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Mesenchymal stromal cells and hematopoietic stem cell transplantation

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ABSTRACT

Mesenchymal stromal cells (MSCs) comprise a heterogeneous population of multipotent cells that can be isolated from various human tissues and culture-expanded *ex vivo* for clinical use. Due to their immunoregulatory properties and their ability to secrete growth factors, MSCs play a key role in the regulation of hematopoiesis and in the modulation of immune responses against allo- and autoantigens. In light of these properties, MSCs have been employed in clinical trials in the context of hematopoietic stem cell transplantation (HSCT) to facilitate engraftment of hematopoietic stem cells (HSCs) and to prevent graft failure, as well as to treat steroid-resistant acute graft-versus-host disease (GvHD). The available clinical evidence derived from these studies indicates that MSC administration is safe. Moreover, promising preliminary results in terms of efficacy have been reported in some clinical trials, especially in the treatment of acute GvHD. In this review we critically discuss recent advances in MSC therapy by reporting on the most relevant studies in the field of HSCT.

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1. Introduction

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Pioneered by Friedenstein in 1968, MSCs were described as adherent cells located in the bone marrow (BM) and exhibiting a fibroblast-like morphology [1,2]. While in the beginning research focused on their role as multipotent cells capable to differentiate into the various mesenchymal lineages, more recently their paracrine and immunoregulatory properties have resulted in their application in clinical trials [3,4].

Recent findings have demonstrated that MSCs actively interact with cells belonging to the adaptive immune system, but also with components of the innate immune response thereby displaying both anti-inflammatory and pro-inflammatory effects. This ability of MSCs to adopt a different phenotype in response to the surrounding environment is crucial for understanding their therapeutic potential in immune-mediated disorders [5–7]. The exact mechanisms by which MSCs exert their functions, either through cell-to-cell contact or secretion of soluble factors or both, have not been completely clarified. Available data on this issue have been mainly obtained in *in vitro* studies [5–7]; the *in vivo* biological relevance of these *in vitro* observations needs to be more precisely unveiled.

MSCs exhibit the ability to home to inflamed sites, where they may promote repair of injured tissues [5,6,8] through their immunoregulatory properties. Based on this concept, MSC treatment has been employed as a therapeutic tool in the context of hematopoietic stem cell transplantation (HSCT), as well as in approaches of regenerative cell therapy. Phase I/II clinical trials [9–12], mainly addressing the feasibility and safety of MSC infusions, have been conducted and to date no major infusional toxicity has been reported after MSC administration. MSCs have been employed to enhance haematopoietic stem cell (HSC) engraftment after HLA-haploidentical, T cell-depleted allografts [9] and UCB transplantation [10], as well as to treat severe, steroid-refractory, acute graft-versus-host disease (aGvHD) [11]. MSCs have also been successfully used to repair tissue injury, outside the allo-transplantation setting, for instance in auto-immune disorders, *i.e.* refractory Crohn's Disease (CD) and Crohn's fistula's [13].

2. MSC characterization and immunoregulatory properties

2.1. *Characterization of* ex vivo *expanded MSCs*

A position paper published in 2006 by the International Society of Cellular Therapy (ISCT) proposed minimal criteria to define

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human MSCs in order to standardize their culture and characteristics across laboratories. According to these guidelines, the first criterion was the ability of MSCs to adhere to plastic surfaces under normal culture conditions. The second major characteristic is represented by a by a combination of positive (CD105, CD73, CD90, HLA class I) and negative (CD14, CD31, CD34 and CD45) surface markers and the third resides in the ability of MSCs to differentiate *in vitro* into osteoblasts, adipocytes and chondroblasts [14].

MSCs obtained from different tissue sources may display phenotypic differences. For example, adipose tissue (AT)-derived MSCs have been shown to contain a significantly higher number of CD34$^+$ cells, particularly during the first passages after plating. In the later passages, no significant differences can be observed between BM- and AT-MSC populations with respect to immunophenotype, expansion capacity and expression of immunoregulatory factors and cell adhesion molecules [15]. Melief et al. have shown that AT-MSC exhibit a higher level of suppression of T cells, on a per-cell basis. However, at optimal cell numbers no difference was observed between these two sources [16].

MSCs can be found in a variety of human tissues including BM, adipose tissue, UCB, placenta and Wharton jelly [17–19]; this suggests that MSCs may be ubiquitous in the human body. Recent evidence proposes that MSCs may adopt a pericyte phenotype and they may be located adjacent to the abluminal surface of microvessel endothelium where normally pericytes reside and may play a role in the maintenance of vascular homeostasis [20]. In line with this theory which suggests that MSCs may represent a supopulation of perivascular cells, Crisan et al. demonstrated that a MSC-like cells can be derived from a pure pericyte population and that these pericytes fulfill the ISCT criteria for MSCs definition [21,22]. In addition, MSCs also express the pericyte marker CD146 [20].

Because MSC numbers are limited in human tissues and since they lack specific markers, it has been troublesome to prospectively isolate a true Mesenchymal Stem Cell. Sacchetti and colleagues demonstrated that CD146$^+$ BM adventitial reticular cells are able to transfer the hematopoietic microenvironment upon transplantation in immune-compromised mice, rendering CD146$^+$ uncultured cells the first primitive, murine MSC population identified [23]. In human BM, however, no true stem cell marker has yet been identified. Therefore, MSC phenotypic characterization is still based on a panel of surface markers which is negative for hematopoietic and HLA-DR molecules and positive for CD73, CD90, CD105, HLA A-B-C molecules [14]. Recently, specific molecules, such as stage-specific embryonic antigen-4 (SSEA-4), STRO-1, the low affinity nerve growth factor receptor (CD271) and MCAM/CD146 (Melanoma Cell Adhesion Molecule) have been utilized for the identification and prospective isolation of human BM-derived mesenchymal progenitors [24–26]. Moreover, it has to be taken into account that both *ex vivo* expansion on plastic surfaces and culture conditions may induce phenotypic and functional changes, implying that culture-expanded MSCs are different from their progenitors.

Due to their low frequency in human tissues, MSCs are extensively *ex vivo* expanded for clinical use [9–11]. Standard conditions for expansion are based on the presence of 10% fetal calf serum (FCS) [9–11]. However, serum-free additives, devoid of the risks connected with the use of animal products, such as human platelet lysate (hPL), have been developed with favorable results [27,28]. Based on its safety and efficiency of expansion, several studies have demonstrated that hPL can be employed as FCS substitute for clinical-scale manipulation of MSCs for therapeutic applications [29,30]. The presence of growth factors in hPL such as bFGF and PDGF may be responsible for the growth-promoting properties of hPL, resulting in enhanced proliferation of MSCs while maintaining their immunophenotype, differentiation potential and immunomodulatory properties [31].

2.2. Immunoregulatory properties of MSCs

MSCs display unique immunoregulatory properties that were first demonstrated *in vitro* and, subsequently, *in vivo* both in animal models and in humans [5–7] toward cells of the adaptive and innate immune system.

2.2.1. MSCs and the adaptive immune response

Autologous and allogeneic MSCs are capable of suppression of T-lymphocyte proliferation *in vitro* induced by alloantigens [32], mitogens [33], CD3 and CD28 agonist antibodies [33–35]. MSCs have been reported to inhibit the effects of cytotoxic T cells (CTLs), probably due to suppression of CTL proliferation [36]. Since the separation of MSCs and peripheral blood mononuclear cells (PBMCs) by transwell experiments does not completely abrogate the suppressive effect, it is likely that this is partly dependent on cell-to-cell contact mechanisms and also to the secretion of soluble anti-proliferative factors (such as TGF-β, hepatocyte growth factor, prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), heme-oxygenase-1 (HO-1)) [37,38]. Inhibition of lymphocyte proliferation by MSCs has not been associated with the induction of apoptosis, but is rather due to inhibition of cell division, thus preventing T-lymphocytes from responding to antigenic triggers, while maintaining these cells in the G0/G1 phase of the cell cycle [32,34].

Several *in vitro* and *in vivo* studies have documented the ability of MSCs to polarize T cells toward a regulatory phenotype [39], which serves as an important mechanism by which MSCs blunt inflammation. *In vitro* co-incubation of human MSCs with PBMCs induces the differentiation of CD4$^+$ T cells into CD25$^+$FoxP3$^+$ expressing regulatory T cells (induced Tregs) [40,41]. The generation of Tregs has been reported to be monocyte-dependent and was not observed in co-cultures of MSCs and purified CD4$^+$ T cells or monocyte-depleted PBMCs, but it could be restored by the addition of monocytes [42]. The polarization of T cells toward a Treg phenotype has been also shown in experimental models of autoimmune and inflammatory diseases [43,44]. Moreover, removal of monocytes from human PBMCs was associated with a reduction in the immunosuppressive effects of UCB-derived MSCs on mitogen-induced T-cell proliferation and monocytes purified from UCB/MSC co-culture showed significantly reduced allo-stimulatory function when tested in subsequent T-cell proliferation assays [45]. Differentiation of both monocytes and CD34$^+$ progenitors into CD1a$^+$-dendritic cells (DCs) is inhibited in the presence of MSCs and DCs generated in this latter condition are impaired in their function, in particular in their ability to induce activation of T cells. Moreover, incubation of MSCs with mature DCs has been demonstrated to favor *in vitro* the induction of regulatory antigen presenting cells (APCs), through which they could indirectly suppress T-cell proliferation [46,47].

Conflicting results have been published on the ability of MSCs to interfere *in vitro* with B-lymphocyte function/proliferation, although the majority of reports suggest that B-cell proliferation, as well as differentiation and expression of cytokines, are inhibited by MSCs [48,49]. Human MSCs have been demonstrated to suppress *in vitro* the proliferation of B cells activated with anti-Ig antibodies, soluble CD40 ligand and cytokines, as well as to interfere with differentiation, antibody production and chemotactic behavior of B lymphocytes, through a block of B cells in the G0/G1 phases of the cell cycle [48]. In contrast with these observations, Traggiai et al. reported that BM-derived MSCs were able to promote proliferation and differentiation into Ig-secreting cells of transitional and *naive* B cells isolated from both healthy donors (highly purified B-cell subsets) and pediatric patients with Systemic Lupus Erythematosus (SLE) [50]. In a recent paper including both healthy subjects and patients with either SLE or experiencing rejection after kidney

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