

## Mesenchymal Stem Cells: The New Immunosuppressants?

Varun Dhir

### ABSTRACT

Mesenchymal stem cells are adult stem cells which can differentiate into cells of mesodermal lineage—osteoblasts, chondroblasts and adipocytes. They have an important property of immunosuppression which is mediated mainly through soluble mediators, like interleukin-1, transforming growth factor- $\beta$ , nitric oxide, indoleamine 2,3 dioxigenase, etc. They have been shown to suppress both naïve and antigen experienced T cells, lead to T cell arrest, and suppress Th1 and Th17 responses. They have also been shown to lead to development of tolerogenic dendritic cells, Th2 response and expansion of T regulatory cells. Importantly, MSCs are cells with a low immunogenic potential and hence have been used both in allogenic as well as xenogenic settings. MSCs have shown efficacy in suppressing the development of autoimmune disease in various animal models, like collagen induced arthritis, MRL-lpr mice, EAE mice, etc. They have been used in small human studies, some of which have shown benefit like in systemic lupus erythematosus. Also, they have been used in graft-versus-host disease in humans with promising results. However, a single randomized controlled trial has been done and, thus, their current status remains investigational. It is hoped that they may become part of the armamentarium to control and abberant or excessive immune reponse.

**Keywords:** Mesenchymal stem cells, Immunosuppression, Autoimmune disease, Adult stem cells.

**Key messages:** (1) Mesenchymal stem cells (MSCs) are adult stem cells that can differentiate only in one lineage (mesodermal). (2) They were first discovered in the bone marrow and this remains a common source, followed by adipose tissue. There are other sources: Synovial fluid, umbilical cord blood, amniotic fluid, placenta, fetal liver. (3) MSCs are immunosuppressive, the mechanism of which is not fully elucidated, but involves action on other cells mainly through soluble mediators, like TGF $\beta$ , IDO, IL-1, NO, etc. (4) MSCs have shown efficacy in various animal models of autoimmune diseases. There have been small human studies, some of which showed benefit, however, a single randomized controlled trial has been done. (5) MSCs may have a role in autoimmune diseases refractory to treatment or as an add onto prevent treatment side effects.

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### INTRODUCTION

Mesenchymal stem cells are a type of adult multipotent stem cells found in a variety of tissues. They express stromal markers but not hematopoietic markers.<sup>1</sup> They can self renew and have lineage commitment, i.e. only differentiate

into cells of the mesodermal lineage, i.e. bone, cartilage and fat.<sup>2-4</sup> They are different from the embryonic stem cells which are totipotent, i.e. can differentiate into any tissue in the body, however, similar to other adult stem cells like hematopoietic stem cells, neural stem cells, intestinal stem cells that have limited differentiation capability. They were first discovered in the bone marrow as plastic adherent cells with a fibroblast like morphology.<sup>5-7</sup> Initially called ‘fibroblast precursors, the name mesenchymal stem cells was proposed later.<sup>8</sup> MSCs found in the bone marrow (BM-MSCs) comprise only about 0.001% of the bone marrow cells. Their main function in the bone marrow seems to be to provide the proper microenvironment to the hematopoietic stem cells. However, MSCs have also been isolated from other tissues as well, including the adipose tissue, skeletal muscle, umbilical cord, blood synovial fluid, dental tissues, palatine tonsil, amniotic fluid, Wharton’s jelly, fetal liver, etc.<sup>9</sup> The best characterized and usual source after the bone marrow is the adipose tissue.<sup>10</sup> There seem to be subtle differences among the MSCs from various sites. The morphology can vary from fibroblastoid to giant fat cells, spindle-shaped cells to small round cells.<sup>11</sup> Their immunosuppressive properties came to the fore, when they were found to suppress the alloantigen stimulated mixed lymphocyte reaction and also prevent the rejection of allogenic skin grafts with reduction in the production of proinflammatory cytokines TNF $\alpha$ , and IFN.<sup>12</sup> The international society for cell therapy has proposed a formal definition for mesenchymal stem cells.<sup>13</sup> A cell is defined as MSC if it fulfills the following criteria:

- Plastic adherence
- Expresses CD 90, CD105 and CD73 but does not express CD 34, CD14, CD11b, CD79 and HLA DR by flowcytometry
- Capable of differentiating into osteoblasts, chondroblasts and adipocytes.

However, although not part of the criteria, MSCs also usually express Stro-1, CD44 and CD71.<sup>14</sup> MSCs have low immunogenic potential and are ‘Immune privileged’ cells. They express low levels of MHC I, lack expression of MHC II and costimulatory molecules.<sup>14-16</sup> Thus, they can be used allogeneically and even xenogeneically. This fact has led to much expectation and excitement in their use, as a major problem with other cell-based therapy has been the limitation of crossing the HLA barrier.

## HOW DO MSCs MEDIATE IMMUNE MODULATION?

MSCs nonspecifically suppress both naïve and antigen experienced CD4 and CD8 T cells.<sup>17</sup> Activated T cells are arrested in the G0/G1 stage. They reduce IL-17 release by Th17 and IFN $\gamma$  release from Th1 effector cells,<sup>18,19</sup> but increase IL-4 secretion by Th2 cells.<sup>20</sup> MSCs lead to T regulatory cells (CD4 + CD25 + FoxP3+) expansion.<sup>18,20</sup> They inhibit the differentiation and antibody production by B cells.<sup>21</sup> They inhibit the immunostimulatory capacity of dendritic cells, leading to a more tolerogenic profile, and secretion of IL10.<sup>22,23</sup> They inhibit activation and expansion of natural killer (NK) cells.<sup>24</sup> They also reduce the levels of NK cell secreted cytokines, such as IFN, IL-10 and TNF.<sup>25</sup>

It has been proposed that a inflammatory environment leads to the development of suppressive ‘powers’ of MSC. Especially, the role of IFN $\gamma$  at an appropriate concentration seems important, which may lead to induction of IDO.<sup>26,27</sup> Also, stimulation of particular toll like receptors (TLRs), like TLR3 might promote an immunosuppressive MSC.<sup>28</sup> Immunosuppressive ‘powers’ of the MSC seem to be mainly related to soluble mediators. Various mediators have been found to be important (Table 1). These include interleukin-1 (IL-1), transforming growth factor (TGF $\beta$ ), hepatocyte growth factor (HGF), prostaglandin E2 (PGE2), indoleamine 2, 3 dioxygenase (IDO), heme oxygenase, nitric oxide (NO) and insulin like growth factor-binding proteins.<sup>29-33</sup> Indoleamine 2, 3-dioxygenase (IDO) is an enzyme that catabolizes the essential amino acid tryptophan to kynurenine, and both the depletion of tryptophan and the accumulation of the toxic product have been proposed to be responsible for the immunosuppressive action. However, which of these molecules is the most important is unclear. There also seems to be a role of cell-to-cell contact by MSCs

**Table 1:** Mechanism of action of MSC immunosuppressive effect

- Action on other cells:
  - Suppression of T cells: Naïve and antigen experienced, Th1 and Th17; Increase Th2
  - Suppression of B cell activation and antibody production
  - Suppression of immunostimulatory dendritic cells (DCs), induce tolerogenic DCs
  - Inhibit activation and expansion of Natural Killer (NK) cells
  - Expansion of T regulatory cells
- Soluble mediators:
  - Interleukin 1 (IL-1)
  - Transforming growth factor- $\beta$  (TGF- $\beta$ )
  - Hepatocyte growth factor (HGF)
  - Prostaglandin E2 (PGE2)
  - Indoleamine 2,3 dioxygenase (IDO)
  - Heme oxygenase
  - Nitric oxide (NO)
  - Insulin like growth factor-binding proteins

as the immunosuppressive effect is weaker in a transwell situation.<sup>34</sup> The T reg expansion may be related to TGF $\beta$  secretion by MSCs.<sup>30,35</sup> Although, the major effect is on the adaptive immunity, MSCs have been shown to inhibit production of reactive oxygen species (ROS) by neutrophils.<sup>36</sup> The action of MSCs seems to be systemic; there is scant evidence that they actually home to the site of injury and actually transdifferentiate. There has been scant evidence of engraftment in the CNS in some studies in neurological disease, like MS and EAE animal model, particularly if directly injected.<sup>37</sup>

## USE OF MESENCHYMAL STEM CELLS IN AUTOIMMUNE DISEASE (ANIMAL MODELS)

### Rheumatoid Arthritis

*Animal models:* Amelioration of collagen-induced arthritis (CIA) has been shown with a single intraperitoneal injection of MSCs.<sup>38</sup> That study found an increase in IL-10 and decrease in proinflammatory cytokines (Th1 and Th17) along with an increase in T-regs that could mediate this improvement. There was a reduction in proliferation of CD4 T cells in the draining lymph nodes on exposure to type II collagen. Also, earlier the injection, the lower was the arthritis score. Another study found daily intraperitoneal injections 5 days after onset of disease, reduced the incidence and severity of arthritis.<sup>39</sup> Also, intra-articular MSCs were less effective than intraperitoneal injections. However, there have been negative studies as well that did not find an improvement (or even found an exacerbation) in CIA.<sup>40-42</sup> One review reconciled these differences as due to the difference in protocols—route, source of MSCs, single vs multiple injections.<sup>43</sup>

*Human:* There is no published study on human studies in rheumatoid arthritis.

### Systemic Lupus Erythematosus

*Animal models:* In the MRL-lpr mice model, clinical improvement and reduced anti-dsDNA titers have been found after allogenic MSC administration.<sup>44-46</sup> There was an increase in T-regs and reduction in Th17 cells. There was also amelioration in the osteoporosis accompanying the disease. However, in the (NZBxNZW) F1 model, there was no clinical improvement or even exacerbation.<sup>47,48</sup>

*Humans:* In human SLE, there have been several studies. Two studies using intravenous infusion of allogenic BM-MSC from family members found improvement in disease score, proteinuria and decreased requirement for immunosuppression on follow-up of around 1.5 years after MSC administration.<sup>45,49</sup> Another study showed similar

improvements with umbilical cord derived MSCs.<sup>50</sup> There was an increase in the CD4+FoxP3+Treg at 3 and 6 months, accompanied by an increase in the levels of TGF and IL-10.<sup>45</sup> However, a shorter study did not find any improvement.<sup>51</sup>

### Systemic Sclerosis (Scleroderma)

A single case report found a decreased skin score in a patient given MSCs from haploidentical allogenic donor 6 months after administration.<sup>52</sup>

### Multiple Sclerosis

*Animal model:* In experimental allergic encephalomyelitis (EAE), intravenous infusion of syngenic MSCs was found to ameliorate the disease when administered at onset or peak of the disease but not in the chronic progressive phase.<sup>53</sup> There was an improvement in the demyelination and T cell infiltration in the CNS. There was engraftment of the MSCs in the secondary lymphoid organs, inducing T cell tolerance, to the immunizing antigen myelin oligodendrocyte glycoprotein. There have been several other studies that have shown improvement in clinical scores using MSCs.<sup>54,55</sup> A later study using adipose tissue MSCs showed ability to improve even established disease.<sup>56</sup>

*Humans:* In multiple sclerosis, three small studies (7-15 patients) using autologous MSCs have been done with administration of MSCs intrathecally (in one additional intravenous).<sup>57-59</sup> These found either no or inconsistent improvement (i.e. clinicoradiological discordance in improvement). The major adverse effect was headache with few developing aseptic meningitis.

### Amyotrophic Lateral Sclerosis

In ALS, three studies of few patients (9-19 patients) using autologous MSCs have been done.<sup>57,60</sup> There was no improvement in disease.

### Myasthenia Gravis

*Animal model:* Use in the experimental autoimmune myasthenia gravis (EAMG) model led to lower titers of acetyl cholinesterase antibodies and improvement in clinical scores.<sup>61</sup>

### Inflammatory Bowel Disease

*Animal model:* In trinitrobenzene sulfonic acid induced colitis, there was improvement on systemic administration of MSCs. In a FoxP3 deficient model which leads to generalized autoimmunity including bowel inflammation,

there was an improvement in ileum inflammation on MSC administration.<sup>62</sup>

In Crohn's disease, few phase 1 studies have been done.

### Type 1 Diabetes Mellitus

*Animal model:* In the STZ induced diabetes model led to higher insulin secretion and larger numbers and size of remaining islets.<sup>63</sup>

## USE OF MSC IN NONAUTOIMMUNE IMMUNE-MEDIATED DISEASE

### Graft versus Host Disease (GVHD)

*Animal models:* A single infusion of MSCs at the time of bone marrow transplant in mice did not prevent GVHD.<sup>64</sup> However, multiple doses could prevent it.<sup>65</sup> Another study found administration of MSCs only in a certain time interval, i.e. from day +2 to +20 leads to an increase in the survival times of recipient mice, which may be related to high levels of IFN $\gamma$ .<sup>66, 67</sup>

*Humans:* First in a single case, and then later in a study on 55 patients, it was shown that MSCs could improve GVHD and lead to better survival.<sup>68,69</sup> However, a study where MSCs were given before hematopoietic stem cell transplant (i.e. before GVHD was there) showed no benefit.<sup>70</sup>

### Organ Transplantation

*Animal models:* One of the first animal experiments regarding MSC involved baboons with allogenic mismatched skin transplants in whom infusion of MSCs led to longer survival of graft.<sup>12</sup> Subsequent experiments involved administration of donor-derived mesenchymal stem cells which prolonged survival of rat cardiac allograft.<sup>71</sup> MSCs have also been shown to synergize with immunosuppressants to improve outcome of allografts—cardiac and solid organ.<sup>72</sup> A recent randomized controlled study in renal transplant recipients, in those who received autologous MSCs along with calcineurin inhibitors had a lower rate of biopsy confirmed acute rejection at 6 months, compared to those receiving calcineurin inhibitors with anti-IL2 therapy. The MSC treated patients also had near half reduction in opportunistic infections. However, survival and graft survival were not different at 30 months.<sup>73</sup>

### Acute Lung Injury (ALI)

*Animal models:* In C57 BL/6 mice in whom ALI was induced with high dose of intra-alveolar endotoxin, administration of MSC via the intratracheal route 4 hours later led to reduction in injury compared to saline control. There was a reduction in pulmonary edema,

pro-inflammatory cytokines and increase in anti-inflammatory cytokines, like IL-10 and IL-13. There was also an improvement in survival.<sup>74</sup> MSCs also reduced mortality in *E. coli* induced ALI. Neonatal experimental models have shown improvement in lung damage in hyperoxic neonatal lung injury models.<sup>75</sup>

## CONCLUSION

Mesenchymal stem cells are an evolving therapy as immunosuppressive agents that may find to use in autoimmune diseases, graft-versus-host disease, organ transplantation and other immune mediated injuries, like ALI. They have a distinct advantage of low immunogenicity that permits allogenic and even xenogenic use. However, although they have shown efficacy in animal models, the human studies have been small and nonrandomized—thus as of now they it remains to be seen whether they will make it form the bench to the bedside.

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## ABOUT THE AUTHOR

### Varun Dhir

Assistant Professor, Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh-160012 India, Phone: +91-172-2756070, e-mail: varundhir@gmail.com