

Structural and functional small intestine regeneration after mesenchymal stem cell infusion

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Abstract

Patients who undergo pelvic or abdominal radiotherapy may develop side effects that can be life threatening. Tissue complications caused by radiation-induced stem cell depletion may result in structural and functional alterations of the gastrointestinal (GI) tract. Stem cell therapy using mesenchymal stem cells (MSC) is a promising approach for replenishment of the depleted stem cell compartment during radiotherapy. In this study, we addressed the question of the therapeutic potential of MSC in the context of radiation-induced GI injury. We tested the regenerative capacity of hMSC on structural and functional alterations in small intestine after radiation exposure in a NOD/SCID mouse model.

NOD/SCID mice, were divided in four groups. Group 1 was a non-irradiated control group that did not receive hMSC. Group 2 received 8.5 Gy abdominal irradiation. The last two groups were transplanted with 5.10^6 human bone marrow-derived MSC. Group 3 was not irradiated before receiving hMSC infusion. Group 4 received 8.5 Gy abdominal irradiation 24 hours before hMSC infusion. The animals were sacrificed 3 days after irradiation and small intestine was collected. Structural alterations of small intestine were studied by morphometric analysis (mucosal depth). Immunohistological analyses were performed to quantify cell proliferation (Ki67) and cell apoptosis (TUNEL). Functional alterations were studied by the quantification of basal and stimulated electrolyte transport in Ussing Chambers.

In non-irradiated mice, hMSC infusion reduced spontaneous crypt cell apoptosis of the small intestine. Moreover, their infusion let to a significant enhancement of proliferating potential of all crypt cells. These effects of hMSC were associated with an increase of small intestine mucosa depth. Finally, hMSC stimulated electrolyte transport through small intestinal epithelium. We then demonstrated that hMSC increased the self-renewal and functionality of small intestinal epithelium.

Following abdominal irradiation, the histological analysis of small intestinal structure confirmed the presence of partial and transient (at three days) mucosal atrophy (villus height reduction). Three days after irradiation, we reported disturbance of physiological cell death/cell regeneration balance (3 fold increase of cell proliferation and 10 fold increase of cell apoptosis). Moreover, we observed a significant reduction of small intestine functionality with significant decrease of electrolyte transport.

Three days after abdominal irradiation, the integrity of small intestine was already regained in hMSC injected mice. We observed many regenerating crypt and an increase of cells in proliferation. Apoptotic cells number returned to a value close to base line. Moreover, the villus height was significantly increased to reach high values greater than control values. At three days, the small intestine functionality also returned to base line. This study showed that hMSC take part in structural and functional full recovery of small intestine damaged by abdominal irradiation.

This work supports, the use of MSC infusion to repair damaged GI tract in patients subjected to radiotherapy. MSC therapy to avoid extended intestinal crypt sterilization is a promising approach to diminish healthy tissue alterations during the course of pelvic radiotherapy.