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Chapter 9

Role of Bone Marrow Derived Mesenchymal Stem Cells in Management of Graft Versus Host Disease

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1. Introduction

Human bone marrow stromal cells, referred as mesenchymal stem cells (MSC) are multipotent unspecialized cells localized in the medullary stroma [1,2]. They have a capacity for self-renewal and differentiation into multiple cell lineages [3-6].

Mesenchymal and tissue stem cell committee of the International society for cellular therapy proposes minimal criteria to define human MSCs. First, MSCs must be plastic-adherent when maintained in standard culture conditions. Second, MSCs must express CD105, CD73 and CD90, and lack the expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules. Third, MSCs must be capable to differentiate into osteoblasts, adipocytes and chondroblasts in vitro [7,8]. In the hand of Delorme B and Charbord P, MSCs can be defined phenotypically with a minimal set of markers as CD31-, CD34-, and CD45-negative cells and CD13, CD29, CD73, CD90, CD105, and CD166 positive cells [9]. MSCs have been used in cell-based therapy in various disease conditions. Experimental evidence and preliminary clinical studies have demonstrated that MSCs, have an important immunomodulatory function in the management of allogeneic hematopoietic stem cell (HSC) transplantation [10,11]. These immunomodulatory effects have been demonstrated in various species, including humans, rodents, and primates and show clinical promise for the treatment of graft versus host disease (GVHD) and graft failure management. In this chapter we will discuss current research finding.

2. General background

2.1. MSC administration

2.1.1. Safety and therapeutic methods of MSC administration

The extensive capacity for expansion in vitro at clinical scale has recently facilitated the development of clinical trials designed to assess safety, feasibility, and efficacy of transplanting MSCs for a variety of diseases [11]. There was no toxicities related to the infusion of expanded autologus MSCs into patients with advanced breast cancer or with haematological malignancy, into hurler syndrome patients and into patients of metachromatic leukodystrophy [12,13].

MSC could be delivered systematically and locally. Systemic delivery circumvent the problems such as tissue damage and unsuitability of delivering multiple doses. Site specific delivery has the advantage of delivering large numbers of cell directly to the required sites. Majority of studies showed that MSC infused systematically homed to injured tissues [14,15].

Successful systemic delivery of MSC is dependent upon efficient homing of the cells to the required sites. In this respect, migration of MSC from the circulation into damaged tissues leading to therapeutic effect s has been documented [16]. Ability of MSC to home to bone marrow (BM) can be affected by in vitro culture, which could be due to decrease of adhesion molecules and Chemokine receptors [17].

2.2. Mechanism of homing of MSC

Homing of leukocytes to inflammatory sites involve selectin, chemokines, integrins and other adhesion molecules [18]. Hemopoietic stem cells (HSC) recruited from blood vessels on similar process to that of leucocytes [19]. MSC recruited to damaged tissues. It is a fair assumption to suppose that they utilize comparable mechanisms of recruitment of MSC. P-selectin play an important role in the trafficking of MSC [20]. MSC roll upon endothelial cells as the first stage in their recruitment. Chemokine receptors are expressed on the cell surface of MSC [21] and their stimulation has been shown to induce cell migration and directing MSC.

2.3. Transplant ability, engraftment and tracking of MSC

Numerous studies have demonstrated migration and multiorgan engraftment of MSCs both in animal models and in human clinical trials. [22-24].

Direct injection of human marrow stromal cells into the corpus striatum of rat brain showed engraftment of 20% of the infused cells [25]. Rat bone marrow stromal cells infused into briefly distally occluded ascending aorta migrated after 8 weeks in the scar and periscar tissue [26]. MSCs injected intravenously into irradiated primate had the ability of engraftment in different injured tissues as the bone marrow, skin, digestive tract and muscle [9,11]. In rat model, MSC engrafted in multiple organs such as lung, liver, kidneys and spleen.

Human MSCs engrafted and demonstrated site-specific differentiation in sheep [27,28] and in murine models [29-31]. The capacity of engrafment of MSCs was not influenced neither by the

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route of administration nor by the difference in conditioning protocols [32]. Clinically, both autologous or allogeneic MSCs were given to patients [33, 34]. Allogeneic HLA-mismatched male fetal MSCs injected into HLA-incompatible female fetus with osteogenesis imperfecta (OI) engrafted and differentiated into bone [35]. Haploidentical MSCs had a low level of engrafment in a patient with aplastic anemia, however there was a partial restoration of bone marrow microenvironement [36]. In contrast, Infused allogeneic MSCs did not expand significantly in patients and they originate from the host [34, 37]. It is of interest to know into which organs MSCs home. Allogeneic and autologus MSCs distributed to a wide range of tissues in baboons [22].

2.4. Transformation of MSCs

MSCs transformed in vitro. The transformation of MSCs is associated with chromosomal abnormalities, increased levels of telomerase activity and c-myc expression [38]. Human MSCs isolated from adipose tissue undergo spontaneous transformation after long-term culture (4-5months) [39]. Others found that short-term culture was sufficient for the transformation of murine MSCs into a cell population with autonomous growth and biological characteristics of osteosarcoma [40]. In contrast, even long term cultures could not induce MSC transformation [41]. Previous study reported that gastric cancer could originate from BM-derived cells, presumably MSCs [42]. Human BM-MSCs cultured extensively, with a high Telomerase activity is capable of forming solid tumors in multiple organs in mice [43].

MSCs could migrate towards primary tumors and metastatic sites. Chemokines secreted by MSCs have been shown to enhance the emergence of pulmonary metastases and such secretion has a strong interaction between breast cancer cells and MSCs. In addition, MSCs have also been found to play a role in drug resistance in various cancer cells. MSCs protect chronic lymphocytic leukemic cells from fludarabine-, dexamethosone-, and cyclophosphamide-induced apoptosis. MSC non-selectively protected chronic myeloid leukemia cells from imatinib-induced apoptosis. [44].

Indeed, the transformation potential in cultured MSCs must be documented before considering infusion of these cells into patients. However, this issue remains controversial, as other studies did not observe transformation of human BM-MSCs.

In conclusion, it is possible that the way MSCs are expanded and long term culture lead to transformation. The safety of using MSCs in humans remains open. The use of MSCs in patients should definitely require precise and limited procedures of expansion to avoid the risk of injecting transformed cells. These finding emphasize the need for accurate studies aimed at investigating the bio safety of these cells

2.5. MSCs and metastasis

So far, very few studies have addressed the question of the effects of MSCs on metastasis. A few studies have supported that MSCs may suppress tumor growth while others believe that MSCs may contribute to tumor protection via antiapoptotic effect, tumor progression, metastasis, and drug-resistance of cancer cells.

Human MSCs played a dual role in tumor cell growth *in vitro* and *in vivo*. It was found that human MSCs inhibited the proliferation of cancer cell lines and caused G1 phase cell cycle arrest and apoptosis *in vitro*. However they enhance tumor formation and growth *in vivo*. MSCs have also been found to prevent apoptosis of acute myeloid leukemia cells by up-regulation of antiapoptotic proteins [44].

The main adverse role of MSCs was its pro-invasive potential [45]. It is likely that other molecules participate to the enhancement of metastasis by MSCs and this will be the challenge of future studies.

To use MSCs in anti-cancer therapies, it will be essential to identify the factors produced by MSCs cells responsible for the inhibition or the enhancement of tumor growth and those governing the response of tumor cells.

Evaluation of the potential use of MSCs in cell-based anti-cancer therapies is just starting. These cells have shown some promise as several studies have reported that a portion (which remains to be defined) of MSCs is able to migrate to the tumor site. However, this homing of MSCs is not selective and it will be important to evaluate possible side effects in organs, which are not affected by the disease. Overall, MSCs represent great hope for cancer therapies, but a thorough evaluation of their potential risk will be pre-required step [46].

3. Immunological characteristics of MSCs

Studies in animal models and in humans demonstrated that co-transplantation of HSCs along with MSCs obtained by ex-vivo expansion enhance hematopoietic reconstitution [47,48]. Experimental and clinical studies demonstrated the safety and immunosuppressive role of MSCs infusion [49, 50].

3.1. Immunological characteristics of MSCs *in vivo*

It has been demonstrated since 1984 that reconstitution of irradiated host with T-cell depleted bone marrow containing both host (syngeneic) and donor (allogeneic or Xenogeneic) components leads to long-term survival of the reconstituted animals and specific prolongation of subsequent skin grafts of donor type. However these animals are fully reactive to third-party allograft and do not appear to manifest signs of graft-versus-host disease (GVHD) [51]. The possibility of the presence of immunomodulatory cells in bone has been noticed after donor specific long-term hypo responsive status obtained by transplantation of bone and HSCs in murine models [52, 53]. MSCs constitute the stromal scaffold which is close to the endostenum and interact tightly with HSCs [54]. They contribute to the formation of HSCs niche, support HSCs engraftment and survival of blood cells in vivo [11]. This indicate the presence of underlying immunomodulatory effect of MSCs.

http://dx.doi.org/10.5772/55013

3.1.1. MSCs immunosuppressive effect in experimental animal models

Various animal models have been used to study the immunomodulatory effects of MSCs in treatment of GVHD, autoimmune disorders and tumor immunity. It seems to be that early and repeated injection of MSCs following HSCs transplantation is primordial to control GVHD [55, 56]. In autoimmunity model only early and re-injection of MSCs at the peak of the disease were effective as compared to injection after disease stabilization [57]. MSCs do not elicit immunological reaction in recipients [49, 56]. MSCs play tolerogeneic effect in recipients [58-60]. However, MSCs had been rejected by mismatched recipients [61] and failed to prevent GVHD [56].

3.1.2. MSCs immunosuppressive effect in humans

In the field of HSC transplantation, there are two applications of MSCs:

- Improvement of stem cell engrafting and the acceleration of hematopoietic reconstitution based on the hematopoesis-supporting ability.
- Treatment of severe GVHD based on the immunomodulatory ability.

3.1.2.1. Role of MSCs in support of hematopoiesis

MSCs constitute the functional and structural support of medullary hematopoiesis by providing growth factors and extracellular matrix [62, 63]. MSCs have a positive impact on hematopoesis and results in rapid hematopoietic recovery [64].

Co transplantation of HSCs and haplotype-mismatched MSCs to patients with high-risk acute myelogenous leukemia result in rapid engraftment [65]. Co transplantation of allogeneic MSCs and multidonor umbilical cord blood (UCB) correlated with a higher overall level of engraftment into NOD/SCID mice [66]. In European phase I-II study co-infusion of haploidentical HSCs and MSCs accelerated leukocyte recovery as compared to control group [67]. In multicentre clinical trial, co transplantation of MSCs with an HLA-identical sibling HSCs after a myeloablative conditioning regimen induced hematopoietic recovery of peripheral mono nuclear cells (MNC) and platelets [68, 69] and resulted in fast engraftment of absolute neutrophils count and 100% donor chimerism [69]. Transplantation of MSCs into immunosupressed patients generated neither alloantibody against MSC nor against fetal calf serum (FCS) [70].

3.1.2.2. Role of MSCs in management of graft versus host disease (GVHD)

Injection of MSCs could cure severe graft versus host disease (GVHD) and promote hematopoietic recovery.

MSC-mediated inhibition of immune response is a complex mechanism involving changes in the maturation of antigen-presenting cells and in cytokine secretion profiles as well as the suppression of monocyte differentiation into dendritic cells [71]. They exert profound immunosuppression by inhibiting T-cell proliferation in response to various stimuli in vitro. They induce regulatory immunosuppressive lymphocytes and CD8 apoptosis. MSCs inhibit cell cycle progression and CD4 allo-proliferation. This immunosuppressive effect of MSCs is mediated through several inducible soluble factors [71].

3.1.2.3 Clinical trials of GVHD management by MSCs

Patients treated with MSCs had less GVHD and less toxicity in a retrospective study comparing allograft of geno-identical HSCs with and without MSCs [72]. No acute side effects occurred after the infusion of haploidentical and mismatched MSCs from unrelated donors into patients suffering from GVHD [50, 73]. Haploidentical MSCs was used to treat grade IV GVHD of the gut and liver that was resistant to conventional treatment. The aim was to use the tissue repair effect shown in vivo in animal models, and the immunomodulatory effects seen in vitro on human lymphocytes. The clinical response was striking with normalization of stool and bilirubin on two occasions. They leads to healing of damaged bowel epithelia [50]. The patient was highly immunosupressed. However, his lymphocytes continued to proliferate in response to lymphocytes of MSCs donor in vitro in several occasions. This could indicate an immunosuppressive effect of MSCs rather than tolerance induction. We would be able to prevent GVHD after MSCs infusion and maintaining in the same time the response of host lymphocytes against alloantigens. Infusion of MSCs into 8 patients with steroid refractory GVHD cause dramatical disappearance of all symptoms and repaired gut in six patients and liver in one. The survival curve was better than that of 16 patients with steroid-resistant biopsy-proven gastrointestinal GVHD, not treated with MSCs [245]. MSCs were used to treat 40 patients with acute and chronic GVHD. More than forty-seven (47.5 %) showed complete response, 22.5 % showed improvement, 10 % had stable disease and 17.5 % had no response. Between 6 weeks up to 3.5 years after transplantation more than half of patients are alive [73].

At the same time of hematopoietic stem cell transplantation (HSCT), 46 patients received culture-expanded MSCs from their HLA-identical sibling donors [74]. Moderate to severe acute GVHD was observed in 13 (28%) of 46 patients. Chronic GVHD was observed in 22 (61%) of 36 patients and 2-year survival was 53%. No MSC-associated toxicities were seen. Stromal cell chimerism was demonstrated in 2 of 19 examined patients at 6 and 18 months after transplantation. MSCs are safe to give, but are difficult to detect after infusion, even in immunocompromised patients who have undergone HSCT [75].

Ten patients undergoing HSCT were treated with MSCs due to tissue toxicity. In five patients, severe hemorrhagic cystitis cleared after MSC infusion. Gross hematuria disappeared after a median of 3 days. Two patients with grade five hemorrhagic cystitis had reduced transfusion requirements after MSC infusions, but both died of multi-organ failure. MSC donor DNA was demonstrated in the urinary bladder in one of them. Two patients were treated for pneumomediastinum, which disappeared after MSC infusion. A patient with steroid-resistant GVHD of the gut experienced perforated diverticulitis and peritonitis that was dramatically reversed twice after infusion of MSCs[76].

In Europe, 55 patients have been treated for steroid-resistant acute GVHD with an overall response rate of 69%. Non responders have died of progressive GVHD and several responders have died from infections with an overall survival of 23 of 55 (42%) from 2 months to 5 years. Although the experience is limited, MSCs seems a promising treatment for severe steroid-resistant acute GVHD [73].

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In a phase I/II clinical trial, ten percent of patients treated for acute refractory GVHD obtained a complete response, 60 % had a partial response and 30 % did not respond. They found that 50% of patients with chronic refractory GVHD did not respond, 12.5 % had complete remission and 37.5% had partial response [77]. Transplantation of MSCs into 15 patients with haematological malignancies was safe and induced complete remission [78].

These preliminary data suggest that MSCs may also play a role in repairing severe tissue toxicity. It seems to be that there is beneficial effect of MSCs infusion in humans. However, The optimal MSCs dose and frequency of administration needed to be evaluated to control GVHD.

The underlying molecular mechanisms of immunosuppression in vivo are unknown. It has been demonstrated that MSCs engrafted to injured tissues rich on inflammatory cytokines [107]. MSCs inhibitory effect is inducible [79] and presence of MSCs in such media could explain partially the beneficial effect of MSCs infusion in the recipients, despite non detectable MSCs in recipients BM.

3.2. Suggested mechanisms for MSC immunomodulatory effect

Co-culture of MSCs with allogeneic lymphocytes failed to stimulate their proliferation, indicating that these cells are innately not immunogeneic. Recent reports suggest that MSCs have immunomodulatory properties and can inhibit lymphocyte antigen presenting cells, natural killer cells, and cytotoxic lymphocyte proliferation in mixed-lymphocyte reactions (MLR). MSCs inhibit CD2, CD4 and CD8 subsets of T lymphocytes. The immunosuppressive effect of human MSCs was higher in cultures with cell contact than in cultures without contact (transwell), and the difference was statistically significant [80, 81]. MSCs produce a variety of growth factors that are likely to play a role in immunomodulation. Human and murine MSCs do inhibit the proliferation of lymphocytes in MLR by soluble factors [80-83]. Indoleamine 2,3 dioxygenase (IDO) inhibit the alloreactivity induced by antigen presenting cells (APC) [84]. The inhibitory effect of MSCs on alloreactivity seems to be due to other mechanisms rather than apoptosis of lymphocytes. Several studies demonstrated reversibility of MSCs inhibitory effect. [81, 85, 86].

Cell anergy is a state of immune unresponsiveness, defines the inability of an immune cell to mount a complete response against its target. MSCs induce anergy due to divisional arrest of T cells. IFN-γ production but not proliferation of murine cells was restored [87]. Restoration of CD4+ cell proliferation but not CD8+ cells after the removal of human MSCs was observed. For the time being we could assume that MSCs do induce anergy [88]. MSCs induced regulatory cells [88]. Regulatory cells have been involved in the regulation of immune response.

Despite the expression of human leukocyte antigen (HLA) by MSCs, they were well tolerated without side effects in allogeneic hosts. Major Histocomaptability Complex (MHC) had no role in MSCs inhibitory effect as autologus and allogenic human [81], murine [89] and baboon [49]. MSCs were capable of inhibiting the proliferation of lymphocytes. In addition, Xenogeneic murine MSCs inhibited the proliferation of human cells [79]. However, one study showed that

transplantation of allogeneic MSCs resulted in rejection by class I and class II mismatched recipients in murine model [61].

The major effectors of the innate immunity are natural killer (NK) cells. They eliminate malignant and virus infected cells. MSCs alter the phenotype of NK cells and suppress proliferation and cytotoxicity against HLA-class I-expressing targets in time and dose dependent manner in cell contact or transwell cultures [90, 91].

Veto activity was defined by Miller [92] as the ability to induce specific suppression of cytotoxic T lymphocyte precursors (CTL-Ps) against antigens present on veto cell surface, but not against those on third-party allogeneic cells. MSCs had veto activity [93]. This is contradictory to all the present data where MSCs were able to inhibit the allo-response to allogeneic lymphocytes in MLR in different species [79, 81]. Even more, veto property contrasts with the proliferation of allogeneic lymphocytes observed in the presence of MSCs by the same team [93].

There was drastic reduction of the recipient's CTL response against injected class I antigens due to veto phenomenon [94]. These findings still keep on with Miller's definition [92]. Veto mechanism could play a role in low immunogenicity of MSCs, but certainly doesn't explain the suppression of allogenic lymphocytes by MSCs [71]. MSCs have no effect on the lymphocyte response to recall antigen [93].

Human MSC inhibited the pro--inflammatory Th1 cytokines (IFN-γ, TNF- α, IL-1α and IL-β) whereas the anti-inflammatory Th2 cytokines IL-3, IL-5, IL-10, IL-4 and IL-13 and the Th2 Chemokine I-309 (a chemo attractant for regulatory T cells) were increased [71, 95]. This could indicate a shift from the prominence of pro-inflammatory Th1 cells towards an increase in anti-inflammatory TH2 cells and support MSC inhibitory properties. MSCs can skew the dendritic cells (DCs) function, thus biasing the immune system toward Th2 and away from Th1 responses [96]. MSC had no effect on neutrophils phagocytosis, expression of adhesion molecules and chemotaxis [97]. This is an interesting finding, as MSCs could not interfere with neutrophils function. Summary of MSCs inhibitory effect is illustrated in figure-1. For further reading, about detailed description of possible MSCs inhibitory mechanisms, refer to this article [10].

3.2.1. Inhibitory effect of autogenic and allogenic MSCs

Allogeneic MSCs have stronger immunosuppressive effects than autologus MSCs [88]. Others found comparable and significant inhibition was elicited by autologus or allogeneic MSCs [81,85]. This could help in management of GVHD in cases where non-matched HSCs are used

4. What starts the first step in induction of inhibitory effect in MSC/Mixed lymphocyte reaction MLR?

It is not known for the time being whether MSCs or lymphocytes do start the first signals to activate the other one to induce the immunosuppressive effect. MSC supernatant failed to

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inhibit T-cell activation and, on the contrary, MSC supernatant had a stimulatory effect on MLR. Surprisingly, cell-free supernatant obtained from MLR had an inhibitory effect similar to that seen with the addition of MSCs [58]. In agreement Djouad et al. found that only MSC conditioned supernatant by lymphocytes was capable to inhibit secondary MLR but less efficiently than the co-culture of cell partners, in indicating that the immunosuppressive properties of MSCs are mediated by inducible soluble factors and the interaction between the MSCs and lymphocytes is a pre-requirement for MSC mediated inhibitory effect [79].

In addition, an enhancement of the MSC immunosuppressive effect was observed after addition of irradiated third party MNC to MSC culture, indicating that the physical interaction between MSC and PBMC increase the suppressive activity [98]. Human MSCs do not constitutively express IDO. But activation by IFN-γ secreted by allogeneic lymphocytes in a dose dependent manner is required for induction of functional IDO activity [99].

It has been demonstrated that auto reactive cells may induce the transdifferentiation of MSCs to neural stem cells. This phenomenon could be due to stimulation of cytokine production and generation of suitable environment that results in differentiation into neural stem cells [100]. All these data could confirm the interaction between MSCs and lymphocytes. Physical interaction between MSCs and T-cells increases the suppressive activity as there was an increased expression of IL-10 and TGF-β genes [80] as compared to non contact cultures. All these data could complicate the issue. Is MSC mediated inhibitory effect is a consequence of MSC activation by IFN-γ secreted by two allogeneic populations of lymphocytes in MLR?. Why there is no stimulation of single allogeneic PBL by allogeneic MSCs?

Are there two separate effector mechanisms, one to escape the immunological recognition and the other to inhibit the alloreactivity? Is the constitutive expression of TGF-β and HLA-G by the MSCs play a role in immunological escape?

Maccario et al. had demonstrated the absence of regulatory cell in co-culture of MSCs with single allogeneic PBMCs as compared to the presence of MSCs in MLR [88]. This could indicate that allogeneic lymphocytes initiate the first signals to stimulate the production of molecules that induce the production of regulatory cells.

It has been found that CD14+ monocyte are the PBMC subpopulation, being responsible for MSC activation through IL-B secretion [101]. MSC inhibitory effect was mediated through CD8+ in human and murine model [97, 88]. CD8+ cells are the executive cells for MSC inhibitory effect rather than being the inducers of MSC inhibitory effect. It has been demonstrated that MSC inhibitory mechanisms differ depending on nature of stimulus [102]. This could indicate that alloantigens or mitogen are responsible for the first stimulating signals in MLR, or at least they are responsible for later on modification of these signals. It has been found that lymphocytes and MSCs are mutually inhibitory on their respective proliferation and indicate the bi-directional interaction and cross talk between lymphocytes and MSCs [103, 104]. More recently, it has been found that IFNγ and concomitant presence of TNFα or IL-1α or IL-1β induce the expression of several chemokine and inducible Nitric oxide synthase by MSCs [105].

This could indicate that lymphocytes start the first signals for MSCs activation, however cross talk between both of them are essential to have the full immunological effects.

In conclusion, MSC must be handled with extreme caution before a large scale clinical trial is performed. it has been found in a pilot clinical study, that co transplantation of MSC and HSC prevent GVHD, but caused a higher relapse rate in hematologic malignancy patients as compared to control [106].

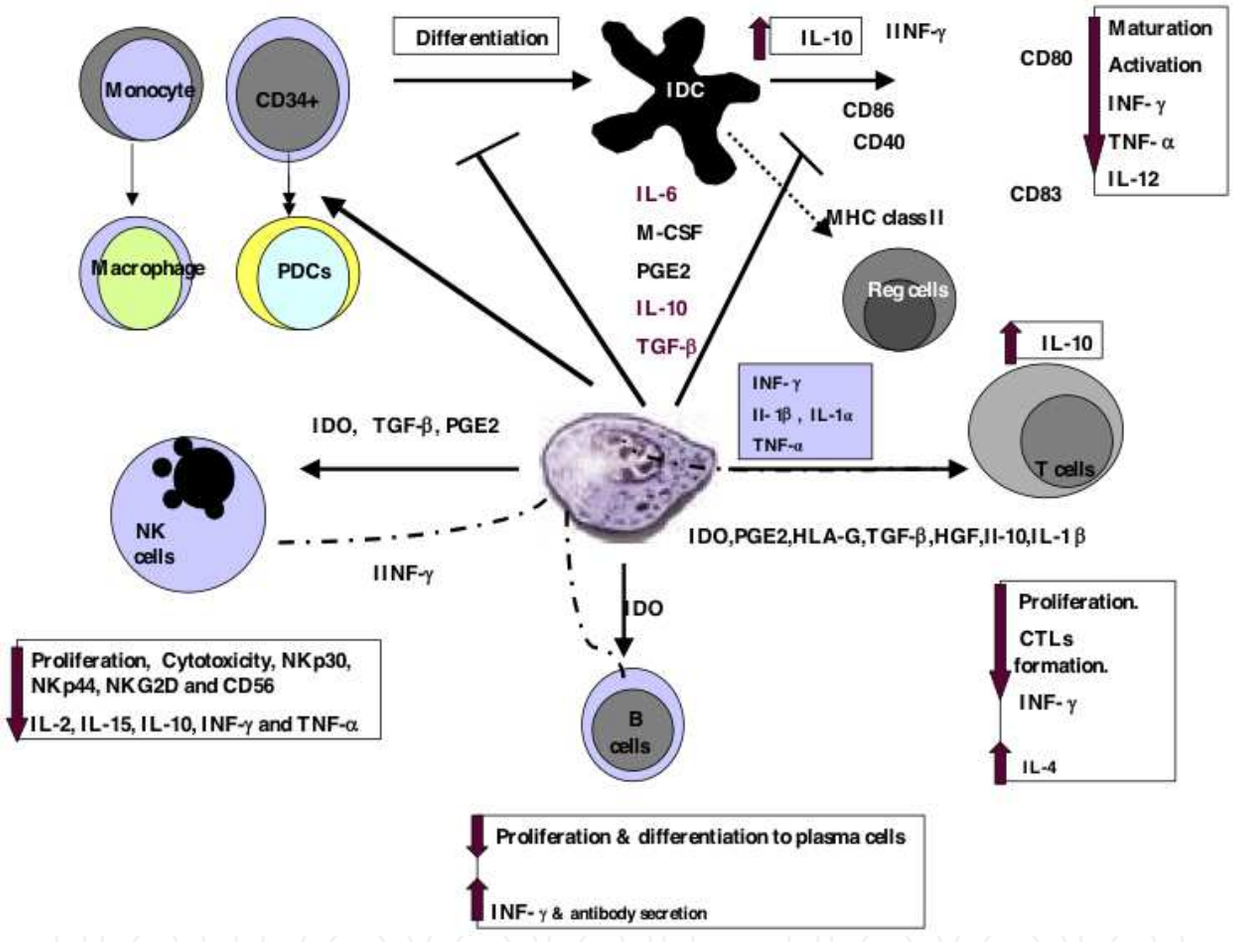

Figure 1. Mechanisms of action of MSCs upon dendrietic, lymphocytes T, lymphocytes B and natural killer cells.

MSCs inhibit monocytes (MO) differentiation into immature DCs (IDC) and skewed them toward macrophage. MSCs reduced percentage of CD34(+) derived IDC and increased plasmacytoid DC (pDC). They inhibit maturation IDC into mature DCs. They inhibit the regulation of HLA-DR, CD80, CD86, CD1a, CD40, CD14 and CD83 antigen on DCs surface through IL-6, M-CSF, PGE2, IL-10 and TGF- b secretion. MSCs increased production of IL-10 and decreased production of Il-12, TNF-a and INF-g by DCs. MSCs induced DC that exhibit a suppressor phenotype (supp APC) and generated alloantigen-specific regulatory cells (Reg cells). MSCs inhibit NK proliferation and change cytokines secretion pattern through IDO, TGF-b, PGE2. MSCs inhibit lymphocytes B Proliferation & differentiation to plasma cells

through IDO. MSCs inhibit lymphocytes T proliferation and cytotoxicity through IDO, PGE2, HLA-G, TGF-b, HGF, Il-10 and IL-1 b.

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