Cytotherapy, 2015; 0: 1–17

International Society for Cellular Therapy
ISCT®

Human mesenchymal stromal cell therapy for prevention and recovery of chemo/radiotherapy adverse reactions

FATEMEH HENDIJANI

Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Cancer treatment plans mainly include chemotherapy, radiotherapy and surgery, which exert serious adverse reactions immediately or during the long term after cancer therapy in many patients. In several cases, treatment-related adverse effects outweigh treatment benefits and worsen the patient's condition. This problem is not avoidable with current cancer therapy procedures; therefore, improved understanding and earlier prevention and reversion of treatment-related complications are particularly important before the lesions become progressive and irreversible. Mesenchymal stromal cell therapy is very promising in recent clinical research and investigations. Their potential properties such as regenerative and reparative functions and anti-inflammatory activity make them proper candidates for cell therapy to recover cancer patients from treatment-related adverse effects or may even prevent them. This article discuss benefits of applying human mesenchymal stromal cell therapy after current cancer treatment plans, with the purpose of prevention and healing of adverse reactions, faster patient recovery after radio/chemotherapy, reducing rates of treatment failure and cancer recurrence and increasing patient quality of life after treatment cessation.

Key Words: *adverse reactions, chemotherapy, mesenchymal stromal cell therapy, radiotherapy*

Introduction

Cancer is the leading cause of death in developed countries and the second cause of death in developing countries [1]. Against the large volume of investigation performed in cancer biology and treatment, this field is still challenging in the clinical setting [2]. Surgery, radiotherapy and chemotherapy are the major medical approaches toward cancer removal. In most of the cases, they cannot reveal the disease thoroughly and exert severe adverse effects. Radiation causes multiple organ damage; chemotherapy also produces a vast majority of adverse reactions, and surgery is a systemic stress for a cancerous patient who fights his existing problem. However, none of the above can make us confident about killing of all cancer cells and having no recurrence or metastatic event after cessation of treatment. Therefore, anti-cancer therapies are deficient because of both their ineffectiveness in cancer removal and generation of adverse effects; in fact they cannot improve patients' quality of life in a large number of cases. In other words, in several cases, treatment-related adverse effects outweigh treatment benefits and worsen the patient's condition. This problem is not avoidable with current cancer therapy procedures; therefore, improved understanding and earlier prevention and reversion of treatment-related complications are particularly important before the lesions become progressive and irreversible and given the recent emergence of new therapeutic leads.

Accordingly, great number of scientists focus on stem cell research as an upcoming strategy in the cancer treatment process [3–5]. Of three types of stem cells, embryonic stem cells and induced pluripotent stem cells are tumorigenic [6]. Therefore, adult stem cells are the only candidate. Adult stem cells are not yet established to be tumorigenic when administered to humans. In this category, mesenchymal stromal cells (MSCs) are the right option because of the feasibility of isolation and multiple available sources such as cord blood and umbilical cord [7,8]. MSCs have regenerative activity and also trophic and protective actions toward the site of injury. In addition, anti-inflammatory effects

Correspondence: **Fatemeh Hendijani**, Pharm.D, Ph.D, Isfahan University of Medical Sciences, Department of Pharmaceutical Biotechnology, Isfahan 6698885422, Iran. E-mail: f_hendijani@pharm.mui.ac.ir; fatemeh_h324@yahoo.com

(Received 31 July 2014; accepted 27 October 2014)

http://dx.doi.org/10.1016/j.jcyt.2014.10.015

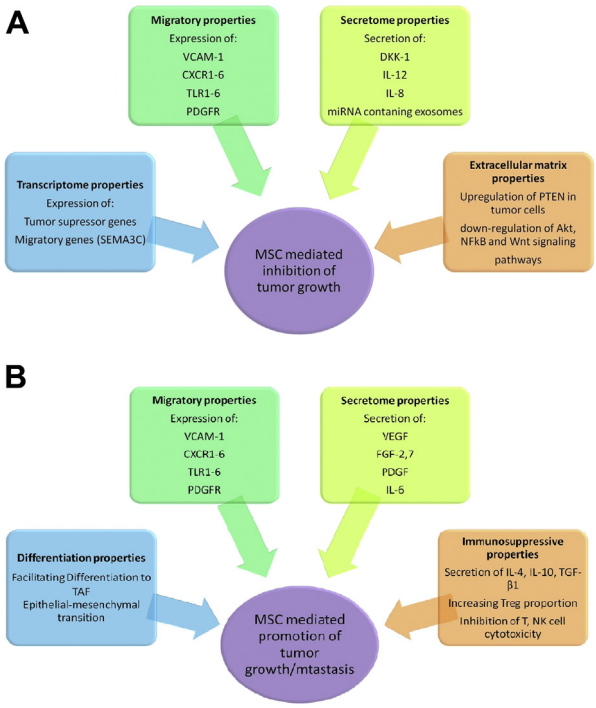

Figure 1. Inhibitory (A) and promotive (B) mechanisms by which MSCs can modulate tumor cells and tumor microenvironment.

of MSCs and their regenerative activities [9–11] can cause them to protect normal cells from both cancer pathological/systemic inflammatory events and chemo/radiotherapy adverse effects. Evidence has shown that MSCs perform many of these functions through paracrine action [10–13].

There is new evidence that shows reparative and regenerative actions of MSCs when faced with chemotherapy or radiotherapy adverse effects [14,15]. This review discusses the benefits of applying human (h) MSC therapy after current cancer treatment plans, with the purpose of prevention and healing of adverse reactions, faster patient recovery after radio/chemotherapy, reducing the rate of treatment failure and cancer recurrence and increasing patient quality of life after treatment cessation.

Human MSC interaction with tumor cells

There is a controversy in the literature regarding MSC anti-cancer or cancer-promoting effects [16]. The results of one group verify MSC anti-cancer activities [17], and another group concluded that MSCs have tumor-promoting properties [18]. However, careful focusing on these studies found detrimental factors such as MSC source [19] and tumor type. For example, approximately all studies on umbilical cord (UC)-derived MSCs concluded that they represent anti-cancer activity [20,21]. Accordingly, it seems that if MSCs were isolated from the right source and applied for the right cancer type at the right time and physiological/pathological condition, anti-cancer effects will be reached, or at least no tumor-promoting effect is observed.

Figure 1 represents briefly potential mechanisms by which MSCs may affect tumor microenvironment [5,16,22–30]. The extent of each function and dominance of inhibitory or promotive effects on the tumor depends on MSC source, MSC dose, study design, tumor type and whether MSCs modulated [23,31]. In following paragraphs, MSCs from different sources were compared according to their interaction with cancer cells.

Bone marrow–derived MSCs (BM-MSCs) and adipose-derived MSCs transformed to tumor-associated fibroblasts (TAF) in the presence of ovarian or breast cancer cells [32–34]. Actually, both of them have been shown to be recruited to sites of ovarian tumors and accompany tumor progression by directly transforming to TAF or indirectly forming vascular/fibrovascular lineages [35]. However, Fong *et al.* [36] showed that human Wharton's jelly (WJ)-MSCs do not transform to TAF when exposed to cancer cell–conditioned medium; they showed that hWJSCs acted differently from hBM-MSCs when exposed to the secreted factors of breast cancer and ovarian cancer cell lines(MDA-MB-231 and TOV-112D). hWJSCs did not transform into TAFs, whereas human BM-MSCs did transform; on the molecular level, TAF biochemical markers (fibroblast activation protein [FAP], fibroblast specific protein [FSP], stromal-derived factor-1 [SDF-1], thrombospondin [TSP], tenascin C [TN-C], fibroblast growth factor, interleukin [IL]-6, α-smooth muscle actin and vascular endothelial growth factor [VEGF]) were expressed significantly higher in the hBM-MSCs than in the hWJSCs [32].

Human WJ-MSCs also have distinct transcriptome profile compared with hMSCs from other sources, especially from bone marrow. Meta-analyses of DNA microarray data of MSCs from different sources show that genes associated with the induction of apoptosis were especially upregulated in hWJSCs, in contrast with MSCs from other sources [36]. Microarray results confirm that hWJSCs express different and higher numbers of tumor suppressor genes and oncogenes compared with human embryonic stem cells (hESCs) and human embryonal carcinoma cells (hECCs). hWJMSCs express anti-tumor cytokine IL-12, which is not produced by BM-MSCs. High levels of IL-8 secretion at the tumor site by hWJSCs may attract immune cells to kill the cancer cells. Semaphorin E (SEMA3C) is also highly upregulated in hWJSCs [36]. Because SEMA3C promotes cell migration [37] and acts as a high-affinity ligand for neuropilin/plexin receptors