

Chapter 2

Immunomodulatory Properties of Stem Cells Derived from Dental Tissues

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2.1 Mesenchymal Stem Cell (MSC)-Mediated Immunomodulation

MSCs are basically characterized by their potential to adhere to plastic surfaces in cell culture conditions, express cell surface markers of CD105, CD44, CD29, CD73, and CD90, but not express hematopoietic stem cell surface markers such as CD45, CD34, CD14, and differentiate into osteo-, adipo-, and chondro-genic cell lines [1]. Along with their high self-renewal and multi-lineage differentiation abilities, they possess an immune-suppressive activity, which make them promising candidates to be used in cell and even tissue mediated treatments of a various immune and inflammation dependent diseases.

MSCs can be easily obtained from various human tissues, preserved in culture conditions, and used in even histocompatibility antigen (HLA) un-matching conditions of transplantation patients. Though they are mainly isolated from bone marrow, they can also be obtained from fat tissue [2], cartilage [3], liver [4], amniotic fluid [5], tooth germ [6], hair follicle [7] and so on [8–10].

Several reports indicate that MSC could be used in vast amount immune disorders. In particular, researchers have found that systematic infusion of allogenic stem cells may offer a new suitable treatment for Graft versus host disease (GVHD) patients [11]. In addition, Prasad et al. described a stem cell derived agent to treat GVHD patients [12]. The ability of MSCs to stimulate activation, proliferation, and

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function of immune cells may take part on tissue healing and regeneration, which would also contribute to treatment of several immune disease including GVHD.

2.1.1 Interactions of MSCs with White Blood Cells

2.1.1.1 T Lymphocyte-Mediated Suppression

The basic role of T cells, one main component of the adaptive immunity which forms immunological memory, is to create specialized immune reactions to particular pathogens [13]. Interaction between MSCs and T cells is critical for the activity of immune system. Direct cell to cell contact of MSCs with CD8⁺ (cytotoxic T cells) or CD4⁺ (regulatory T cells) helper T cells moderates the expression of cytokines for signaling and inhibition of T cell activation [14, 15].

Recent studies have demonstrated that MSCs express Fas ligand (FasL) known as a death receptor which inhibit T cell migration [13], triggering stimulated T cell death via direct cell interaction [16]. Even though inhibition of T cell proliferation via MSCs action has partially known, suppressive effect of MSCs has not been elucidated in the manner of autologous or allogeneic respective [17, 18]. One possible action of MSCs is suppression of CD8⁺ cytotoxic T cell proliferation, rather than a direct suppression of cytolysis [19, 20]. Furthermore, MSCs can enhance secretion of interferon gamma (IFN γ) and interleukin (IL)-17, while they induce T helper cells to produce IL-4 [21, 22].

It has been reported that MSCs can promote the proliferation of regulatory T cells and increase their modulatory ability directly or indirectly. When peripheral blood mononuclear cell (PBMCs) are triggered by mitogens, modulatory phenotype presenting CD4⁺ CD25⁺ T cells start to proliferate in the existence of MSCs. Inhibition of T cell proliferation by MSCs is triggered by allogeneic, mitogenic, or antigen specific stimuli [23].

Notably, scientists found that suppressed T cell proliferation via triggering apoptosis when T cells were stimulated by foreign mitogen, had no influence on latent T cells [23]. However, the proliferation of inactive and separating thymocytes was repressed via MSCs once treated in absence of systemic elements. These findings propose that MSCs can be capable of stimulating the endurance of T cells in a latent state. Furthermore, it has also been revealed that MSCs can repress T cell activation but not their toxicity by arresting T cells in G0/G1 cell cycle phase through suppression of cyclin D and increment of p27kip1 expression [24–26]. As a mechanism of action, it has been reported that MSC-mediated repression of T cell proliferation was not found to be because of soluble HLA-G5 isoform, but of the surface expression of HLA G1 [24].

In last decade, many studies using the heading ‘MSCs in Solid Organ Transplantation (SOT)’ were designed to understand what is unknown about the MSCs use in the setting of SOT, and how to progress best in clinical trials [27]. Although there is not any clinical studies evaluating the efficiency of MSCs against Solid Organ Allograft (SOA) rejection, a plentiful and increasing quantity of evi-

dences obtained from animal models propose that this methodology may be promising. Based on *in vitro* and *in vivo* animal models, a possible role of these cells on the prevention of acute tissue allograft rejection has been recommended [28–31].

General MSC-based treatment studies have proved that allogenic MSCs can diffuse into related tissue during SOT. Enhanced allograft persistence or abolition in the simultaneous suppression is few of the frequently reported conclusions. Although human clinical trials are not adequate, preclinical studies have shown that MSCs could be important therapeutic tools for organ transplantation approaches not just as they have the ability to modulate the host immunity in a way that may promote tolerance of the transplanted organ, but also their regeneration capability and trophic factor expression profiles may also help to lessen inflammatory responses to the allograft. One of the main aim of SOT studies is to inhibit T cell response against external antigen. In this line, MSCs can suppress the proliferation of cytotoxic T cells while enhancing the activities of helper and regulatory T cells. Some immunomodulation-related studies have proposed that these properties of MSCs may be the key reasons for their ability to prevent the allo-immune reactions *in vivo* [32]. More research must be carried out because lack of knowledge about MSCs-mediated immune suppression; nevertheless, the fewer toxicity and possible long term immunosuppression effect of MSCs make them a potentially striking therapeutic applicant with respect to outmoded T cell modulatory agents. Another advantage of MSCs use for the inhibition of SOA rejection is the infusion of these cells while SOT may hold the potential to endorse a state of cell chimerism and continuing tolerance of the transplanted organ via host immune system [33, 34].

2.1.1.2 B Lymphocyte-Mediated Suppression

Even though the main player of the immune suppression response is the T cells, B cells can also secrete antibodies to regulate immune response, and they closely cooperate with T cells. The exact mechanism of MSCs on B cells still remains unknown. However, most of the immune suppression related studies have shown that MSCs can suppress B cell proliferation, differentiation, and cytokine production in *in vitro* co-culture assays and *in vivo* multiple sclerosis models [35–38]. In contrast, it has also been shown that MSCs increase B cell proliferation and trigger cytokine productions from B cells [38, 39].

MSCs can enhance the production of IgG from peripheral blood and spleen originated B cells, but they can also inhibit IgG secretion if a heavy primary stimulus is used to trigger B cells. One of the possible actions of B cell dependent MSCs-mediated suppression can be formed by differentiated B cell or the direct effect of the local stimulating signals. MSCs can inhibit B cell proliferation when B cells starts to secrete activation signals to the culture medium in co-culture system, suggesting that MSCs need activation indicators derived from B cells to inhibit B cell stimulation. This cross talk between MSCs and B cells lead to inhibition of B cell proliferation. Some of the important factors secreted from MSCs are transforming growth factor (TGF)- β , hepatocyte growth factor (HGF), prostaglandin E2 (PGE2),

and indoleamine 2,3-dioxygenase (IDO), which conduct MSC-derived immunosuppressive action on B cells [40].

As a conclusion, important part of B cell stimulation is carried out via T cell dependent pathways; hence, the effect of MSCs on T cell activity may also indirectly inhibit B cell actions [37]. Furthermore, MSCs seem to display a direct stimulus on B cells by direct cell to cell interactions and via production of vital inducer signals [36, 40]. One other critical issue is that majority of these experiments have been made in in vitro conditions, not in vivo or ex vivo. Therefore, actual immunosuppression effect of DSCs on B lymphocytes in vivo still remains to be determined.

2.1.1.3 Dendritic Cell-Mediated Suppression

MSCs have also been proposed to be effective against monocytes, monocyte derivative dendritic cells, macrophages, natural killer cells and neutrophils. Several in vitro works have presented that MSCs can inhibit the evolution of monocytes into dendritic cells via suppressing the antigen presentation role of these cells [41, 42]. As recently suggested, dendritic cells are an important part of immune reaction in regards of immune response and tolerance, depending on the stimulation and maturation period and the cytokine environment at locations of inflammation [43]. The inhibitory effect of MSCs on dendritic cell differentiation, maturation and function could be via suppressing CD14⁺ monocyte differentiation into matured dendritic cells and triggering the production of inducer molecules [44, 45]. In addition, MSCs can suppress the differentiation of allo-antigen stimulated monocytes toward mature dendritic cells [45]. Immature dendritic cells can induce cytokine production characterized by a reduced secretion of pro-inflammatory molecules including tumor necrosis factor alpha (TNF α), IFN γ and IL-12, and an amplified secretion of the anti-inflammatory molecule such as IL-10, when cultured in the presence of MSCs [44–47]. Similarly, as MSCs cultured with mature dendritic cells, they started to display decreased function of antigen-presenting, and down-regulated IL-12 production [45].

2.1.1.4 Natural Killer Cell (NKs)-Mediated Suppression

NK cells take crucial roles in intrinsic immune response, particularly in anti-tumor and anti-viral functions due to their cytotoxic activity, and they have the ability to produce large amount of pro-inflammatory molecules, including TNF α and IFN γ [48]. Impulsive cytotoxic function of NK cells especially target the cells displaying decreased HLA-I expression. Moreover, MSCs suppress IL-2 and IL-15 mediated NK cell proliferation, IFN γ secretion, and cytotoxic function of both latent and stimulated NK cells [20, 21, 49]. Recently, researches have demonstrated that cell-cell interaction is the most critical event in the MSC-mediated immunosuppression, whereas other cells were driven by soluble elements dependent on HLA-I characteristic. Donor cells isolated from HLA incompatible patients are much more vulnerable

to be lysed by triggered NK cells via secretion of high amount of IFN γ and TNF α ex vivo [50]. MSCs suppress the expression of NKp30 and NKG2D surface receptors which are take part in NK cell function and lysing of targeted cells [51].

Direct cell to cell interaction of MSCs with active immune cells leads inhibition or limitation of inflammatory responses and enhances the mitigating and anti-inflammatory pathways. Depending on activation type and expression profile resulted via danger signals, inhibition or limitation can be chosen by MSCs [52]. In addition, transition of MSCs into infected and damaged tissue might interfere to secondary lymphoid organs which are crucial for the immunity. They can also diffuse into the damaged tissue or organ to trigger healing process, resulting in functional tissue or organ regeneration and local immunity. While these studies enlarge our understanding about MSC-mediated immunosuppression, further studies must be strictly conducted to fully elucidate exact action of mechanism underlying these suppressive, regenerative, and anti-inflammatory functions [11, 14].

2.2 Immuno-Modulation of DSCs

Immunomodulation properties of MSCs make them outstanding candidates as immunosuppressive drugs for the prevention and treatment of various inflammatory and autoimmune diseases [38, 53]. Starting from the 2000, unique MSC sources have been obtained from several dental tissues, which exhibit remarkable tissue regenerative and immunosuppressive properties [54]. These dental tissue derived cells include dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), gingival mesenchymal stem cells (GMSCs), tooth germ stem cells (TGSCs), apical papilla stem cells (SCAPs), exfoliated deciduous teeth stem cells (SHEDs), and dental follicles stem cells (DFSCs) [55–57]. Other than having spectacular self-renewal property and multipotency, DSCs have powerful immunosuppressive functions comparable to other stem cell types, making them promising cell sources for MSC-mediated transplantation treatment [58].

2.2.1 DPSCs

DPSCs have great regeneration capacity which can create pulp and blood vessels containing fibrous tissue resembling human tooth like structure [55]. Studies exploring the immunosuppressive characteristics of DSCs showed that DPSCs could suppress the proliferation of activated T cells better than bone marrow MSCs (BMMSCs) [17, 57]. This remarkable immunosuppressive function of DPSCs could make them appropriate cell type for allogenic bone marrow replacement therapy [59]. In addition, proliferation of PBMCs could be inhibited by TGF- β secreted from DPSCs, indicating the immunosuppressive role of MSCs triggered by signaling molecules derived from stimulated DSCs [60].

DPSCs have been used in an important transplantation study to treat Duchenne Muscular Dystrophy (DMD) of dogs carrying congenitally golden retriever muscular dystrophy (GRMD). Researchers found that DPSCs displayed immune suppression in GRMD dogs and helped to relieve disease symptoms [61]. In addition, DPSCs has been shown to trigger T cell apoptosis in vitro, and improve inflammation dependent tissue injuries as given to a murine colitis model in vivo. siRNA mediated inhibition of FasL expression, a trans membrane protein, involves in induction of the Fas/ FasL apoptotic pathway in DPSCs, leading to partial suppression of T cell apoptosis in vitro, and reduction in therapeutic effects of DPSCs in mice colitis models in vivo. Moreover, it has been proposed that FasL expression levels could regulate duplication rate and differentiation capacity of DPSCs.

2.2.2 PDLSCs

Periodontal ligament (PDL) tissue is originated from neural crest, and it can be obtained from dental follicle. Mainly, PDL cells connect the cementum to the bone, and support the tooth organ in the alveolar socket [62, 63]. These cells could also arrange the tooth nutrient source, homeostasis, restoration and regeneration of injured tissues [64, 65].

Several comparative studies showed that both PDLSCs and BMMSCs demonstrated suppressive effects on the production of allogeneic and xenogeneic PBMCs by blocking the cell doubling via secretion of TGF- β , HGF, and IDO [66]. Another study exploring the immunosuppressive role of PDLSCs has indicated that the inflamed PDLSCs displayed considerably reduced suppressor effects on T cell activation compared to healthy cells. In vitro co-culture studies showed that stimulated PBMCs displayed significantly less activation of CD4⁺CD25⁺Foxp3⁺ regulatory T cells, and IL-10 production when inflamed PDLSCs were used. Additionally, inhibition of Th17 differentiation and IL-17 secretion from inflamed PDLSCs was significantly less compared to healthy PDLSCs, proving inflamed PDL tissue serve less immunosuppressive stem cells [67].

2.2.3 TGSCs

TGSCs derived from third molar tooth germs of young adults are MSCs with high proliferation and differentiation capacity [68]. Besides their availability in adult body and having no ethical problems associated with embryonic stem cells, human TGSCs can be converted into osteogenic, adipogenic, myogenic, neurogenic, odontogenic [6, 69–71] and endothelial cell lineages [72]. Human TGSCs were used as immunosuppressive agent in rat tooth socket. It has been reported that TGSCs not only suppressed the immunity but also they regenerated the tooth socket at early

dental organogenesis [73]. Exact mechanism of immunomodulatory properties of tooth germ stem cells are still unknown; hence, further studies are required in vitro and in vivo.

2.2.4 GMSCs

GMSCs were firstly isolated at 2009, and they have been shown to be easily obtained from waste materials of routine dental treatment. GMSCs exert stem cell-like characteristics and immunosuppressive properties similar to other DSCs [54, 74]. GMSCs have the ability to stimulate a strong inhibitory action against immunity cells by enhancing the IFN γ -dependent IDO, IL-10, cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS) synthesis [75].

Zhang et al. showed that when macrophages were co-cultured with GMSCs, they developed an anti-inflammatory M2 phenotype, which might enhance wound healing process [76]. Another study reported that systemic infusion of GMSCs intensely improved contact dermatitis as revealed by a reduced penetration of dental cells, CD8⁺ T cells, Th17, and Mast Cells (MCs) [77]. Many in vivo transplantation studies have shown that stimulated GMSCs exerted stronger regeneration ability than non-stimulated healthy GMSCs, supporting the idea that GMSCs contribute to the pathogenesis of drug-stimulated gingival hyperplasia.

2.2.5 SCAPs

SCAP cells are obtained from cervical loop which contributes to tooth formation and pulp tissue development [78, 79]. SCAP cells showed a two-fold higher cell doubling rate compared to DPSCs. Moreover, SCAP cells can suppress T cell proliferation in an apoptosis independent way [57]. Further studies are necessary to explore the potential usage of SCAP cells as an immunosuppressive agent.

2.2.6 SHEDs

SHED cells are obtained from the coronal pulp of exfoliated deciduous teeth [56]. SHED cells exert MSC characteristics but high levels of alkaline phosphatase (ALP) were detected under osteogenic induction conditions. SHEDs have been shown to suppress Th17 function proposing that SHEDs could be used to treat systemic lupus erythematosus (SLE) in vivo [54].

Available data in the literature provides valuable information about MSC-regulated immune suppression. However, advanced in vivo and clinical studies should be completed to reveal multiple signals and complicated mechanisms controlling immune regulatory pathways.

2.3 Relation Between Immunosuppression and Stem Cell Expression Profiles

The discovery of DSCs in the pulp tissue by Gronthos et al. was a milestone for MSC research and expanded new horizons for the development of alternative treatment strategies [55]. MSCs residing in dental tissues are characterized by differentiation ability into many cell types such as adipocyte, osteocyte, chondrocyte and myocyte under appropriate culture conditions [80]. In addition to MSC-like behavior at culture conditions, DPSCs are positive for MSC surface markers such as CD29, CD73, CD105 and CD 90. It has been revealed that stage-specific embryonic antigen-4 (SSEA-4), a globo-series ganglioside, is also expressed in DPSC populations, and can be used to sort DPSCs [81]. Moreover, STRO-1, which is a cell surface protein expressed by BMMSCs, is also expressed by DSCs [82]. Although STRO-1 is used as a specific marker to characterize DSCs, some STRO-1⁺ cells express typical hematopoietic stem cell markers such as CD117 and CD34 [83, 84].

Use of DSCs for regenerative medicine could be problematic in some situations. Inflammation in periapical and pulp tissues could restrict the regeneration potential of DSCs [85]. In the case of inflammation caused by bacterial infection, several immune cells such as macrophages, neutrophils, T and B lymphocytes take in charge as immune protector [86]. In this situation, MSCs express certain cell surface markers providing the interaction with the immune system to suppress the immunity [86]. The immune system and MSC interactions are well-known for BMMSCs which express receptors for plenty of cytokines such as IL-4, IL-6, TNF α , IFN γ , and growth factors including epidermal growth factor (EGF), TGF- β and bone morphogenetic proteins (BMPs) [87, 88]. Moreover, MSCs express vital molecules necessary for cell to cell interactions with immune and hematopoietic cells, particularly various adhesion molecules.

Although similar expression profile of DSCs with other well-studied MSCs is expected, currently, there is not a comprehensive research for the investigation of surface proteins of all types of DSCs. Some receptors for distinct mediators expressed by DSCs are TGF- β , vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and insulin-like growth factor (IGF) [89–93].

MSCs can receive signals from the inflammatory environment via several receptors. They express some growth factors and cytokines such as IL-11, IL-8 and IL-6, and involved in the early maturation of T cells [87]. It was shown that MSCs modify cytokine release of distinct types of adaptive immune cells like T cells or suppress their proliferation [94–96]. Immunomodulatory potential of MSCs have been described for BMMSCs, and also have been confirmed for DPSCs. Responses of activated T cells are prohibited by DPSCs and SCAPs [97, 98]. It has also been reported that in the existence of DPSCs and PDLSCs, repression of PBMC proliferation has been observed [99]. Similar effects have also been demonstrated for gingival fibroblast [95].

MSCs derived from dental tissue express some critical receptors for inflammatory agents, which can be produced by injured cells and inflammatory cells.

They can also be released from dental tissues. Released cytokines and growth factors are able to decrease or increase the proliferation or differentiation potential of MSCs derived from dental tissues.

2.4 Clinical Applications

Clinical study is the process of experiments and trials, observational studies in medical and other types of research. The aim of a clinical study is to investigate the activity, safety and mechanism of action of an investigated product, drug or device. In this regard, MSCs are being currently used in clinical applications for the treatment/prevention of various disorders including immunity related disorders. In particular, human MSCs derived from adult donors are isolated and cultured in the laboratory conditions, and they have displayed the ability to find injured tissue, reduce and control the inflammation [100]. In addition, BMMSCs are evaluated for the treatment of GVHD [101] and their safety, tolerability and effectivity after liver or kidney transplantation are also being investigated in clinics [102]. Currently, there are no clinical studies investigating immunosuppression properties of DSCs. However, as DSCs have been proven to display comparable immunosuppression properties with other well-studies MSCs, it is worth to conduct clinical trials using different DCSs. For instance, DPSCs have exhibited 18 % higher suppression rate of T lymphocyte growth in comparison with BMMSCs, indicating possible superior immunosuppression potential of DSCs. In addition to their outstanding immunosuppressive activity, DSCs have several advantages which makes them promising candidates to be used in various clinical trials including;

- They are cost-effective, easily obtainable and do not need ethical and safety concerns as long as they are derived from regular orthodontic procedures [103].
- They can be easily cryopreserved, stored long-term, and combined with many structural materials [104].
- They have neuro-protective effects on dopaminergic neurons and motor neurons in spinal cord [105, 106].

2.5 Safety Issues

Absence of clinical studies investigating in vivo survival of MSCs after tissue or cell transplantation can bring serious doubts to usage of MSCs in human cases. Few human studies have indicated that long term side effects of MSCs are still unknown. Not just only immunosuppressive effect of DSCs against immunogenic cells, but also their anti-inflammatory role, tissue repairing function, and interaction between these actions must be studied before performing clinical studies. In addition, several questions including “is this immunogenic suppression mediated by MSCs stable for long time”, “do DSCs cause malignant transformation in the related or un-related

tissue or organs”, or “do they result in any ectopic tissue transformation” should be answered. Until these questions will be resolved, usage of MSCs can remain doubtful in transplantation cases or treatment of immune-related disorders.

2.6 MSC Paradigm; Suppression or Modulation

Do MSCs only act as an immunosuppressive agent or do they have much more complicated modulatory function? Warning signals which are expressed from foreign microbial infection, trigger toll like receptor (TLR) production from immune cells. Expression of TLR from induced immune cells leads a great host response, leading homeostasis [107–109]. MSCs can recognize the warning signal from foreign agent to find the damaged tissues to exert their suppressive function. Recently, researchers founded that MSCs not only suppress immune cells but also they can suppress inflammation at related area [52]. TLR-3 expression causes production of immune suppressive signals secreted from MSCs, while stimulation of TLR-4 with lipopolysaccharide (LPS) causes production of pro-inflammatory factors [110]. This process can be shifted by specific TLR expression depending on reaction against foreign warning signal. TLR-3 expression leads to T cell derived immune suppression and increased deposition of fibronectin [111]. However, TLR-4 expression results in the suppression of inflammation related mediators and suppression of T cell suppression [111]. Exact mechanism of this dual role of MSCs in immune system needs to be evaluated by further in vivo and ex vivo analysis.

2.7 Conclusion

In short time after Gronthos et al. isolated MSCs derived from dental pulp tissue of permanent teeth, the immunomodulatory properties of DSCs have gained wide attraction from scientists. In this manner, many properties of DSCs including their remarkable immune suppression effects are explored. Researchers showed that DSCs are much more usable in the manner of accessibility, strong immune modulation capacity, low frequency of exposure to the inflammatory environment, and also, they have higher proliferation rate compared to other well-known MSCs [54, 60, 112].

Although there is not any systemic clinical study, pre-clinical and in vitro studies have proved that DSCs could serve a promising immune suppressive in human cases. This unique property of MSCs is not only important for tissue transplantation treatments but also for allogenic-based regenerative medicine and tissue engineering tools. As additional approaches such as pre-treatment of DSCs with cytokines including IFN γ , TNF α and IL-1 β increase suppression effect and anti-inflammatory mediator secretion, stem cell culture and treatment should be optimized before treatment. Second important issue could be the time of application. It has been

proposed that although same MSC type have been used, one of them failed to treat GVDH in mice due to having different infusion time [113]. Such parameters should be optimized to increase success rate in MSC-based treatments. As all communications and interactions between DSCs and immune cells are not completely elucidated yet, further *in vitro*, *in vivo*, and *ex vivo* studies are highly warranted to fully clarify critical roles and the fundamental mechanisms of immunomodulatory features of DSCs to increase DSC use in clinics.

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