+ labels a unique ISC, distinct from Lgr5+ CBCs and located above the +4 region. Under normal homeostasis, K19+ cells can give rise to Lgr5+ cells and the entire intestinal and colonic epithelium. Furthermore, interconversion between Krt19+ and Lgr5+ ISCs occurs readily *in vivo* (19). Importantly, in contrast to Lgr5+ and Dll1+ cells that are radiosensitive, Krt19+ stem cells are radioresistant, and thus in response to 12 Gy WBI, robust intestinal regeneration occurs from Krt19+ cells. These two studies used 12 Gy WBI and BMT as a model, and found that BMT was able to extend the survival in mice and allowed for complete lineage tracing experiments for up to 60 days post-WBI. In contrast, studies by Saha et al (4) indicated that at higher radiation doses (>12 Gy), BMT alone was not efficient and mice succumbed to RIGS within 2 weeks post-AIR. This latter study also showed that the SPC population was essential for mitigating RIGS. Taken together, these studies also emphasized the important role of both myeloid and stromal progenitor cells in intestinal epithelial regeneration and post-irradiation survival.

Microvascular endothelial cell injury in Radiation-Induced Gastrointestinal Syndrome (RIGS)

Irradiation induces apoptosis in endothelial cells primarily via the ceramide pathway (20). Previous studies have demonstrated that microvascular endothelial apoptosis represents a critical response to tissue damage in the irradiated lungs of C3H/HeJ mice, and intravenous administration of an endothelial growth factor, such as basic fibroblast growth factor (bFGF), partially abrogated the radiation injury (21). In a similar study, angiogenic growth factors, such as bFGF and VEGF, were found to be radioprotective for RIGS when administered 24 h before or 1 h after irradiation (22). Since these factors did not stimulate crypt proliferation, the mechanism of radioprotection remained elusive. Paris *et al.* reported that a single large dose of radiation administered to the mouse gastrointestinal tract primarily damages the endothelial cells of the gut microvasculature (23). Since ISCs reside in the crypts of Lieberkühn and are separated from the microvasculature by a very short distance (~100 µm), this close apposition enables endothelial cells and epithelial progenitors to communicate with each other by release of growth factors and hormones, in addition to diffusion of nutrients and oxygen from blood vessels to the ISC niche. Thus, these investigators concluded that the death of ISCs might be a secondary event, resulting from the demise of the niche endothelial cells upon which stem cells depend.

In support of this postulate, these investigators prevented RIGS by inhibiting endothelial cell apoptosis pharmacologically with intravenous bFGF, or genetically in mice by deletion of the acid sphingomyelinase gene that encodes the enzyme necessary for the production of the second messenger, ceramide, a proapoptotic lipid that facilitates endothelial cell death (23). Microvascular endothelial cells express the receptor for bFGF, whereas epithelial stem cells of the intestinal crypts do not, suggesting that bFGF protects the gut mucosa from radiation

damage through its effects on endothelial cells. The relative contribution of endothelial, as opposed to epithelial, injury in the ARS syndrome remains to be established, and remains controversial. For example, Coderre and colleagues applied a selective microvasculature radiation technique using intravenous administration of ^{10}B Boronated liposomes (24). In this model, the threshold dose for death from RIGS after neutron-beam-only irradiation was $9.0 \pm 0.6\text{Gy}$, whereas there were no deaths from RIGS, despite calculated absorbed doses to endothelial cells as high as 27.7Gy from boronated liposomes. This suggests that endothelial cell damage is not causative in the loss of intestinal crypt stem cells and the eventual development of RIGS. Therefore, a two-compartment model has been proposed (25), where radiation-induced cell death in both intestinal endothelial and crypt stem cells contribute to RIGS. Thus, when mouse intestines were protected against microvascular apoptosis by bFGF administration, higher radiation doses ($>16\text{Gy}$) are needed to activate the ceramide synthase-mediated crypt stem cell apoptosis program required to initiate intestinal damage.

Therapeutic application of Stromal Progenitor Cells (SPC) in Radiation injuries of the gastrointestinal tract

Mitigation of RIGS—Radiation-induced gastrointestinal syndrome (RIGS) results from stem cell and villi depletion, loss of mucosal barrier, infiltration of enteric bacteria into circulation, endotoxemia, and acute inflammatory response. The response of pathogen-free mice to whole body irradiation (WBI), where rapidly proliferating hematopoietic progenitor cells are also damaged, is quite different from that observed with the abdominal irradiation (AIR) model, where the hematopoietic progenitors are not damaged (26). Gastrointestinal injury related to RT is similar to the AIR model, where as the injury observed in a WBI model is more typical of multiorgan failure. In addition to the GI toxicity related to RT, RIGS is a critical concern for a mass casualty scenario, where a large population is exposed to a high dose of ionizing radiation, likely involving both whole body (WBI) or partial body (PBI) exposure, with a high risk of gastrointestinal toxicity and related injuries. To date, there are no treatment options available to remedy RIGS in humans. Studies by Saha et al (4) demonstrated that bone marrow adherent stromal cells (BMASC) given 24 and 72 h post-lethal doses of WBI mitigated acute radiation injury to the gastrointestinal tract, and improved post-irradiation survival dramatically by stimulating stem cell proliferation and crypt regeneration, thereby reducing mucosa disruption and permeability. The bone marrow adherent cell population used in the studies was characterized as a combination of mesenchymal stem cells (MSC), endothelial (EC) and myeloid cells. Depletion of either the myeloid or non-myeloid fraction led to significant loss of post-irradiation survival, indicating that the mitigating mechanisms involved both MSC and myeloid cells. These effects were observed in a WBI model where host bone marrow was also exposed to a lethal dose of radiation, and in an abdominal irradiation model (AIR), where most of the BM was spared; thus, the effect of BMASC was primarily from donor derived cells. Interestingly, depletion of host myeloid cells by clodronate liposomes resulted in reduction in post-irradiation survival by BMASC treatment, implying a critical supporting role for host-derived macrophages (4). This study indicated that donor BMASC and host cells are equally important in the mitigation of radiation injury.

Similar results were obtained in independent studies reported by Chang et al (27), where a different source of MSC - human adipose derived mesenchymal stem cells (Ad-MSC) - were used to mitigate acute injury from lethal dose of AIR in rats. The authors described the mechanism of action as a combination of (i) reduction in inflammation as hallmarked by reduced myeloperoxidase (MPO) activity and increased IL10 levels, (ii) increased neovascularization in the irradiated tissue, and (iii) increase proliferation in Bmi1- positive intestinal stem cells. Studies by Ch'ang et al (5) reported that BMT in lethally irradiated mice rescued intestinal mucosa, increased stromal cell proliferation and improved post-irradiation survival. Although these studies utilized a conventional BMT strategy and not the stromal or adherent population, the results indicated that BMT increased the recruitment of host stromal and myelomonocytic cells in the irradiated intestines, despite poor engraftment of donor cells in the intestine. Depletion of host myelomonocytic cells by carrageenan abolished the increase in post-irradiation survival in mice by BMT. It is important to note that the efficacy of BMT was somewhat limited, and beneficial only to at specific radiation doses. Garg et al (28) also reported that BMT was able to rescue intestinal mucosa in mice exposed to 8–10 Gy WBI, a dose where hematopoietic damage is the major causative factor leading to death. The author showed increases in peripheral blood cells as a result of BMT, but also a subsequent increase in the recruitment of donor macrophages to the intestine and a reduction in intestinal permeability. Beneficial effects of SPC in mitigating radiation induced gastrointestinal injuries are summarized in Table 1.

Radiation Enteritis (RE)—RE is the most prevalent complication from RT of abdominal and kidney cancers, and ~75% of cancer patients undergoing abdominal RT treatment suffer from side effects related to RE. Recent studies (29) show a positive correlation between systemic inflammation, nutritional status and chronic RE. Acute RE occurs around 2 weeks post-treatment and is associated with mucosal barrier loss, epithelial denudation, nutrient loss, infiltration of leukocytes into the lamina propria and inflammatory responses such as mucosal ulceration. Ischemia, necrosis and fibrosis, on the other hand, are the classical features of chronic enteritis, which typically manifests around 8–12 months post-treatment (30). Currently there is no standard evaluation system for assessing radiation enteritis, other than symptoms, and the use of pharmacological intervention is not approved. Albeit several mouse studies show promising effects of BMSC in radiation injury, few reports show their therapeutic efficacy in large animal models. Xu et al (31) demonstrated that BMSCT significantly increased intestinal epithelial regeneration, reduced the clinical symptoms associated with chronic enteritis, and improved survival in lethally irradiated dogs. BMSCT significantly reduced the frequency of nausea and vomiting, a prognostic indicator of radiation injury and mortality.

Pelvic Radiation Disease (PRD)—Cancers in the pelvic region are one of the most frequently diagnosed cancers and the treatment often requires RT (32, 33). The incidence of radiation toxicity from pelvic RT depends on the volume and duration of the treatment course, about 4–10% patients experience life threatening effects of pelvic RT (34). As survival is prolonged following successful treatment, the incidence of pelvic radiation disease continue to rise, with the number of patients developing PVD now twice the number of that with Crohn's disease (32). Because the symptoms of PRD are similar to many other

bowel disorders, comprehensive care and management of symptoms tailored to RT toxicity are not currently available, with limited interventional strategies including hyperbaric chamber and surgery (30). Additionally, the toxicity also depends on several risk factors such as diabetes, inflammatory bowel disease, body mass index (BMI) and smoking (35). Acute toxicity develops during the second week of radiation treatment, and peaks by the 5th week, where histological changes are most prominent. Delayed toxicity (after the 5th week) is more common, with almost 90% patients developing permanent changes in the GI tract, and 50% of patients end up with a significant decline in quality of life (33). The most frequently reported symptoms of toxicity from pelvic RT include rectal bleeding, bloating, vomiting, abdominal cramps, constipation, diarrhea, fecal incontinence, lactose intolerance, abdominal, rectal and anal pain. Use of probiotics or antibiotics relieves some of the symptoms such as diarrhea, and motility changes; however most of the symptoms remain refractory to treatment. Delayed toxicity effects such as ulceration, stricture formation, and obstruction are even more critical and newer approaches are needed to prevent these complications (33).

Several interventional strategies are used to reduce the extent of PRD, including antioxidants such as amifostine, and probiotics (35). Amifostine was shown to be beneficial for reducing acute toxicity, but did not improve chronic PRD, while probiotics had similar effect with no significant benefit in delayed toxicity. Studies by Semont et al (36) used a rat model to establish PRD histologically comparable to human disease. The authors demonstrated that infusion of BM-SPC (devoid of hematopoietic cells) reduced radiation-induced colonic ulceration, increased recruitment of host MSC to the irradiated tissue, and induced colonic epithelial regeneration by non-canonical Wnt activation, consequently leading to improvement in post-irradiation survival. Additionally the authors also analyzed other functional endpoints, including improvement in colonic mucosal damage, extent of fibrosis, vascular sclerosis and muscular dystrophy, leading to overall improvement in late injury in presence of MSC with the exception of the fibrosis scoring. This model did not analyze other organs in the pelvic cavity that may have shown radiation-induced acute and delayed injury. Feasibility studies using systemic administration of MSC in patients with intestinal lesions showed substantial benefit in hemorrhage reduction (34). The treatment was well tolerated and the MSC cultures exhibited genomic stability. Further studies are being currently undertaken based on these results.

Radiation proctitis—Radiation proctitis is defined as a radiation injury to the lining of the rectum primarily as a result of prostate radiation (37, 38). The onset of acute toxicity is observed as early as 2 weeks into the radiation treatment, and observed in ~13% of patients with intermittent bleeding, cramps, constipation and mucoid discharge. Currently there are no medical interventional strategies to treat radiation proctitis and alleviate the symptoms other than surgery. Studies by Linard et al showed successful administration of autologous bone marrow-derived MSC for mitigation of radiation proctitis in pig model (39). Endoscopic and histological evaluation of pigs treated with MSC showed significant reduction in acute inflammation, infiltration of leukocyte at the site of injury, and delayed effects such as vascular injury, remodeling and fibrosis.

Effects of SPC on intestinal stem cells and the niche factors

Histological evidence suggests that SPC treatment mitigates RIGS via accelerated regeneration of irradiated host intestinal stem cells, rather than simply replacement of host stroma with donor derived cells (4, 27, 40). Saha et al (4) demonstrated that bone marrow stromal transplant increased Lgr5-GFP cells in irradiated mice, indicating direct effect of SPC on ISC proliferation, Semont et al also independently demonstrated reduction in apoptotic cells, increased ki67 staining in the crypt region, and increased miRNA levels of Lgr5, mTERT and Sox9 in response to Ad-MSCT in irradiated mice (36, 40), indicative of elevated ISC activity in response to stromal cell transplant. Studies by Saha et al (4) also demonstrated several-fold increases in mRNA levels in cells isolated from the crypt region of intestinal growth factors and inflammatory cytokines, such as fibroblasts growth factor 10 (FGF10), keratinocyte growth factor (KGF), epidermal growth factor (EGF), fibroblast growth factor 2 (FGF2), vascular endothelial growth factor (VEGF), and anti-inflammatory cytokine interleukin 10 (IL-10) with BMSC treatment. These changes were not observed with a conventional BMT devoid of stromal progenitor cells. Recent studies by Kamprad et al (41) also reported elevated mRNA levels of stromal cell-derived factor 1 (SDF1), insulin-like growth factor 1 (IGF1), placental growth factor (PIGF), fibroblast growth factor 2 (FGF2), angiopoietin 1 (ANGPT1), angiopoietin 2 (ANGPT2), vascular endothelial growth factor (VEGF), interleukin 6 (IL6), interleukin 8 (IL8) in MSC obtained from bone marrow and placenta derived MSC, indicating direct role of MSC in angiogenesis. Independent studies involving use of R-spondin-1 (42), KGF (43), VEGF (22) have shown that these growth factors have beneficial effects in regeneration of intestinal epithelium after radiation injury. Together, these results suggested that stromal progenitor cells can modulate the regenerative signals in the intestinal microenvironment.

Paracrine functions of SPC: Secreted microvesicles as a new therapeutic regimen

The most well documented properties of SPC include (i) targeting to the injured site, (ii) recruiting host MSC to the injured site, (iii) supplying growth factors to the injured stromal and stem cells, and (iv) controlling inflammation at the local level. However, it is now recognized that several of these functions by SPC are exerted via paracrine mechanisms involving secreted factors, most likely via extracellular vesicles (4, 27, 31, 44–48). Several of the studies have reported that SPC secrete stromal growth factors such as basic fibroblast growth factor (FGF2), platelet derived growth factor (PDGF), R-spondins, Wnts (Wnt 4, 5) (4, 45), anti-inflammatory cytokines such as Interleukin-17, glucocorticoids (49), and angiogenic factors such as VEGF (4, 45). These studies demonstrated that the culture medium from SPC was equally effective in exerting beneficial effects of SPC as an alternative to cell transplant. Growth factors and cytokines secreted by SPC that are responsible for various biological activities of SPC are summarized in Table 1. Additionally, reports also indicate that SPC exosomes increase ATP levels in cardiomyocytes, preventing ischemia injury associated (50).

Potential role of stromal progenitor cells in Mitochondrial replacement therapy

More recently, mitochondrial replacement therapy is being viewed as a new paradigm shift in regenerative molecular medicine. In addition to mitochondrial genetic disease (51),

altered biogenesis and mitochondrial exhaustion is the leading cause of several oxidative disorders, including Chronic obstructive pulmonary disease (COPD) and aging related degenerative pathologies (52). Beneficial effects of mitochondrial transfer are observed in ischemic perfusion model and in metastatic cancer cells (53). An interesting study by Islam et al (54) showed that bone marrow-derived stromal progenitor cells were able to transfer mitochondria containing microvesicles to the epithelial cells of a rat exposed to lipopolysaccharide (LPS) injection in an acute lung injury model; this transfer was also associated with increased ATP activity. Thus, MSC are also emerging as a source of healthy mitochondria for treatment of diseases associated with mitochondrial mutation and defects in bioenergetics.

CONCLUSION AND FUTURE PERSPECTIVES

Overall, SPC exert their effects by repairing, replacing or reprogramming damaged cells. Although the mechanisms by which they exert these various effects remain incompletely defined, recent studies have emphasized the role of secreted extracellular vesicles as a dominant pathway in their mechanism of action. The development of stromal progenitor cells (SPC) or MSC into a highly evolved regenerative cell-based therapy for a variety of diseases - ranging from inflammatory (colitis, enteritis, inflammatory bowel disease, pulmonary fibrosis, bladder fibrosis), autoimmune (graft versus host disease in transplants), regenerative (wounds, burns, scars, radiation injury) - is striking but not surprising. However, transition from preclinical studies into clinical studies has been somewhat limited due to uncertainties regarding the multipotent nature of SPC and technical difficulties in their expansion. BM-derived SPC are poorly proliferative compared to the adipose-derived SPC, and the difference in their proliferative capacity has been attributed to higher expression of SDF-1 in Ad-SPC (27). The stability of transplanted and engrafted SPC remains one of the critical concerns in future clinical studies with MSCs; however, MSC have been shown to be highly immune-tolerant and genomically stable, and thus they continue to be highly promising. Use of secreted vesicles from SPC is another emerging area that could in theory render whole cell transplants obsolete, since all of the beneficial effects of MSC might be transferred to patients in the form of their secreted vesicles. In the context of radiation injury, especially of the GI where epithelial, mucosal, endothelial and immune components are simultaneously destabilized and damaged, SPC therapy offers great therapeutic promise.

Acknowledgments

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Figure 1.
Beneficial effects of stromal progenitor cells in various stages of acute and chronic radiation injuries

Table 1

Therapeutic applications of SPC and SPC derived growth factors against radiation induced intestinal injuries

A. Therapeutic application of SPC in various radiation induced pathologies			
Cells	Targets/Mechanisms	Application (disease model)	Ref
Bone marrow stromal progenitors, epithelial progenitors, myeloid progenitors	Lgr5 positive ISC proliferation Crypt maintenance Mucosal integrity	Radiation induced gastrointestinal syndrome (mouse)	4
Bone marrow transplant	Recruitment of host myelomonocytic and MSC to the irradiated tissue	Radiation induced gastrointestinal syndrome (mouse)	5, 11
Adipose derived mesenchymal stem cells	Increase in Bmi-1 positive ISC proliferation Reduction in inflammation Increase in anti-inflammatory Increase in vascularization	Radiation induced gastrointestinal syndrome (mouse)	26
Bone marrow transplant	Recruitment of host myeloid cells Reduction in GI permeability	Radiation induced mucosal injury (mouse)	27
Bone marrow derived mesenchymal stem cells	Increase in intestinal epithelial regeneration	Radiation Enteritis (dogs)	30
Bone marrow derived mesenchymal stem cells	Activation of non-canonical signaling Increase colonic epithelial regeneration Reduction in ulceration Recruitment of host mesenchymal stem cells to colon	Radiation induced Pelvic Disease (moues)	35
Bone marrow derived mesenchymal stem cells	Reduction in acute inflammation Reduction in infiltration of leukocytes Reduction in fibrosis and vascular remodeling	Radiation Proctitis (pigs)	38
B. SPC derived cytokines and growth factors			
Growth Factors	Targets/Mechanisms	Application (disease model)	Ref
Vascular endothelial growth factor	Vascularization	Radiation induced gastrointestinal syndrome (mouse)	4, 41, 40, 45
Rspondin1	Lgr5-ISC proliferation	Radiation induced gastrointestinal syndrome (mouse)	4
Platelet derived growth factor	Stromal proenitor cell proliferation	Radiation induced gastrointestinal syndrome (mouse)	4, 40, 45
Fibroblast growth factor	Intestinal Sub-epithelial myofibroblasts proliferation	Radiation induced gastrointestinal syndrome (mouse)	4
Keratinocyte growth factor	ISC and Transit amplifying cell growth factor	Radiation induced gastrointestinal syndrome (mouse)	4
Interleukin10	Anti-inflammatory	Radiation Proctitis (pigs)	40
Hepatocyte growth factor	Growth factor for epithelial and endothelial cells	Radiation induced epithelial and endothelial injury	45
Interleukin 17	Anti-inflammatory	Radiation induced inflammatory response (ulcers, proctitis, cystitis)	44
Stromal cell derived factor 1	Stem cell proliferation Recruitment of host MSC	Acute radiation injury	40, 45

A. Therapeutic application of SPC in various radiation induced pathologies			
Interleukin 6	Proliferation Hematopoiesis	Acute radiation injury	40, 45
Angiopoietin 1, 2	Vascular growth factor	Radiation Proctitis (pigs)	40

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