REVIEW

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Mesenchymal stromal cells: tissue engineers and immune response modulators

Lieke C. J. van den Berk, Carl G. Figdor and Ruurd Torensma

Department of Tumor Immunology, Nijmegen Centre for Molecular Life Sciences, Nijmegen, the Netherlands

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Abstract

Mesenchymal stromal cells (MSCs) show significant immune-suppressive properties both *in vitro* and *in vivo*. Based on their immune-stealth properties, allogeneic MSCs are used to treat several diseases, for example the injection of MSCs in infarcted heart tissue or their use in bone-cartilage regeneration. The most spectacular treatment was recently described. MSCs were able to down-regulate the severity of graft-versus-host disease, leading to an impressive 20 to 50% increase in the two-year survival of bone marrow transplantation patients. Here the current literature is reviewed to elucidate the different mechanisms involved in these two clinical treatment modalities of MSCs.

Key words: MSC, T cell proliferation, DC differentiation and maturation, transplantation, immunomodulation, GVHD.

Abbreviations: BM – bone marrow, CTL – cytotoxic T lymphocyte, DC – dendritic cell, GVHD – graft-versus-host disease, HGF – hepatic growth factor, IFN-γ – interferon-γ, IL – interleukin, MHC – major histocompatibility complex, MI – myocardial infarction, MSC – mesenchymal stromal cell, NK – natural killer, TGF-β – transforming growth factor-β.

Corresponding author: Ruurd Torensma, Department of Tumor Immunology, Nijmegen Centre for Molecular Life Sciences, Nijmegen, the Netherlands, e-mail: r.torensma@ncmls.ru.nl

INTRODUCTION

Mesenchymal stromal cells (MSCs) were initially described by Friedenstein in 1970 [18]. Although previously named "mesenchymal stem cells", most plastic adherent bone marrow (BM) cells do not meet the established stem-cell criteria. As such, these cells have recently been reclassified as multipotent mesenchymal stromal cells and defined according to phenotype, growth, and differentiation characteristics [16]. MSCs were originally isolated from adult BM with frequencies ranging between 0.01 and 0.001% of BM cells [9]. However, subsequent studies showed that MSCs can also be obtained from a variety of other tissues, among which are peripheral blood, umbilical cord blood, fat, and placenta [25]. MSCs from BM and other tissues possess unique immunological characteristics that make them very attractive for potential clinical applications [1, 5, 30, 47, 48].

IMMUNOSUPPRESSIVE EFFECTS OF MSCs

MSCs are not inherently immunogenic because human MSCs do not constitutively express major histocompatibility complex (MHC) class II antigens or the T cell costimulatory molecule B7. Furthermore, it is well established that MSCs can inhibit T cell proliferation induced by allogeneic cells *in vitro* and mediate a systemic immunosuppressive activity *in vivo* [5, 14, 27]. Although the immunosuppressive role of MSCs is extensively studied, the underlying mechanism is still unclear. Table 1 depicts the cells affected by MSC. Both direct cell-cell contact and soluble factors that act on T cells are reported to cause the immunomodulatory function of MSCs. Several reports describe the influence of soluble factors produced by the MSCs which mediate the suppression of T cell proliferation. Amongst others, these mainly include PGE2 [1], hepatic growth factor (HGF) [14], transforming growth factor

Table 1. Immune cells targeted by MSCs

Cell type	Observed effect
T cells	Inhibition of proliferation
Dendritic cells	Inhibition of differentiation, maturation, and function
Cytotoxic T cells	Inhibition of formation
B cells	Stimulation of proliferation

(TGF)-β [14], interferon (IFN)-γ [26], interleukin (IL)--10 [36], LIF [36], HLA-G [37], and indoleamine 2,3--dioxygenase (IDO) [34]. In contrast to these studies that support a central role for soluble factors in immunosuppression by MSCs, others suggest that cell-cell contact is more important [7, 42]. Even others conclude that MSCs exert their immunosuppressive effects both through soluble factor(s) and cell-cell contact and that T lymphocytes and MSCs are mutually inhibitory on their respective proliferation [50]. Yet another study explains the mechanism by which MSCs inhibit T cell proliferation by down-regulating cyclin D2 expression without interfering with early T cell activation [19]. Analysis of the cell cycle showed that T cells stimulated in the presence of MSCs were arrested at the G1 phase. Removal of MSCs and restimulation of the T cells did not restore proliferation, which is fully consistent with that observed in division arrest anergy.

Recent data have demonstrated that the ability of MSCs to inhibit T cell proliferation is independent of the MHC, as both autologous and third-party MSCs exerted an immunomodulatory effect [5, 32]. Additionally, Le Blanc et al. [31] showed that whereas MSCs have multiple differentiation characteristics, neither undifferentiated nor differentiated MSCs elicited alloreactive T lymphocyte-proliferative responses. Chen et al. [11], however, showed that chondrogenic differentiation, but not osteogenic and adipogenic, does alter the immunosuppressive property of MSCs and that this effect is partially due to the up-regulated expression of B7 molecules.

MSCs INHIBIT DIFFERENTIATION, MATURATION, AND FUNCTION OF MONOCYTE-DERIVED DENDRITIC CELLS

Dendritic cells (DCs) are the most potent antigen--presenting cells (APCs) specialized in the uptake, transport, and presentation of antigens and have the unique capacity to stimulate naïve and memory T cells [3]. DCs exist in at least two different stages: immature and mature. Depending on their activation and maturation stage, DCs play a key role in the initiation of primary immune responses and tolerance [4]. Immature DCs behave as sentinels in peripheral tissues, possessing a high ability in antigen uptake and and a low ability in T cell stimulation. Maturation from an antigen-capturing to an antigen-presenting mode is promoted by locally produced inflammatory cytokines or microbial components. This is characterized by the up-regulation of the MHC and co-stimulatory molecules and the production of IL-12. The sessile immature DCs attain a migratory status which allows them to migrate with their antigen cargo to lymphoid tissue. DC maturation is a prerequisite for inducing immunogenic T cell responses, whereas tolerance is observed when antigens are presented by immature or semi-mature DCs [33]. Although the effects of MSCs on T cells have been extensively studied, their effects on the initiators of immune responses, the DCs, have remained relatively unknown. Therefore, a number of recent studies have focused on the influence of MSCs on DC function [7, 15, 17, 23, 24, 38, 51]. Zhang et al. [51] first described the effects of MSCs on the development of DCs. They showed that MSCs significantly inhibited monocyte differentiation into DCs by preventing the up-regulation of CD1a, CD40, CD80, CD86, and HLA-DR expression during differentiation. During the maturation process, MSCs significantly prevented the up-regulation of CD40, CD83, and CD86 and reduced the secretion of IL-12. Furthermore, cells exposed to MSCs during either differentiation or maturation poorly induced T cell proliferation. In summary, combining data from all the studies mentioned above we can conclude that MSCs influence monocyte differentiation towards immature DCs and that they disrupt the three major functions that characterize the transition of DCs from immature to mature stages, namely 1) up-regulation of the expression of antigen presentation and co-stimulatory molecules, 2) the ability to present antigens, and 3) the capacity to migrate towards the lymph node-derived chemokine gradient. Interestingly, chondrogenically differentiated MSCs promote DC maturation, causing higher CD83 expression in DCs, whereas osteogenically and adipogenically differentiated MSCs, like undifferentiated MSCs, showed an inhibitory effect on DC maturation [11]. In addition, Rasmusson et al. [43] studied the effect of MSCs on other cell types, such as cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells. Their findings demonstrated that MSCs escaped recognition by CTLs and alloreactive NK cells and inhibited the formation of cytotoxic T cells by secreting a soluble factor.

Thus far, the mechanisms of MSC modulation of DC maturation have yet to be elucidated fully. Studies by Djouad et al. [15] have demonstrated a role of IL-6 in MSC modulation of maturation marker expression. A possible role for IL-6 had also been alluded to by Nauta et al. [38] and English et al. [17], who found that MSC-derived IL-6 prevented up-regulation of DC maturation marker expression, while HGF and TGF-β did not. These data concerning MSC modulation of DCs therefore seem in contrast to MSC modulation of allo-antigen-driven responses as discussed in the previous section, indicative of different mechanisms involved. Additionally, some investigators put forward that direct contact between DCs and MSCs plays a more important role during the differentiation and maturation of DCs rather than the action of cytokines, since the addition of MSC supernatants, thus lacking a physical MSC-DC interaction, does not influence DC differentiation [51].

In the end these data support the hypothesis that MSCs influence host immunity by modulating DC function, suggesting that injection of allogeneic MSCs does not require profound immunosuppression during clinical application.

APPLICATION OF MSCs IN TRANSPLANTATION STUDIES

MSCs are not only able to evade the immune system and suppress immune responses directed against third-party cells, they can even induce tolerance towards other tissues of the same origin when transplanted following intravenous infusion of MSCs [5]. Studies conducted in both human and animal models have demonstrated that MSCs are capable of long-term engraftment and multilineage differentiation *in vivo* [21, 39]. Allogenic MSC transplantation also has a therapeutic effect in acute myocardial infarction (MI) [22]. Despite the low immunogenic profile of MSCs *in vitro*, rendering them ideal and promising candidates for transplantation studies, one still has to be cautious in using MSCs for allogeneic transplantation studies without immunosuppression [41]. Transplantation of a complete donor heart often leads to rejection by the recipient; therefore it has to be ascertained that allogeneic MSCs differentiated into cardiomyocytes are not rejected as well. In a series of papers describing MSC injections in patients suffering from MI, only very low numbers of the injected cells could be traced back [22, 35]. Immune rejection could be one explanation of the observed low numbers of MSC-derived cardiomyocytes after injection. Most studies on MSC injection in MI show improvement in left ventricle function, but those benefits disappear in time. No significant contribution to long-term functional improvement was seen nor did the injected MSCs contribute to new cardiomyocyte formation [13]. More and more data are becoming available attributing the initial benefit of MSC injections to the local production of angiogenic factors such as VEGF [10, 20]. In addition, less fibrosis is observed in MSC-treated hearts [6]. Thus far, no clear conclusions can be drawn about MSC injections in infarcted hearts.

Since the live span of MSCs seems to be limited, more potent cells that also have stem-cell properties should be considered [45]. Unseparated BM cells can contribute to tissue cells, as was seen in female patients who underwent BM transplantation. Up to almost 50% of their endometrium cells were of donor origin. A possible explanation is that the environmental cues that drive proper differentiation are still intact in endometrium, while those cues are heavily disturbed in an infarcted heart, where fibrosis and low oxygen tension occurs. In conclusion, further research is necessary before any meaningful clinical application can be envisioned with allogeneic MSCs.

Graft-versus-host disease (GVHD) is a life-threatening complication of allogeneic BM-transplantation in which functional immune cells in the transplanted marrow recognize the recipient as "foreign" and mount an immunological attack. MSCs can successfully treat ongoing GVHD [2, 29, 44], presumably due to their ability to suppress donor T cell proliferation, although little is known about the potential of MSCs to prevent GVHD. A recent study shows that when IFN-γ-treated MSCs were given at the time of BM transplantation, activated MSCs could prevent GVHD mortality (100% survival, $p=0.006$) [40]. Recently, the results of a multicenter phase 2 study using MSCs in 55 patients with severe and steroid-resistant acute GVHD were published [28]. They found that infusion of *in vitro* expanded MSCs, irrespective of the donor, might be an effective therapy for patients with GVHD since more than half of the patients responded well to treatment with MSCs. Whether the cell donor was HLA matched or unmatched did not influence the outcome of this treatment. This suggests that third-party cells can be prepared and stored frozen to be used for GVHD treatment. Importantly, MSCs also positively influence the proliferation and differentiation of B lymphocytes into immunoglobulin-secreting cells. This raises critical questions on the potential use of MSCs in autoimmune diseases in which B cells play a crucial role [46].

MSCs show immune-suppressive properties *in vitro* as well as *in vivo*. Though this property is undisputed, the mechanism involved is not yet clear. Possible reasons for these different data sets are 1) the heterogeneity of MSCs [8], 2) the different culture protocols that could select for certain subtypes [49], and 3) the number of population doublings that occurred before testing [12].

In conclusion, MSCs behave as modulators of the immune system, acting not only directly on T cells, but also at the initial step of the immune response through inhibition of DC differentiation, maturation, and function. Since DCs play a very important role in the body's immune system, it seems likely that by suppressing DC function, be it by hampering antigen uptake, processing, or presentation, the likelihood of graft rejection could be significantly reduced. More valuably, the effects of MSCs on DCs are reversible, which will circumvent the flaws of the long-lasting immune deficiency following transplantation.

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