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Mesenchymal stem cell administration attenuates colon cancer progression by modulating the immune component within the colorectal tumor microenvironment

Alain Chapel

Institute for Radiological Protection and Nuclear Safety (IRSN), France

Abstract

We here determine the influence of MSC therapy on the progression of solid tumors. An immunocompetent rat model of colorectal carcinogenesis representative of the human pathology was used as preclinical model. MSC treatment significantly reduced both cancer initiation and cancer progression by increasing the number of tumor-free animals while decreasing the number of tumors in tumor-bearing animals thereby extending their lifespan. The attenuation of cancer progression was mediated by the capacity of the MSCs to modulate the immune component. Specifically, in the adenocarcinoma of MSC-treated rats, the infiltration of CD68+ monocytes/macrophages was attenuated while the presence of CD3+ lymphocytes increased. The MSCs reprogrammed the macrophages to become regulatory cells involved in phagocytosis thereby inhibiting the production of pro-inflammatory cytokines. Furthermore, the MSCs decrease NK and rTh17 cell activities, Treg recruitment, the presence of CD8 + lymphocytes and endothelial cells while, restoring Th17 cell activity. Importantly, the expression of Mi-150 and miRNA-7 increased up to 5-fold indicating a role in the modulation of tumor growth. Specifically, Mi-150 is known to attenuate tumor invasion while mi-RNA-7 is a negative regulator of the EGFR/AKT pathway thereby favouring tumor cell death. Importantly, MSC administration was also able to attenuated damage of healthy tissues as well as attenuating tumor growth following radiotherapy, suggesting that MSC treatment of patients with clinical complications after irradiation may be a safe therapeutic option. Taken together, we here demonstrate that MSCs have durable action on colon cancer development by modulating the immune component of the tumor microenvironment. In addition, we are the first to identify two mi-RNAs associated with the capacity of MSCs to attenuate cancer growth.

Biography

Alain Chapel has been developing gene and cell therapy using non-human primates, immune-tolerant mice and rats to protect against the side effects of radiation. He collaborates with clinicians to develop strategies for treatment of patients after radiotherapy overexposures. He has participated in the first establishment of proof of concept of the therapeutic efficacy of mesenchymal stem cells (MSCs) for the treatment of hematopoietic deficit, radiodermatitis and over dosages of radiotherapy. He has contributed to the first reported correction of deficient hematopoiesis in patients (graft failure and aplastic anemia) thanks to intravenous injection of MSCs restoring the bone marrow microenvironment, mandatory to sustain hematopoiesis after total body irradiation. He is scientific investigator of clinical phase II trial evaluating the efficacy of systemic MSC injections for the treatment of severe and chronic radiotherapy-induced abdomino-pelvic complications refractory to standard therapy.

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