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# Mesenchymal stem cell (MSC) as a potential cell therapy for immune related disease



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## ABSTRACT

Mesenchymal Stem Cell (MSC) is a type of stem cell that not only has the ability to differentiate into several different lineages, but also has an immunomodulator activity. MSC modulate immune system by secreting several different cytokines those act synergistically like IL6, IL-10, TGF $\beta$ , PGE2, and HLA-G which inhibit T-cell differentiation and maturation of macrophage. Because of its immunomodulatory properties, several researches had attempted to study its potential application in autoimmune management. So far, preclinical and clinical study in

Graft versus Host Disease (GVHD) and several autoimmune diseases like Systemic Lupus Erythematosus (SLE), and diabetes had yield promising results. However, the efficacy of its application in Inflammatory Bowel Disease (IBD) is still unclear. Overall, MSC has shown great promise as novel modality in autoimmune management. However, further studies are still needed to evaluate its application in each autoimmune disease as well as determining the effective dose of MSC for each type of autoimmune disease.

**Keywords:** Mesenchymal Stem Cell (MSC), Autoimmune Disease, Immunomodulator

**Cite This Article:** Hadi Kartiko, B., Milas Siswanto, F., Purwata, T. 2017. Mesenchymal stem cell (MSC) as a potential cell therapy for immune related disease. *Bali Medical Journal* 6(1): 38-43. DOI:10.15562/bmj.v6i1.378

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## INTRODUCTION

Stem cell is a very popular term in the health and medicine recently. The various features and capabilities of stem cells in the proliferation and differentiation has make it as a major topic among many researchers, scientists, health practitioners and even ordinary people. Stem cells are believed to be the key to develop treatment for degenerative diseases which is until now could not be cured, such as stroke, diabetes mellitus type I, atherosclerosis, myocardial infarction, and other degenerative diseases.<sup>1</sup>

Mesenchymal Stem Cell (MSC) particularly popular among stem cell researchers. MSC can be considered as prolific stem cell since it has been tested in a various kind of diseases such as myocardial infarction, chronic obstructive pulmonary disease (COPD), osteoarthritis, stroke and spinal nerve damage.<sup>2,3</sup> The results of those researches were particularly significant and there were even evidences of successful differentiation of MSC into neuron, cardiomyocyte, and chondrocyte both in culture and in vivo.<sup>4,5</sup> However, recent researches reveal that differentiation capability of MSC may not the only factor that contributed to its effectiveness.

Muruguma et.al and Jones et.al first reported that MSC could modulate the function of surrounding cells including cardiomyocyte, neuron and epithelial cells.<sup>6,7</sup> It was revealed that MSC could produce paracrine growth factors that help increase the survivability of nearby cell as well as increase angiogenesis both by recruiting stem cell from bone marrow and by inducing vessel growth

from existing capillaries.<sup>6</sup> MSC could also produce cytokines that modulate immune response including IL-10, IL-8, and TGF- $\beta$ .<sup>7</sup> These cytokines tend to repress immune response and induce tissue healing. It is this function that attract immunologist for its potential application in immune related disease.

Phase I and II clinical trial had been conducted to evaluate the potential of MSC therapy in autoimmune disease.<sup>8,9</sup> The trials cover wide array of disease including Graft versus Host Disease (GvHD), diabetes, Systemic Lupus Erythematosus (SLE), Crohn's Disease and Ulcerative Colitis. Research in GvHD, SLE, and diabetes yielded compelling evidence that MSC could be applied as novel treatments.<sup>9,10,11</sup> However, there are only few evidences yet regarding the use of MSC in Inflammatory Bowel Disease (IBD) (Chrohn's Disease and Ulcerative Colitis).<sup>12,13</sup>

This review will discuss about the characteristics and properties of MSC. The potential of immune-modulation of MSC and its potential application will be described deeply thereafter.

## Autoimun Disease Overview

Whereas immune system normally recognizes and eliminate foreign antigen, in several occasions it attacks the host itself which is known as autoimmune disease.<sup>14</sup> The main cause of autoimmune disease is alteration of self-tolerance due to genetic factor, hormone disorder, environment, diet, and some drugs. Whether most clinicians believe genetic factor is the dominant one, in fact it only contributes to 30% of the disease.<sup>15</sup>

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The mechanism of autoimmune disease can be classified into 2 categories: antibody mediated and cell mediated.<sup>16</sup> Most of autoimmune diseases are marked by the presence of auto-antibody targeted specifically to certain molecule (e.g collagen, nuclear antigen). The attachment of anti-body to tissue surface or certain organ leads to tissue damage mediated by inflammatory cells and complements activation.<sup>17</sup> On the other hand, cell mediated autoimmune disease usually not dependent on self-auto-antibody. Instead, cellular cyto-toxicity mediated by cyto-toxic T cell or natural killer cell play important role in tissue damage. Alternatively, cell mediated immune system could also aggravate the damage caused by auto-antibody by antibody mediated cellular cyto-toxicity (ADCC).<sup>18</sup>

The basis of aforementioned process is inappropriate T cell activation.<sup>19</sup> Inappropriate T-cell response will alter plasma cytokines balance and hence the appearance of auto immune diseases. Th1 specific cytokine like IFN- $\gamma$  has been known as risk factors for organ specific auto-immune disease like type 1 diabetes mellitus and thyroiditis.<sup>20</sup> Meanwhile, Th2 specific cytokines IL-4 cause Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis.<sup>21</sup> Aside from those T-cell types, the third type of T-cell, regulatory T-cell (Treg), is responsible for regulating the activation of both Th1 and Th1 cells by secreting IL-10.<sup>22</sup> So it can be predicted that Treg population is usually low in autoimmune patients.

Autoimmune disease range from specific organ type like thyroiditis and type I diabetes mellitus to systemic type like systemic lupus erythematosus (SLE) or rheumatoid arthritis. Regardless of its type, autoimmune diseases cause great disability and almost impossible to cure. Current management of autoimmune disease relies on corticosteroid and cyto-toxic drug to suppress auto-reactive immune system.<sup>23</sup> However, there are several side effects associated with these drugs such as immunodeficiency, alopecia, nausea, and also bone marrow suppression.<sup>24</sup> For this reason, researchers have been constantly developing new approach in autoimmune disease. One of them is stem cell therapy with specific attention to mesenchymal stem cell (MSC).

### Characterization and Source of Mesenchymal Stem Cells (MSCs)

Mesenchymal Stem Cells (MSCs) is one of the adult stem cells that can be found in the bone marrow, peripheral blood, umbilical cord blood and adipocytes tissue.<sup>25</sup> MSC generally act as supporting cell, either structurally or chemically. As structural support, it induces connective tissue formation

**Table 1** The Source of Mesenchymal Stem Cell in the body

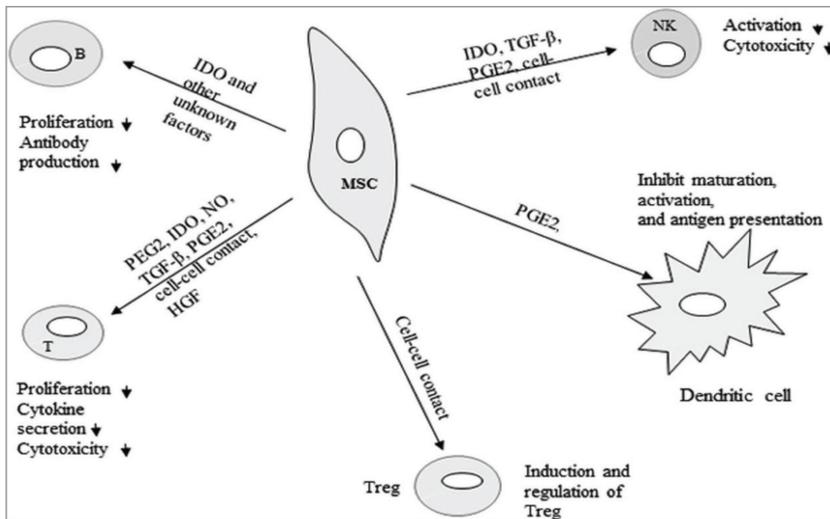
Mesenchymal Stem Cell Sources	
Peripheral blood	Placenta
Menstrual blood	Breast milk
Foetal membrane	Adipose tissue
Dental pulp	Umbilical cord vein
Chorionic Villi	Wharton's Jelly
Amniotic membrane	Cord membrane
Amniotic fluid	Umbilical cord
Ligamentum flavum	Umbilical cord blood
Decidua basalis	Bone marrow

and fibroblast differentiation providing histological network in which corresponding cell could attached.<sup>26</sup> Chemically, it secretes various cytokines that maintain cellular homeostasis within microenvironment.<sup>6</sup> It is also found that MSC had differentiability capability which enables it to replace damaged or dying cell within corresponding tissue or organ.<sup>4,5</sup>

Various sources had been evaluated to yield satisfying amount of MSC but with variable degree of differentiability capabilities.<sup>27,28</sup> For example, adult MSC from bone marrow had been used extensively in experimental model of many diseases but its differentiation into target cell is questionable.<sup>29</sup> On the other hand, MSC derived from wharton's jelly as well as adipocyte derived MSC is known for its efficient differentiation into functional neuron and cardiomyocyte.<sup>30</sup> However, the most accessible source is adipose tissue due to its abundance and yield high amount of MSC.<sup>31</sup> The potential sources of MSC are listed in Table 1.

MSC is hard to identify morphologically because of its similarity with fibroblast.<sup>32</sup> However, there are several molecular markers that can be used to identify MSC. Based on "Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy", minimum criteria for MSC identification is > 95% cell population positive for CD105, CD73 and CD90 and less than 2% negative for CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA class II.<sup>33</sup>

The differentiability capability of MSC has been attract the interest of stem cell scientists as well as medical personnel. In vitro and in vivo analysis showed that MSC could differentiate into functional adipocyte, neuron, chondrocyte, myocyte, and fibroblast. It also even had been known to differentiate into HSC and resume hematological differentiation into various blood cells. These differentiability capabilities mark the potential of MSC as main modality in stem cell therapy. However, there are other mechanism played by MSC that also held great therapeutic potential and this is just recently revealed.<sup>4,5</sup>



**Figure 1** Immunomodulatory mechanism of MSC<sup>47</sup>

Several researchers found that the presence of MSC could induce cell survival and differentiation in many organs without differentiability evidence of corresponding MSC.<sup>6</sup> In vivo studies of myocardial infarction mouse model by injecting MSC into infarct area also reveal that the infarct size was significantly smaller compared with untreated mice.<sup>34</sup> It also observed that granulocyte infiltration was significantly lower in MSC treated mice. Observation in stroke induced mice also yield the same result with marked decrease in granulocyte infiltration and reactive gliosis within infarcted area.<sup>35</sup> These evidences suggest that MSC had another property that had great therapeutic potential especially for autoimmune disease: immunomodulation.

### Immunomodulator Effect of MSCs

A wide array of evidences proved that MSC had immunomodulation properties. Principally, MSC modulate immune response by suppression of T cells and maturation of dendritic cells, reducing B-cell activation and proliferation and inhibiting proliferation and cyto-toxicity of NK cells, and promote the generation of regulatory T cells, therefore covering both innate and adaptive immune responses.<sup>36,37</sup> The mechanism appears to be mediated by soluble factors and direct cell to cell contact (Figure 1).

MSC secreted various soluble factors including PGE-2, Hepatocyte Growth Factor (HGF), Transforming Growth Factor-β1, indoleamine-pyrrole 2,3-dioxygenase (IDO), Interleukin-10 (IL-10), and Nitric Oxide (NO).<sup>38,39</sup> Main inducer of immunomodulation by MSC is Interferon-γ (IFN-γ), either alone or in combination with Tumor Necrosis Factor-α (TNF-α) or IL-1β.<sup>40</sup> In adaptive sector, stimulation by IFN-γ and its

co-stimulator induce MSC to secrete aforementioned factors, resulting in suppression of immune response by several mechanisms. Elevated IDO secretion by MSC inhibits functional status of leukocytes. It inhibits lymphocyte proliferation, CTL differentiation, and decrease IFN-γ secretion.<sup>41</sup> In addition, it increases IL-4 secretion and enhances Treg differentiation, thus shifting immune status toward Th2 immune response. Subsequently, Treg secretes IL-10 that had wide range of immunosuppressive properties, causing systemic immunosuppression. PGE is also play important role in decreasing B-cell proliferation and, hence, strengthening MSC modulation of adaptive immune response.<sup>42</sup>

In innate sector, IDO secreted by MSC, together with PGE and TGF-β, also contribute in suppression of proliferation capacity, cytotoxicity and IFN-γ secretion of Natural Killer Cell (NK-cell).<sup>43,44</sup> In addition, various factors from MSC also inhibit monocyte proliferation and its differentiation as well as maturation into dendritic cell.<sup>45</sup> Dendritic cell and NK-cell is known for their role in initiating adaptive immune response so their functional inhibition means elimination of stimulation of adaptive immune response.

These evidences highlight the potent immune-modulatory effect of MSC. The effectiveness of MSC immunomodulation can be seen from its effect toward various kinds of leukocytes at both innate and adaptive sector of immune response. Because of this reason, MSC has great potential application in autoimmune disease.

### Mesenchymal Stem Cells (Msc) as Novel Therapy for Autoimmun Disease

Because of its potent immunomodulatory properties, MSC had been thoroughly evaluate as novel management in several immunoreactivity diseases.<sup>46,47,48</sup> MSC also had great inter-individual and inter-species tolerance which made it attractive candidate in regenerative or immunology research, ensuring lower rate of rejection by recipient. Early evidence of its potential application was conducted by Bartholomew et.al in 2002.<sup>46</sup> It showed great immunosuppressive capabilities as being able to inhibit T-cell proliferation by 50% in baboon receiving skin transplant, decreasing immunorejection of transplanted skin. It also observed that the effect was in direct correlation with dosage given so greater dose will result in greater immunosuppression.<sup>46</sup>

Other preclinical studies also proved the immunomodulator properties of MSC. MSC from bone marrow, adipose tissue, umbilical cord and other tissue had been shown to have adequate

immunosuppressive effect.<sup>47,49,50</sup> This is also evident in autologous, allogenic, and xenogenic MSC.<sup>50,51</sup> Of note, systemic administration of human MSC to mouse model of autoimmune disease (immune thrombocytopenia and autoimmune encephalitis) revealed that MSC effectively suppress T-cell proliferation, decrease blood pro-inflammatory cytokines level (IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$ ) while increasing anti-inflammatory cytokines (TGF- $\beta$ , IL-10).<sup>52,53</sup> Other experimental observation in mouse model of Graft Versus Host Disease (GvHD), SLE, and Multiple Sclerosis also yield same result with clinical delay in proteinuria development, reversal of multi-organ dysfunction, as well as reconstruction of bone osteoblastic niche.<sup>9,10,11</sup> Similar result was also observed in other mouse model of autoimmune diseases including autoimmune thyroiditis, Myasthenia Gravis, hearing loss, and primary biliary cirrhosis.<sup>54,55</sup>

Several clinical trials had been conducted as continuation of pre-clinical MSC evaluation. Most studies focused on Graft versus Host Disease (GvHD) but several researches also evaluate SLE, diabetes, Crohn's Disease, and Ulcerative Colitis.<sup>56,57,58,59</sup> Phase I and II clinical trial had been conducted to evaluate effectiveness of MSC treatment in GvHD. Intravenous infusion of autologous BM-MSC effectively counter GvHD reaction. From 55 patients, complete response was observed in 30 patients and 9 patients experience partial response in grade I-II GvHD.<sup>56</sup> Total and transplant related mortality rate were also observed to be decreased. In these studies, no adverse effects were observed in all subjects.

MSC also has shown great promise in treatment of SLE which resistant to conventional therapy. In clinical trial conducted by Wang et.al, clinical remission was observed in 50% of subjects after 4-years follow up although 23% experienced disease relapse.<sup>59</sup> Other study also proved that MSC infusion induced remission of lupus nephritis, diffuse alveolar hemorrhage, and refractory cytopenia.<sup>60,61</sup> Major clinical response was observed in 32.5% subjects with partial response observed in 27% subjects. However, there was 17% relapse rate during the course of the study. Mostly after 6 months follow up. This fact indicates the need of re-infusion 6 months after initial therapy.<sup>59</sup>

In contrast with GvHD and SLE, MSC therapy in inflammatory bowel disease is still in infancy.<sup>57,61</sup> So far only few clinical studies had been conducted. Nevertheless, the result of phase I study seems to be compelling. Onkan et.al conducted MSC infusion in 10 IBD patients who failed infliximab therapy and observed decreased CDAI score in day 28.<sup>61</sup> Another phase I study shown 70-point decrease in

CDAI score in 3 out of 9 subjects with all subjects experienced decrease CDAI score.<sup>57</sup> However, no sign of remission was observed in these studies and there is also evidence that HSC therapy was superior to MSC therapy. Nevertheless, it will need more studies to reveal the true value of MSC in management of IBD.

In case of diabetes mellitus, several studies had evaluated the efficacy of MSC therapy.<sup>63,64,65</sup> Of three type of MSC tested (Umbilical cord blood (UCB), Umbilical cord (UC) and BM), BM showed greatest potential since transformation from insulin dependent into insulin independent only observed in BM-MSC infusion.<sup>63</sup> Other subjects that received BM-MSC infusion shows decrease in insulin requirement. UCB and UC-MSC treated patients also showed decrease in insulin requirement and significantly lower HbA1C albeit not as much as BM-MSC.<sup>62,64</sup> However, since these two types of MSC were administered via intravenous infusion, it still too early to conclude the real efficacy of these MSC.

## CONCLUSION

MSC is a type of stem cell known for its differentiative capabilities and paracrine effects. Of all paracrine effects of MSC, its immunomodulatory properties had attracted lots of attention and made it as great candidate for autoimmune disease treatment. The potency of MSC in autoimmune disease is already studied extensively in vitro, in vivo and in phase I and II clinical trial which overall showed promising results. However, further studies still needed to evaluate the effective dose of MSC in each kind of autoimmune disease as well as evaluating the most effective delivery route to preserve MSC immunomodulatory capacity as well as ensuring the best outcome for recipients.

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