Review

Employing Mesenchymal Stromal Cells (MSC) for Managing Acute and Chronic Graft-versus-Host-Disease

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Employing Mesenchymal Stromal Cells (MSC) for Managing Acute and Chronic Graft-versus-Host-Disease

Mohini Mendiratta [1], Meenakshi Mendiratta [2] Sujata Mohanty [2,*], Ranjit Kumar Sahoo [1,*] and Hridayesh Prakash [3,*]

[1] Department of Medical Oncology, Dr. B. R. Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India-110029
[2] Stem Cell Facility, All India Institute of Medical Sciences, New Delhi, India-110029
[3] Amity Centre for Translational Research, Amity University, Sector 125, Noida, India 201313
* Correspondence: drmohantysujata@gmail.com (S.M.); drranjitmd@gmail.com (R.K.S.); hprakash@amity.edu (H.P.)

Abstract: Mesenchymal Stromal Cells (MSCs) are multipotent, non-hematopoietic progenitor cells with a wide range of immune conditioning and regenerative potential which qualify them as potential component of cell based therapy for various autoimmune / chronic inflammatory ailments. Their immunomodulatory properties include the secretion of immunosuppressive cytokines, the ability to suppress T-cell activation and differentiation, and the induction of regulatory T-cells. In view of this and our interest, we here discuss the significance of MSC for the management of Graft-versus-Host Disease (aGVHD), one of the autoimmune manifestation in human. In pre-clinical models, MSCs have been shown to reduce the severity of aGVHD symptoms, including skin and gut damage, which are the most common and debilitating manifestations of this disease. While initial clinical studies of MSCs in aGVHD cases were promising, the results were variable in randomized studies. So, further studies are warranted to fully understand their potential benefits, safety profile, and optimal dosing regimens. In view of these inevitable issues, here we discuss various mechanisms, how MSCs can be employed in managing aGVHD, as a therapeutic option for this disease.

Keywords: Mesenchymal Stromal Cells; Graft-versus-Host-Disease; immunomodulation; apoptosis; efferocytosis; secretome

Introduction

Mesenchymal stromal cells are well known for their potential to improve the outcomes of allogeneic hematopoietic stem cell transplantation (HSCT). Allogeneic HSCT is a life-saving procedure in which a healthy donor's stem cells are transplanted into a recipient with an abnormal or malignant hematopoietic system to restore normal functioning. The primary goal of allogeneic HSCT is to successfully engraft donor stem cells into the recipient, allowing for the production of healthy and functional blood cells. However, allogeneic HSCT is associated with a high risk of graft-versus-host-disease (GVHD), which can be fatal and is caused by the donor's immune cells attacking the recipient's healthy cells. MSCs have been studied for their ability to reduce GVHD, improve donor stem cell engraftment, and modulate the recipient's immune system in a beneficial way. This review will provide an overview of the role of MSCs on GVHD. Alexander Friedenstein and his colleagues studied the bone marrow microenvironment and first isolated MSCs from the bone marrow in the late 1960s and early 1970s [1–5]. Mesenchymal stromal cells are multipotent heterogeneous populations of adult non-hematopoietic stem cells that can self-renew, have fibroblast-like-morphology and can be isolated from various sources such as bone marrow, umbilical cord, umbilical cord blood, Wharton jelly, amniotic fluid, amniotic membrane, dermal, skeletal

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muscle, adipose tissue, the dental pulp, synovial fluid, menstrual blood, peripheral blood, and many more. The persistence of MSCs in various organs leads to the notion that MSCs reside in the perivascular niche and show that the perivascular progenitor cells are precursors of MSCs as these shared similar immune-phenotypic expression of stemness-associated surface markers with a few different markers such as CD146. Additionally, available evidence shows that naïve MSCs share little functionality with pericytes and adventitial cells, leading to the concept that MSCs might derive from blood vessel-associated cells mainly, pericytes. Thus, all MSCs are pericytes but all pericytes are not MSCs as the pericytes do not demonstrate multipotency. In 2006, the International Society for Cellular Therapy (ISCT) defines three minimum criteria for the identification and characterization of MSCs- 1) Adherence to plastic; 2) Exhibiting ≥95% expression of CD105, CD73, CD90, CD29, lower expression of HLA-I, and absence or ≤ 2% of lineage-specific markers (CD34, CD45, CD14, CD16, CD11b), HLA-II molecule; 3) ability to differentiate into mesodermal (osteogenic, chondrogenic and adipogenic) lineages under in vitro conditions [6,7].

However, surface markers may not be the ideal parameters to characterize MSCs due to the plasticity in the expression of CD34 surface markers under in vitro and in vivo conditions. Mesenchymal stromal cells stably express CD34 in vivo, however this often remain unstable in vitro which depends on culture conditions (cell-culture media, plastic adherence), donor, and passage [8]. Additionally, the expression of HLA-DR was also upregulated due to the addition of IFN-γ in the culture media [8–10]. Thus, in 2019, ISCT committee members recommends using the acronym "MSC" with tissue-source and functional assays to demonstrate tissue-specific and therapeutic properties of MSCs respectively [8,11]. Additionally, the stemness of the MSC population should be confirmed in vitro and in vivo [12,13].

In 2019, the ISCT proposed the following criteria to define MSCs: 1) Adherence to plastic, 2) Marked by ≥95% expression of CD105, CD73, CD90, CD29, lower expression of HLA-I, and absence or ≤ 2% of lineage-specific markers (CD34, CD45, CD14, CD16, CD11b), HLA-II molecule, 3) Trilineage differentiation to mesodermal lineage. 4) Specify the tissue origin with the acronym MSC. 5) Stemness of MSCs must be established by in vitro and in vivo data. 6) Assay matrix should provide either qualitative or quantitative data with precision or a detailed mechanism of action of MSCs.

Arnold I Caplan argued that 'stem cell' is not an appropriate term for MSCs due to their variability in the functional properties in vitro and in vivo. Another aspect is related to the variability in their in vivo behavior. MSCs home to sites of inflammation or tissue injury and secrete massive levels of bioactive agents that have both immunomodulatory and trophic properties. Thus, Arnold I Caplan suggests the term "Medicinal Signaling Cells" due to its in vivo behavior [14].

Therapeutic Mechanism of MSCs

Owing to their potential of migrating to injury sites, secreting bioactive factors with pleiotropic effects such as anti-apoptotic, angiogenic, anti-inflammatory, anti-fibrotic, immunomodulatory, and antioxidant, and eventually lead to the repair of injured tissue [13,15–17], MSC are now competent tool of regenerative medicine and/or immune conditioning approaches. In [18] such as GVHD [17,19], Crohn's disease [17,20], Liver diseases [17,21,22], Aplastic anemia [23], Rheumatoid arthritis [17,24], Multiple sclerosis [25], neurodegenerative diseases [17,26,27], spinal cord injuries [17,28], COVID-19 [29], and others. Together, MSCs bear the capacity of overcoming the barrier of immune rejection due to their ability to lower down expression of MHC class-I molecules and the absence of MHC-II molecules, facilitating their administration without donor-recipient HLA matching [30] and exerting their immunoregulatory effects through cell-cell contact [31], transfer of mitochondria through tunnelling nanotubes and microvesicles to target cells [30,32] and paracrine secretion of soluble factors and microvesicles containing RNA and other molecules [13,30,33]. The utilization of MSCs in inflammatory diseases might reflect two different functions of MSCs: 1) Engraftment and 2) Tissue homeostasis. Depending on the extent of inflammation and stimulation of MSCs through Toll-like receptors, these can switch between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes [34]. Nevertheless, MSCs are not inherently immunosuppressive while these are conditioned by in vivo milieu to modulate the immune system [35].

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The immunosuppression caused by MSCs in GVHD dependents on the type of death (largely apoptosis) of MSCs by activated cytotoxic T lymphocytes and to some extent by natural killer cells [36,37] followed by the clearance of dead MSCs by monocytes / DC, termed efferocytosis [37,38]. This in turn, release an array of immunosuppressive mediators (HLA-G, PGE-2, IDO, TGF-β, COX-2, PD-L1, IL-1RA, IL-10, IL-6, CCL2) [39–42] which promote differentiation of effector/regulatory phenotype of immune cells like NK / T cells and Macrophages for attaining immune homeostasis [39]. Therefore, apoptosis and efferocytosis are two prime requirements for MSCs-mediated immune conditioning in GVHD, depicted in Figure 1. Furthermore, majority of the infused MSCs are undetectable within a few hours in vivo, thus, MSCs can act as "a drug instead of a cell". Intriguingly, the efficacy of apoptotic-MSCs is still controversial in various immune-mediated disorders. In preclinical mice model of GVHD, the potency of apoptotic-MSCs is ineffective or comparably low as compared to their live counterparts [43] suggesting that viability of MSCs is pre requisite for their therapeutic potential . Apart from the immune condioning in GVHD, MSCs potentially contribute to the repair of injured tissues also by their differentiation to damaged tissues and paracrine secretion of trophic factors [18,44]. The exact chemokines, cytokines, and growth factors released by MSCs that mediate tissue repair in GVHD are still unclear.

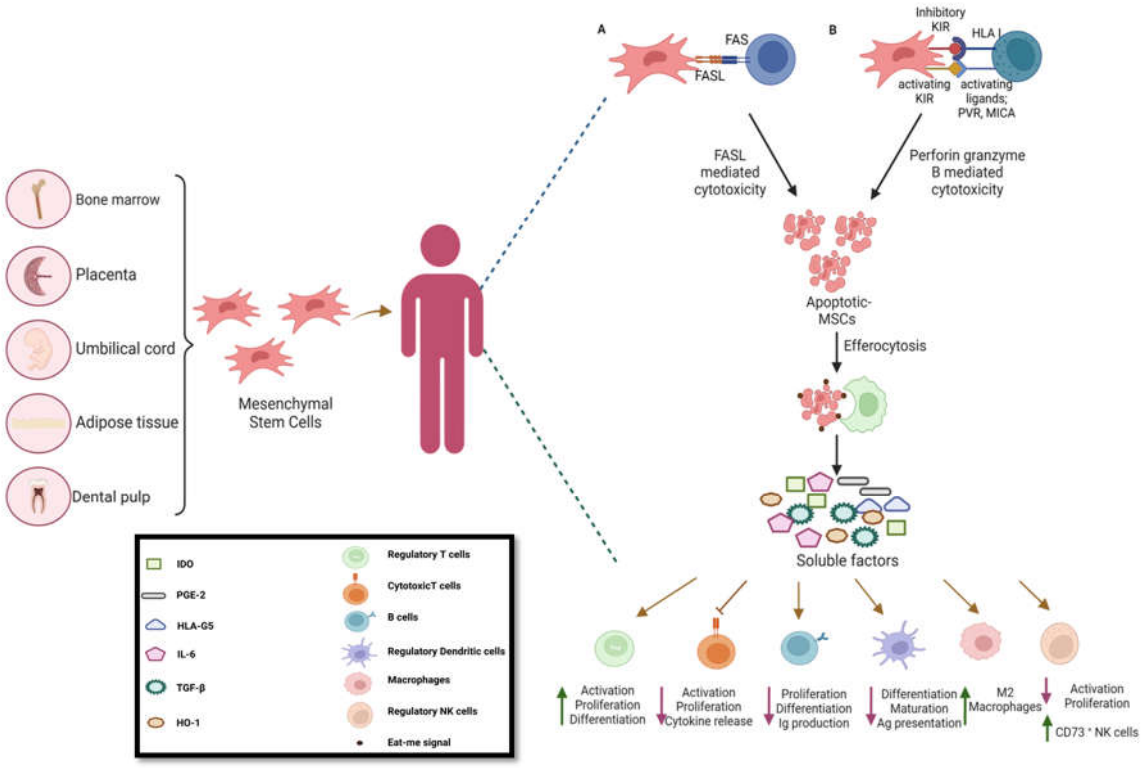

Figure 1. Schematic representation of the mechanism of MSCs in GVHD. Mesenchymal stem cells (MSCs) are believed to alleviate acute GVHD through a number of mechanisms. MSCs release anti-inflammatory cytokines, which can help reduce the inflammatory response associated with GVHD. In addition, MSCs can also modulate the immune system by decreasing T-cell activation and immunological memory, and by inducing T-cell apoptosis. MSCs have also been shown to reduce the production of pro-inflammatory mediators and promote the production of regulatory T-cells, which can suppress the immune system and reduce the severity of GVHD. Finally, MSCs can also promote tissue repair and regeneration, helping to restore damaged tissue that may have been caused by GVHD.

There is increasing evidence that transplant-associated thrombotic microangiopathy (TA-TMA), and endothelial dysfunction contributes to the pathogenesis of steroid-refractory GVHD [45,46] and is linked to high mortality and morbidity rates after HSCT [45,47,48]. The pathogenesis of TA-TMA

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has 3 major contributors: endothelial cell activation, complement dysfunction, and microvascular haemolytic anemia that leads to the dysfunctioning of multiple organs and ultimately to the death of transplant recipients due to delay in diagnosis [49].

Previous pre-clinical / clinical studies reported that MSCs have a shorter life span in vivo due to their sensitivity for perforin-dependent apoptosis causing by activated cytotoxic T cells and subsequent Efferocytosis [36,43,50–52]. Moreover, MSCs activate the complement system that not only caused the death of MSCs by forming a 'membrane attack complex' [50,53] but also causes the release of anaphylatoxins C3a, and C5a, that in turn bind to their receptors on neutrophils followed by the activation of neutrophils that cause apoptosis of MSCs through the oxidative burst [50,54–56]. Additionally, MSCs express complement regulatory proteins such as CD46, CD55, CD59, and soluble factor H that confer protection from complement-mediated lysis of MSCs [53,55–58]. Nonetheless, these mechanisms are not sufficient to protect MSCs from cell death. Thus, additional unknown factors are likely attenuating complement activation and contributing to immunosuppressive potential of MSCs thus advocating the clinical application of MSCs in complement-mediated disorders such as TA-TMA. Previous pre-clinical studies also demonstrated that the persistence of MSCs can be enhanced by depleting neutrophils and inhibiting the production of anaphylatoxins using monoclonal antibodies and surface modification of MSCs by complement inhibitors [50,59].

Clinical Scenario of MSCs In GVHD

There is no gold standard treatment for steroid-refractory GVHD (SR-GVHD) despite the availability of second-line treatments such as Ruxolitinib (JAK inhibitors) [60], and TNF-α inhibitors [61,62]. Owing to the immune condioning potential of MSCs, these have become ideal tools for cell-based therapeutic approach for (SR-GVHD). The first clinical application of MSCs for managing SR-GVHD was reported in 2004. In this case, allogeneic BM-MSCs were administered intravenously to the patient twice (a first dose on D+73 and another dose on D+150) to treat SR-GVHD. MSCs were well tolerated by the patient as he showed a little improvement at the first infusion while the second infusion remarkably enhanced the recovery of the patient [30,63]. This study showed promising results for GVHD and augmented the clinical use of MSCs which was approved by the FDA as the name of Prochymal for the treatment of SR-GVHD in paediatric patients. In 2012, Prochymal was the first MSCs-based drug that was approved in a few countries such as Canada, New Zealand, and Japan but not in USA and China [64]. Later on, the therapeutic efficacy of Remestemcel-L, a commercial off-the-shelf MSCs product was assessed in a phase-III randomized trial [65,66] but the study failed to demonstrate their promising results over the placebo with second-line therapy in terms of complete response (CR) and overall response (OR) [66,67]. However, the post-hoc analysis demonstrated that Remestemcel-L had a higher OR rate than the placebo arm [65,66]. Moreover, another commercial BM-MSC product, TEMCELL, was approved in Japan for the treatment of SR-GVHD patients in 2016, and interestingly, the therapeutic efficacy of TEMCELL was found to be equivalent to a prospective study of Remestemcel-L and identified elements that could predict OR and non-relapse mortality (NRM) in SR-GVHD patients [66,68]. Moreover, in 2020 phase-III trials were conducted by Osiris Therapeutics Ltd. using Remestemcel-L for paediatric SR-aGVHD patients in the absence of immunosuppressive agents. Infection-related adverse events were recorded, and the OR and CR rate was 70% and 44.6% on D+28 and D+100 respectively [69].

Induced MSCs (iMSCs) are more homogeneous than primary MSCs since iMSCs originated from a single induced pluripotent stem cell (iPSC) clone. This concept led to the development of therapeutic intervention based on iPSCs-derived MSCs for GVHD by Cynata's Therapeutics in 2016. Further, Cynata's Therapeutics got approval for the clinical phase I study involving iPSC-derived MSCs for SR-aGVHD and the results demonstrate the clinical efficacy of iPSC-derived MSCs [70]. A brief overview of clinical trials involving MSCs-based therapy for GVHD, registered in ClinicalTrials.gov is summarized in Table 1.

However, phase I/II clinical trials involving MSCs for the treatment of immune-related disorders yielded unpredicted outcomes in terms of the complete response (CR) over the placebo. Thus, the efficacy of MSCs in clinical trials is variable and unpredictable and the underlying mechanism of its efficacy/inefficacy has not been explored fully. The heterogeneous response of MSCs in immune-

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mediated disorders is attributed to the heterogeneity/viability of MSCs and pathological scores of the patients. Other factors like tissue source, age, sex, genetic makeup, the health status of the donor, culture conditions, long term-preservation, passage number, and other parameters including the severity of GVHD, heterogeneity of the disease, organ involvement, diverse patient characteristics, dose, mode and frequency of administration of MSCs [71] also potentially contribute to the efficacy of MSC. Additionally, there is no available biomarker that could predict the response of GVHD/SR-GVHD patients to MSCs.

Preconditioning of MSCs to Improve Clinical Efficacy

In view of heterogencity of MSC in various diseases discussed above, There is a need to augment the therapeutic immunomodulatory potential of MSCs in GVHD. Various strategies have been suggested to enhance the immunoregulatory potency of MSCs while maintaining their stemness and therapeutic efficacy. It is well known that an in vivo milieu could dictate the fate of MSCs and several approaches have been designed to enhance their therapeutic efficacy in immune-mediated disorders, discussed in followed section.

1) Preconditioning with cytokines:

Several reports suggested that preconditioning of MSCs using Th17 effectors (IFN-γ +TNF-α+IL-1β+IL-17) enhances their immunosuppressive potency through increasing homing of MSCs to injured tissues and production of immunosuppressive soluble factors. This promotes the differentiation of effector immune cells to their respective regulatory phenotype (Tregs, Th2, M2 macrophage). Preclinical studies with IFN-γ pre-conditioned MSCs in NOD/SCID mice model imposed a positive impact on their survival while reducing GVHD by activation of JAK/STAT and nd IDO [92,93]. These promising results led to Phase I clinical trial (NCT04328714) that involves the use of IFN-γ primed BM-MSCs as prophylactic conditioning of GVHD [94]. Nonetheless, inflammatory cytokines activated a specific signaling pathway that exerted an immune regulatory effect employing immunomodulatory trophic factors which are summarized in Figure 2 and Table 2. Additionally, they enhanced the homing of MSCs by increasing the expression of chemokines (CXCL9, CXCL10, and CXCL11) and adhesion molecules (VCAM-1, ICAM-1) [94].

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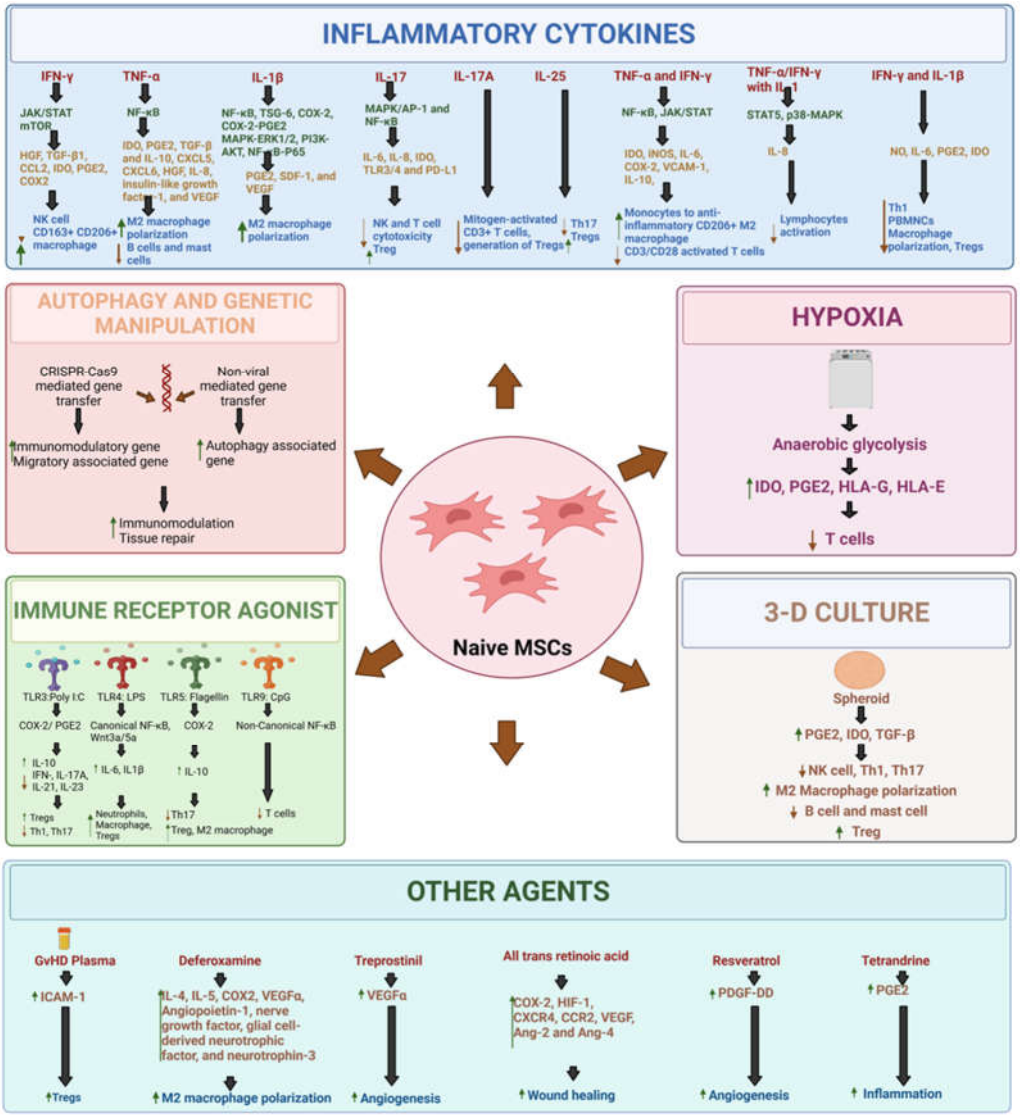

Figure 2. An overview of available strategies for preconditioning of MSCs to enhance the immunomodulatory potential. Preconditioning of mesenchymal stem cells (MSCs) is the process of exposing them to certain conditions or stimuli that alter their state and behavior. This can be achieved through various methods, including hypoxia, chemical (growth factors, cytokines, and drugs), and genetic stimuli (introduction of genes, small molecules, and microRNAs).

2) Hypoxia preconditioning:

Hypoxia is one of the intrinsic factor which is known to promote angiogenic switch and augment immunosuppressive / Th2 microenvironment. Hypoxia enhances glycolysis of MSCs that leads to an increase in lactate level while the combination of IFN-γ and hypoxia enhanced the expression of IDO, PGE2, HLA-G, HLA-E, leading to inhibition of T cells activation [94]. Hypoxia with calcium ions causes a significant reduction in GVHD due to an increase in the polo-like kinase-1 (PLK1), zinc-finger protein-143, dehydrogenase/reductase-3, and friend-of-GATA2 [92,121]. Overall, hypoxia increases the homing ability of MSCs, ultimately leading to the rapid repair of injured tissue [100]. However, prolonged exposure of MSC to hypoxic microenvironment disrupt their vitality and compromise differentiation potential of MSCs [122]. Thus, an appropriate dose and exposure time for hypoxia is paramount for immune condioning potential of MSCs.

3) Immune receptor agonist:

Mesenchymal stromal cells express a variety of Toll-like receptors (TLR) which can interact with their specific ligands such as microbiome derived factors , which results in modulation of the immune response [34,123] by activation of phagocytic cells [34,124]. Various preclinical studies employed

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priming of MSCs with TLR-3 agonists (CpG island) to modulate the immune response which is candidly summarized in Table 3.

4) 3-dimensional (3D)-culture:

Paracrine signalling is main mechanism of MSC induced immune conditioning which is mediated through various transmembrane adhesion molecules on MSC [94,97,131–134]. This is known to mimics in vivo milieu and exert immunomodulatory effects due to the secretion of MMP-2, VEGF, and TSG-6 [94]. Additionally, 3-dimensional (3D)-spheroid culture enhance the stemness potential and increase the secretion of various immunomodulatory factors such as PGE-2, IDO, TGF-β, and many anti-inflammatory cytokines and soluble factors [106,135]. Therefore preconditioning the MSCs with pro-inflammatory cytokines using 3D-spheroid culture with bioactive materials such as hydrogels, and extracellular matrix increase cell-cell communication, can augment paracrine effect of MSCs [94]. Along with this, a few preclinical studies involve the use of scaffolds and biocompatible nanomaterials (gold nanoparticle, graphene derivatives) that might also enhance the biological properties of MSCs such as differentiation, homing, and migration [136–139]. Overall, the use of bioactive materials warrant their use in promoting the tissue repair and regeneration efficacy of MSCs.

5) Genetic manipulations:

Several factors such as HIF-1α [132,140], IL-10, IL-4, TGF-β, CXCR4, GATA-4 [132,141], and HGF [142] (Figure 2) can increase the migration, cell survival, proliferation, and immunosuppressive potential of MSCs. Recently, CRISPR Cas-9 technology has been employed to alter the m/miRNA content corresponding to above factors inMSCs or MSCs-derived extracellular vesicles, and transient epigenetic modifications [132,143] to augment their potential in regenerative medicine. However, these are at the early stage of research, so, it is difficult to predict their translational value.

6) Autophagy alteration:

Several studies have reported that either upregulation or down-regulation of autophagy in MSCs enhances their immunomodulatory effect in inflammatory diseases such as inflammatory bowel disease, colitis, and liver fibrosis. Alteration in autophagy enhances Tregs and decreases Th1 polarization and ultimately decreases the levels of inflammatory cytokines (IL-17A, IFN-γ, IL-2) and mediates immunosuppressive effect through PGE2 secretion [94].

7) Other agents:

A recent study demonstrates that host derived factors such as serum, plasma or IVIG can potentially influence immunomodulatory potential of MSCs which can be included as component of personalized MSCs therapy. Therefore, MSCs are primed with GVHD patient-derived plasma as GVHD is characterized by cytokine storm and their patient-derived plasma is marked heterogeneous in the proportion of inflammatory cytokines. GVHD plasma enhances the immunomodulatory potency of MSCs by alteration in their morphology, upregulating the expression of cell-adhesion molecule (ICAM-1), and induction of Tregs [144]. Moreover, various bioactive agents and various drugs such as tacrolimus, and rapamycin [132] can be used to enhance homing, survival, and immunoregulatory potential of MSCs so that the efficacy of MSCs augment in clinical trials. In the upcoming section, we are discussing the use of bioactive compounds that can enhance their therapeutic potential as immunoregulatory agents, summarized in Figure 2 and Table 4.

Conclusion of Clinical Perspective

Mesenchymal stromal cells have shown promising results in clinical studies of immune-mediated disorders. However, the response of the recipients towards MSCs-based cellular therapy is quite variable and unpredictable which limits the efficacy of MSCs-based intervention in clinics. It is well demonstrated that MSCs exert their immunoregulatory effect through paracrine secretion of growth factors, cytokine, and other immunoregulatory soluble factors. Owing to this potential, MSCs secretome could be a better therapeutic or prophylactic approach for immune disorders due to the following advantages, 1) it can be manipulated and stored more easily than cells, 2) with fewer costs, it can be a used asready-to-use product suitable for emergency interventions, 3) the possibility of pharmaceuticalizing MSCs-secretome into freeze-dried and stable powder products, could be easily acceptable by the community as a cell-free intervention. Moreover pharmaceuticalization of MSCs

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derived secretome into a high-quality safe and effective immune pharmaceuticals by exploiting large-scale and GMP procedures. Additionally, there is dire need of developing MSCs secretome, specific for a disease. However, a recent study, paradoxically demonstrates that the secretome of MSCs consists of solely pro-inflammatory cytokines (MCP-1, IL-6, IL-8) while barely consisting of any anti-inflammatory cytokines (IL-10, IL-4) [150] In the clinical scenario, MSCs-derived EVs or whole secretome have not been used for GVHD as a therapeutic or prophylaxis but there are a few preclinical studies that demonstrate that the MSCs-derived EVs have the potential to neutralize GVHD [151] to some extent These studies revealed that MSCs (BM/WJ) derived EVs exert their immunoregulatory effect by decreasing the levels of IL-21, IL-22 [151,152], IFN-γ, TNF-α [151,153], IL-2 [151,154], increasing the levels of IL-10) [151,154], and also modulating the immune cells such as differentiation of $CD4^+$ T cells to a regulatory phenotype (Tregs) [151,155], suppression of $CD4^+$ [151,152] and $CD8^+$ T cells into effector phenotype [151,156] and together improving the survival of GVHD mice model [151,153].A major hurdle in MSCs from the clinical perspective is to identify responders and non-responders of GVHD for MSCs therapy as most of the phase 2/3 clinical trials show the ineffectiveness of MSCs therapy for GVHD. Generally, it is required to develop a biomarker in respect of either cellular or plasma/serum protein that can predict and monitor the clinical response and efficacy of MSCs or their secretome for GVHD patients.

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