Mesenchymal Stem Cells in Autoimmune Diseases

Subjects: Cell & Tissue Engineering

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Mesenchymal stem cells (MSCs) modulate immune responses and maintain self-tolerance. Their trophic activities and regenerative properties make them potential immunosuppressants for treating autoimmune and autoinflammatory diseases. MSCs are drawn to sites of injury and inflammation where they can both reduce inflammation and contribute to tissue regeneration. An increased understanding of the role of MSCs in the development and progression of autoimmune disorders has revealed that MSCs are passive targets in the inflammatory process, becoming impaired by it and exhibiting loss of immunomodulatory activity. MSCs have been considered as potential novel cell therapies for severe autoimmune and autoinflammatory diseases, which at present have only disease modifying rather than curative treatment options.

Keywords: mesenchymal stem cells ; immunogenicity ; immunomodulation ; mesenchymal stem cell dysfunction ; mesenchymal stem cell transplantation

1. Introduction

Mesenchymal stem cells (MSCs) are multipotent progenitor stromal cells that self-renew and differentiate toward multiple mesenchymal cell lineages [1]. With the rapid expansion of research into tissue-specific stem/progenitor populations, in 2006 the International Society for Cellular Therapy (ISCT) defined the minimal criteria for MSC characterisation to include the following: (1) adherence to tissue culture plastic and fibroblastic morphology; (2) positive/negative expression of panels of surface antigens; (3) multi-lineage differentiation toward chondrogenic, adipogenic, and osteogenic cell lineages. The establishment of internationally recognised and standardised criteria for determining what is an MSC population has been fundamental to advancing their role in biomedical research. Identification of MSC phenotype markers and characterisation of their multipotency has led to optimised methods for their isolation and culture from rare populations within tissues. Measurements of phenotype and function provide biological context to tissue-specific differences exhibited between MSC populations and the changes that occur in response to physiological and pathophysiological stimuli. Standardisation of criteria also facilitates the characterisation of MSCs as they undergo bioprocessing protocols in the manufacture of cell-based therapeutics.

MSCs have been successfully isolated from almost all post-natal mesodermal tissues, including bone marrow (BM), umbilical cord (UC), adipose tissue (AT), amniotic fluid (AF), placenta, dental tissue, synovial membrane, and peripheral blood. Tissue-dependent differences in cell surface antigen expression are indicative of variation in cell migration and cell-homing potential. The reported intra- and inter-tissue functional heterogeneity between MSC clones highlights the need for further understanding of the biology of MSCs and how they can be used effectively in developing cell-based therapeutics [2]. Bone marrow is arguably the most researched tissue source as a result of the seminal work of Friedenstein and colleagues. These studies demonstrated that a sub-population of BM cells, constituting 0.001–0.01% of the total cell number within the tissue [3], was able to undergo osteogenic differentiation and form osseous tissue following heterotrophic transplantation [4][5]. Provided with appropriate stimuli, MSCs have potential for differentiation toward multiple specialised cell lineages of mesenchymal origin, including chondrocytes, osteocytes, tenocytes, ligamentocytes, and myocytes [6]. Differentiation to non-mesodermal cell lineages has been reported with examples of hepatocytes, epithelial cells, alveolar cells, astrocytes, neural precursors, and mature neurons, alluding to the putative role of MSCs in endogenous tissue repair. The understanding of the intrinsic properties of self-renewal and multipotent differentiation is fundamental to their importance in developing advanced regenerative medicine strategies. Specifically, this encompasses the ability to develop and optimise protocols for ex vivo expansion in culture, prior to directed differentiation toward functional cell populations and the manufacture of autologous and allogeneic products that repair and regenerate tissues which have been damaged by injury or disease (**Figure 1**) [6].

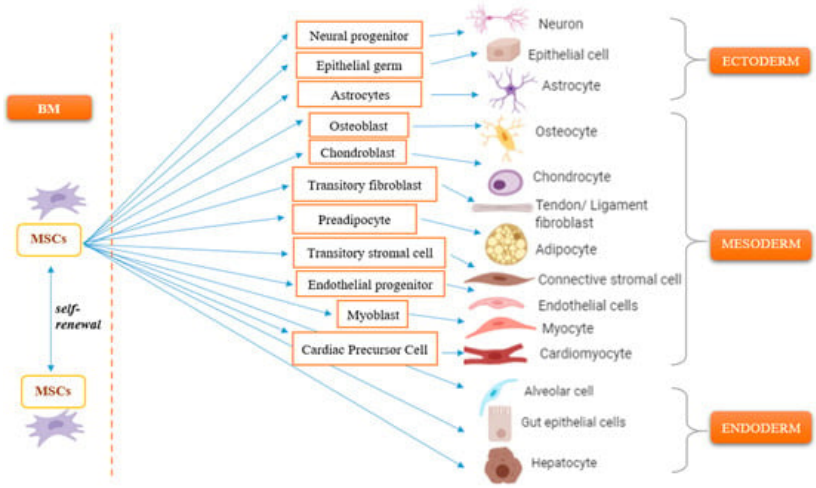

Figure 1. Summary of the mesenchymal stem cell lineage differentiation. MSCs demonstrate multipotent differentiation to cells of mesodermal origin: osteogenic, adipogenic, and chondrogenic pathways. There is some evidence of ectodermal germ (neural, epithelial) and endodermal origin such as alveolar cells, gut epithelial cells, and hepatocytes. Bone marrow, (BM). Created with BioRender.com.

2. Migratory Response of Mesenchymal Stem Cells

The migratory response of MSCs is critical to their function. They are recruited in from peripheral blood and home into the site of damaged tissue in response to biochemical cues, where they can moderate inflammatory and immune cell activity, and begin to effect repair [7]. MSC migration and homing to sites of tissue injury is regulated by chemokines, cytokines, and growth factors. It is dependent on the expression of homing receptors and activation of integrins that promote adhesion of MSCs to extracellular matrix proteins. MSCs express a wide range of chemokine receptors including CXCR3, CXCR4, and CCR5 which are involved in the recruitment of MSCs from the bone marrow to the peripheral circulation prior to their migration to the site of injury [8]. The chemokine stromal cell-derived factor-1 (SDF1, known also as CXCL12) is critical for stem/progenitor and mesenchymal cell chemotaxis and organ-specific homing in injured tissue through interaction with its cognate receptor CXCR4 on the surface of these cells [9]. CXCR4 is highly expressed by freshly isolated BM-MSCs from young adults, but becomes reduced with the ageing of endogenous tissues and in vitro ageing as the cells are repeatedly passaged in culture. This therefore limits their ability to respond to homing signals and hence reduces their regenerative capability [8]. Senescence of MSCs has significant consequences on the biology of MSCs, including their self-renewal and proliferative capacity, as well as effector functions, including immunomodulation and cell lineage differentiation and specialisation. CXCR4 gene deletion in young-donor MSCs was associated with the increased production of reactive oxygen species (ROS) and subsequent DNA damage and replicative senescence, which is characteristic of prematurely aged phenotypes [10].

Bioactive molecules play an important role in immune homeostasis. Growth factors, such as basic fibroblast growth factor-2 (FGF2), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF1), platelet-derived growth factor (PDGF), and transforming growth factor-β1 (TGFβ1), play a prominent role in regulating MSC migration. FGF2 promotes upregulation of αVβ3 integrin and activation of MEK/ERK pathways that stimulate the migration of BM-MSCs and homing to sites of injured tissue [9]. VEGF regulates BM-MSC migration and proliferation through platelet-derived growth factor receptors (PDGFRs) and SDF-1α expression. PDGF has been shown as a prominent factor for BM-MSC migration, binding to PDGFRα and PDGFRβ [9]. Production of TGFβ1 is increased at the site of tissue damage where it stimulates expression of CXCR4 on BM-MSCs and promotes their migration and their homing to myocardial injury [11]. This is most likely by activation of the TGFβ type I receptor and downstream non-canonical signalling by Akt, extracellular signal-regulated kinase 1/2 (ERK1/2), focal adhesion kinase (FAK), and p38 [12].

Another molecule responsible for MSC migration is osteopontin (OPN), which has been reported to be upregulated in response to tissue damage and subsequent inflammation in the heart, bone, kidney, and lung [9]. OPN promotes BM-MSC migration through the increased expression of integrin β1 and lamin A/C expression, leading to a decrease in nuclear stiffness via the FAK-ERK1/2 signalling pathway [13].

Migration of MSCs is also stimulated by pro-inflammatory cytokines, including interleukin-1β (IL1β), tumour necrosis factor-α (TNFα), and interferon-γ (IFNγ) [14]. TNFα is involved in tumour progression and plays an essential role in epithelial-mesenchymal transition [15]. TNFα and IFNγ act in synergy to induce the production of superoxide anions, with corresponding up-regulation of inflammatory responses. IL1β cytokine activates mast cells and induces histamine

production, which increases membrane permeability [15]. IL1β was found to promote the expression of CXCR3 on the surface of MSCs through activation of the p38 MAPK signalling pathway [14]. At the same time, IL1β upregulated CXCL9 (both at the mRNA transcript level and measured ligand secretion) in umbilical vein endothelial cells, and this was concurrent with an increase in the chemotaxis and trans-endothelial migration potential of MSCs [14]. However, pro-inflammatory cytokines could play a dual role in MSC migration and immunomodulatory function.

3. Immunomodulatory Properties of MSCs

The immunomodulatory ability of MSCs is of significant interest within the context of understanding the underpinning scientific mechanisms that contribute to the dysregulation of immune homeostasis and the causal relationship to the onset and progression of autoimmune and autoinflammatory disorders. Advancing this understanding will have a significant impact on the development and production of therapeutic interventions. MSCs regulate both innate and adaptive immune responses through cell–cell contact and production of paracrine mediators. The immunomodulatory mechanisms of MSCs have been studied using in vitro and in vivo experimental animal models of autoimmune disorders [16][17][18].

3.1. Paracrine Activity of MSCs

Paracrine activity of MSCs includes the secretion of growth factors and cytokines that regulate immune cell biology, promote angiogenesis, and suppress fibrotic remodelling. Predominant growth factors involved in these processes include VEGF and FGF2, which have both been reported to promote myocardial recovery and improve cardiac function by mediation of angiogenesis and induction of neovascularisation following ischemic injury [19].

Production of IGF1 and TGFβ regulates the MSC-mediated suppression of $CD8^+$ T-cells, while HGF and FGF2 suppress fibrotic remodelling [19]. BM-MSCs contribute to lymphopoiesis and regulate the development of T- and B-lymphocytes through the secretion of these growth factors and cytokines, as well as the expression of cell adhesion molecules. HGF and macrophage colony stimulating factor (M-CSF) regulate MSC modulation of dendritic cells (DCs) by inducing differentiation of mature DCs into tolerogenic dendritic cells (DCregs) via the AKT signalling pathway [20]. MCP1 stimulates the activity of regulatory T-cells (Treg), a sub-population of T-cells that regulates immune responses and reduces the onset and progression of autoimmune disease.

MSC-mediated immunosuppression is dependent on IFNγ activation in combination with TNFα or IL1β [21][22]. This phenomenon has been coined the term “licensing” and may offer a mechanism for a role of MSC dysfunction in the activity and remission of autoimmune and autoinflammatory disease states [21]. On stimulation with a combination of IFNγ with TNFα or IL1β, MSCs produce nitric oxide (NO), a powerful cytotoxic molecule that inhibits T-cell proliferation [23][24]. Prostaglandin E2 (PGE2) programs macrophages to release IL10 and inhibit T-helper cell activity and IL2 production. Inhibition of this prostaglandin has been shown to result in a decrease in the anti-proliferative effect exhibited by MSCs on T-cells. Another soluble mediator that contributes to MSC-mediated immunosuppression is indoleamine 2,3-dioxygenase (IDO), an enzyme that catabolises the essential amino acid tryptophan in the kynurenine pathway [25]. IDO released by MSCs in response to IFNγ reduces tryptophan availability and the production of metabolite derivatives in NK cells and T-cells and therefore inhibits their proliferation [25]. In addition, MSCs secrete immunosuppressive cytokines, including IL7, IL11, IL14, and IL15, and stimulate an increase in anti-inflammatory cytokine IL10 production by DCs and monocytes [26].

3.2. Regulatory Effects of MSCs on Immune Cells

Contact-dependent mechanisms of MSC-mediated immunosuppressive activity inhibit the proliferation and activation of the major immune cell populations, including T-lymphocytes, B-lymphocytes, DCs, pro-inflammatory macrophages, and natural killer (NK) cells by arrest in the G0/G1 phase of the cell cycle [27]. Cell–cell interactions between MSCs and immune cells are mediated by adhesion molecules, including P-selectin, intercellular adhesion molecule-1 (ICAM1), and vascular cell-adhesion molecule-1 (VCAM1, CD106). It was found that chemokines and adhesion molecules trigger T-cells rolling, arrest, and then transmigration through the endothelium. An inflammatory environment induces MSCs to secrete multiple chemokines and upregulate the expression of ICAM1 and VCAM1, which attract and engage T-cells to MSCs [23]. The clinical relevance of these interactions is highlighted by showing that the blockade or deletion of ICAM1 and VCAM1 could significantly reverse MSC-mediated immunosuppression in vitro and in vivo [28]. Moreover, high expression of ICAM1 and VCAM1 is associated with greater immunosuppressive capacity of MSCs [28]. MSCs inhibit the proliferation of T-cells, specifically pro-inflammatory populations of T-helper cells (Th17 and Th1), decrease the ratio of Th1/Th2 T-helper cell populations, and promote an anti-inflammatory profile by activation of Treg cells [21]. These findings could be translated into therapies for autoimmune and autoinflammatory diseases such as rheumatoid arthritis (RA), which are characterised by a predominance of pro-inflammatory $CD4^+$ T cells with the hyper-proliferative capacity to differentiate into

Th1 and Th17 pathogenic T cells [29]. Th17 cells participate in the pathogenesis of different autoimmune diseases, such as systemic lupus erythematosus, type 1 diabetes, multiple sclerosis, and bowel disease [30].

Additional evidence has shown that MSCs can inhibit the differentiation, maturation, and activation of DCs [31]. DCs are highly specialised antigen-presenting cells that play an exclusive role in naïve T-cell stimulation during the primary immune response. MSCs inhibit the initial differentiation of monocytes to DCs by dampening the expression of CD86, CD1a, and HLA-DR. Furthermore treatment of DCs with MSC-derived EVs demonstrated a reduced ability to migrate toward the CCR7-ligand CCL21 [31]. MSCs significantly influence DC antigen presentation to $CD4^+$ T-cells and cross-presentation to $CD8^+$ T-cells because of the inability of DCs to migrate to the draining lymph nodes [32]. The influence of MSCs on B-cells has been less well studied, although it is known that the interaction between MSCs and B-cells is complex with the interplay of multiple different contributing factors. MSCs can regulate B-cell activation indirectly through T-helper cell activity or directly through the production of soluble factors, including the IL1 receptor antagonist.

4. Immunogenicity of MSCs

MSCs are considered immune-privileged, having low expression of major histocompatibility complex (MHC) class I, minimal expression of MHC class II, and deficiency in co-stimulatory molecules required for immune cell activation, including B7-1, B7-2, or CD40 [25].

Contrary evidence suggests that MSCs can also be immunogenic. Animal studies have revealed that despite low level immunogenicity, allogeneic MSCs are immune-rejected via MHC ClassI and MHC ClassII in mice [33]. Oliveira et al. (2017) suggested that rejection of MSCs might be dependent on the context of the inflammatory environment into which the cell population was transplanted. The study showed that prior treatment of MSCs by IFNγ and TNFα could modulate MHC class I and II expression, increasing their immunogenic potential [25]. This immune recognition of MSCs has been proposed as an important mechanism in attaining an immunomodulatory therapeutic effect. Witte et al. (2018) showed that allogeneic Umbilical Cord (UC)-MSCs were recognised by host immune cells and phagocytosed by monocytes post-infusion into mice. The subsequent UC-MSCs-primed monocytes demonstrated an increase in IL10 and TGFβ gene expression and reduced TNFα expression; moreover, monocytes primed by UC-MSCs have been shown to induce Treg cell differentiation in mixed lymphocyte reactions [34]. However, prolonged treatment of MSCs with pro-inflammatory cytokines IFNγ, TNFα, IL17, and IL1β resulted in not only activation but also increased expression of MHC class I/II [35]. Considering potential clinical applications of MSC delivery into the inflammatory tissue, this may influence the balance between immunosuppressive activity and MHC Class II expression by MSCs [36].The safety concerns of MSCs transplantation have also included the potential of the risk of thrombosis. Intravascular transplantation of tissue factor (TF)-bearing cells provokes an instant blood-mediated inflammatory reaction (IBMIR) resulting in thrombotic complications and reduced engraftment [37]. Plasma levels of TF/CD142 are correlated with activation of the IBMIR and vary between MSC from different sources [37]. AT- and UC-MSCs demonstrate higher levels of TF, reduced hemocompatibility, and increased clot formation dependent on coagulation factor VII [37]. MSCs highly express pro-thrombotic tissue factor (TF/CD142) and collagen type-1, which activate the coagulation cascade [38]. The tissue factor (TF)-mediated pro-coagulant activity could be reverted by heparin co-administration in MSC transplantation.

Long-term ex vivo expansion in the production of MSC therapies has been reported to increase pro-thrombotic properties. Infusion of large cell doses of higher passage MSCs (passages 5–8) have been shown to elevate the coagulation cascade, cause activation of complement marker C3a, and increase the expression of thrombin, FVII, FXIa, and FXIIa clotting factors that may cause thrombosis or embolism [38]. This highlights the need for hemocompatibility assessment of MSC products before intravascular delivery.

5. Impairment of MSC Biology as a Key Moment in Disease Pathogenesis

There is now an increased understanding of the role of MSCs in the mechanisms of development and progression of autoinflammatory and autoimmune diseases. MSCs respond to tissue damage by reducing inflammation and repairing injured tissue as a normal physiological response. In pathophysiological autoimmune and autoinflammatory conditions, which are characterised by consistent chronic inflammation, MSCs are passive targets in the inflammatory process. They become impaired and exhibit loss of immune modulatory function. Impairment of MSC biology has been identified in RA, ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), chronic obstructive pulmonary disease (COPD), Parkinson’s disease, type 2 diabetes, and idiopathic pulmonary fibrosis (IPF). MSC impairment is manifest by a reduction in proliferative capacity and immunoregulatory properties, altered morphology, dysregulated cytokine secretion, and altered cell–cycle regulation with enhanced senescence and reduced capability in supporting the hematopoietic system [39][40][41][42][43][44].

MSCs are negatively influenced by the high concentrations of pro-inflammatory cytokines that are present within the pathogenic environment of autoimmune and autoinflammatory diseases [45][46]. Pro-inflammatory cytokines, specifically IFNγ and TNFα, synergistically impair proliferation and differentiation of MSCs via NFκB [47][48]. It has been shown in previous research that treatment with high levels of IFNγ and TNFα for a period of 21 days resulted in NFκB–mediated upregulation of the oncogenes c-Fos and c-Myc, followed by increased susceptibility to MSCs in tumorigenesis. Medications that reduce the levels of IFNγ and TNFα (e.g., aspirin) block malignant transformation of MSCs by inhibition of NFκB/SMAD7 and NFκB/c-FOS and c-MYC pathways in mice [47][48].

Moreover, MSCs stimulated by TNFα and IL1β for up to 18 days obtained what was described as a cancer-associated fibroblast (CAFs) morphology, inclusive of increased cell size, detected by calcein and Hoechst staining, accompanied by elevated levels of vimentin and fibroblast activation protein (FAP), and reduced expression of α-smooth muscle actin (αSMA). These cells were characterised by the release of pro-inflammatory factors and stimulated cancer cell migration by CCR2, CCR5, CXCR1/2, and Ras-activating receptors and therefore may be considered as pro-carcinogenic [49].

Another crucial mechanism in the impairment of MSC function is highlighted in RA by the reduced ability to downregulate Th17 cell activity [41]. RA-derived MSCs have lower proliferative potential and migration capacity, which does not correlate with previous treatment with methotrexate or biological agents, including TNFα inhibitors and anti-IL1.

MSCs isolated from AS patients showed normal rates of proliferation, cell viability, expression of cell surface CD antigens, and potential for multi-lineage differentiation. However, their immunomodulatory properties measured in two-way mixed-lymphocyte reaction (MLR) or PBMC proliferation in the presence of phytohemagglutinin were weaker compared to MSCs from healthy volunteers [42]. MSCs obtained from AS patients have decreased phosphorylation of Beclin-1, an important molecule required for the initiation of autophagy, resulting in the deficiency of autophagy, and as a consequence MSC dysfunction [50]. Autophagy is a lysosome-mediated catabolic process that eliminates molecules and cellular components, including nucleic acids, proteins, and lipids [51].

BM-MSCs derived from patients with SLE show impaired immunomodulatory properties and reduced proliferation rates. This phenomenon was coupled with increased ROS production, DNA damage, expression of senescent p16 and p53, altered cytokine profile with overexpression of pro-inflammatory IL6 and IL8, and downregulation of TGFβ1, IDO, and LIF [52]. SLE BM-MSCs that have been chronically stimulated by pro-inflammatory cytokines within the native tissue environment exhibit a pathophysiological and senescent phenotype with over production of pro-inflammatory mediators that promote inflammation and cellular dysfunction [52]. It was shown that SLE MSCs have a five-fold increase in IFNβ and increased IFNβ-induced mRNAs, including mRNA for the intracellular nucleic acid sensing adaptor protein MAVS. Lin et al. (2017) proposed that the IFNβ-MAVS feedback loop may alter the development of immune cells and contribute to autoimmune progression in SLE [52].

6. Pre-Clinical Studies of Mesenchymal Stem Cells

The combined properties of immunomodulation and differentiation, hematopoietic support, and pro-regenerative features account for the promising therapeutic potential of MSCs. Particular attention is given to their potential efficacy in cases of severe autoimmune or autoinflammatory diseases that are refractory to conventional therapy, and the opportunity for fewer side effects when compared to the need for repeated administration of immunosuppressive drugs. Recent pre-clinical studies focused on stem cell therapy have demonstrated the efficacy and safety of MSC transplantation [53][54][55].

MSC transplantation was proposed as a promising new direction for chronic lung disease. Pre-clinical investigations revealed the efficacy of intratracheally, intranasally, or systemically administered MSCs obtained from BM, AT, UC, or placenta in lung injury models [56]. MSCs are localised to the lung after systemic administration by their ability to home into the sites of injury through the engagement of chemotactic proteins, such as SDF1/CXCL12 with CXCR4. In injured lung animal models, MSCs regenerated lung tissue, reduced inflammation, and limited fibrosis by upregulating anti-inflammatory and downregulating pro-inflammatory cytokine release [56]. MSCs localised to the lung following bleomycin-induced injury in mice arrested the progression of fibrosis and decreased inflammation [56]. Studies using MSCs in experimental murine models of asthma identified immunosuppressive effects of MSC by recruitment of $CCR2^{+}$ monocytes and increased IL10 production [57]. The immune suppressive effects of MSC in the model of asthma also included elevated levels of TGFβ, transfer of mitochondria to airway epithelial cells, and increased numbers of Tregs [57]. However, MSCs display a dual role in the progress of fibrosis. Despite the immunomodulatory and anti-inflammatory properties of MSCs, TGFβ is a primary factor in driving fibrosis via activation of Smad-based and non-Smad-based signalling pathways. This results in activation of myofibroblasts, enhanced production of extracellular matrix (ECM), and inhibition of its degradation [58].

MSCs have successfully promoted myelin repair in an experimental mouse model of autoimmune encephalomyelitis (EAE). Transplantation of BM-derived MSCs into myelin oligodendrocyte glycoprotein (MOG) 35–55-induced EAE demonstrated an 80% reduction in demyelination and a decrease in inflammatory cell infiltrates, including T-cells (50%), B-cells (51%), and macrophages (51%). This was coupled with a decline in disease progression measured by a 41% decreased cumulative score and a 60% lower maximal clinical score [18]. These results indicate that MSCs may be beneficial for the treatment of multiple sclerosis (MS) at the onset of disease when the immune response against myelin plays a major role in pathogenesis. MSCs derived from embryonic stem cells (ES-MSCs) have a greater neuroprotective potential than those derived from amniotic fluid (AF-MSC) and adult tissues and may therefore have a better therapeutic effect for the treatment of neurological diseases [55]. ES-MSCs showed a higher proliferative capacity in comparison to AF-MSCs, and higher anti-inflammatory potential due to increased NFκB-mediated release of anti-inflammatory cytokines [55].

7. Clinical Application of Mesenchymal Stem Cells in the Treatment of Autoimmune and Autoinflammatory Diseases

Following pre-clinical evaluation in experimental animal models, the therapeutic application of MSCs in the clinical setting has been considered for autoimmune and autoinflammatory diseases that currently have analgesic, i.e., symptom-alleviating, rather than curative treatments. Autoimmune and autoinflammatory diseases are mostly treated by immunosuppressants, but these are not always successful within a heterogeneous patient population. Continuous administration of medications can amplify side effects and long-term suppression of the immune system increases the risk of infections. Currently effective treatment options are limited and there is a need for new therapeutic approaches [59].

There is an historical context for the use of haematopoietic stem cell (HSC) transplantation that precedes MSC application. HSCs have been applied to poor prognosis and refractory treatment of severe autoimmune diseases since 1995. MSCs are considered as an attractive source for co-transplantation with HSCs because of their role in forming the microenvironment niche and their immunosuppressive properties that support allogeneic transplant viability. The first clinical application of BM-MSCs was performed in 1995, where the cells were used in the treatment of hematologic malignancy patients [60].

Later, the efficacy of MSC treatment was proven in a phase II experimental trial for the treatment of leukaemia by co-delivery of MSCs with allogeneic HSCs. Results of the trial showed the ability of MSCs to modify innate and adaptive immune responses and provide an immunosuppressive effect that resulted in improved outcome measures for patients with steroid-resistant acute GVHD [61][62]. MSCs have now been used in the treatment of many autoimmune diseases, where standard therapeutic methods have proved ineffective. BM has been considered to be the preferred tissue source for MSCs in therapeutic approaches, most likely because of the historical developmental pathway where BM-MSCs were first identified and characterised with relative abundance in BM tissue [3].

As well as exhibiting biological variation and heterogeneity of regenerative and immunomodulatory function, the source of tissue from which MSCs are derived is influential in the production of a cell-based therapeutic that can translate effectively to clinical application. For instance, invasive harvesting of tissues, including bone marrow, may not always be an appropriate option for patients compromised by inflammatory pain. Furthermore, MSCs derived from tissues affected by the pro-inflammatory environment of autoimmune and autoinflammatory disorders may not be of sufficient quality to effect repair [63][64][65].

Clinical trials have investigated the safety and efficacy of MSCs in the treatment of inflammatory kidney diseases, including nephritis associated with lupus and diabetes, autosomal dominant polycystic kidney disease and atherosclerotic renovascular disease [66][67]. Intravenous transplantation of allogeneic BM- and UC-MSC in severe and drug-refractory SLE patients demonstrated statistically significant improvement in proteinuria, serum albumin, complement C3, peripheral leucocytes, and platelet numbers at 24-h post-infusion. There was also a significant decline in disease activity measured against the systemic lupus erythematosus disease activity index (SLEDAI) at the fifth year of follow-up [66]. The 5-year overall survival rate of patients with severe drug-refractory SLE after MSC transplantation was 84% (68/81 patients), with 27% of patients (22/81) achieving complete clinical remission and 7% of patients (6/81) achieving partial clinical remission [66].

Analysis of eight pilot trials in which MSCs were co-delivered with renal transplantation showed prolonged graft survival and reduction in dose of immunosuppressive drugs, including tacrolimus, mycophenolate mofetil, or cyclosporin A, and this was predicted to be a result of the immunosuppressive, anti-oxidative, and reparative-regenerative properties of MSCs [68].

In the area of arthritis, the first studies to investigate MSCs were in patients with RA who had not responded to conventional pharmaceutical therapy. Studies investigating the role of allogeneic BM-MSCs and UC-MSCs by infusion into patients with RA have demonstrated a moderate response according to EULAR criteria [69][70]. Sixty-four RA patients who underwent UC-MSCs therapy combined with DMARDs demonstrated reduction in HAQ and DAS28 scores, as well as reduction in C-reactive protein (CRP), ESR, and anti-cyclic citrullinated peptide (anti-CCP) at 1-year and 3-year follow-up [70]. Clinical efficacy was maintained for 3 years post-MSCs transplantation without any serious side effects reported during or after UC-MSCs infusion [70].

Intravenous infusion of UC-MSC for the treatment of multiple sclerosis (MS) showed an 11.7% reduction in disease activity measured by the Kurtzke Expanded Disability Status Scale (EDSS) test, and a 2% decline in the Scripps Neurological Rating Scale with significant improvement in bladder, bowel, and sexual function [25]. In addition, an increase in non-dominant hand average scores and in walk times ($p < 0.02$) were registered after 1 year compared to baseline [71]. MRI scans of the brain and the cervical spinal cord demonstrated no disease progression or no new or active lesions in 83.3% patients at 1-year post-treatment [71].

8. Risks and Challenges of Stem Cell Transplantation

MSCs have been widely investigated in the treatment of several very severe refractory inflammatory diseases and has included thousands of participants with GVHD, MS, ALS, RA, and SLE. Treatment-related adverse events associated with MSC administration have been evaluated by systematic reviews. One of the biggest meta-analysis projects to review MSC safety included 62 randomised clinical trials involving 3546 participants and highlighted an association with transient fever at 48 h post-MSC administration (odds ratios (OR), 3.65, 95% confidential intervals (CI) 2.05–6.49, $p < 0.01$), and adverse events at the administration site including injection site bleeding, swelling, itchiness, pain, or local infection (OR, 1.98, 95% CI 1.01–3.87, $p = 0.05$) [72]. Minor adverse events associated with MSC transplantation were sleeplessness (OR, 5.90, 95% CI 1.04–33.47, $p = 0.05$), fatigue (OR, 2.99, 95% CI 1.06–8.44, $p = 0.04$), and constipation (OR, 2.45, 95% CI 1.01–5.97, $p = 0.05$) [72].

Other side effects have been reported and include the presence of acute transient side effects such as nausea/vomiting and blurred vision during MSC infusion in 2 of 46 patients with steroid refractory GVHD (4.3%) [62]. Thromboembolism induced by stem cell transplantation was described in two patients with renal transplantation and chronic kidney disease although the total cohort size was not reported [73]. MSC infusion caused venous obstruction and swollen extremities, but in these cases thrombosis was successfully treated with urokinase and warfarin thrombolytic therapy [73].

The key question is whether the generation of tumorigenic cells is a result of ex vivo MSC expansion in culture. Senescent MSCs that have exited a cell cycle obtain a senescence-associated secretory phenotype (SASP) characterised by the secretion of a cocktail of pro-inflammatory cytokines (IL6, IFNγ, TNFα), chemokines (IL8, MCP1), growth factors (FGFb, HGF, GM-CSF), proteases (MMPs, TIMP-2), soluble adhesion molecules and cell surface receptors (ICAM, VCAM, EGFR), extracellular matrix (ECM) components (fibronectin, laminin), some non-protein small molecules (NO, PGE2), growth-related oncogene (GRO), and macrophage-derived chemokine (MDC). The SASP is also associated with systemic inflammation and is responsible for a paracrine-mediated ‘bystander effect’ in which surrounding cells are induced to senescence, amplifying the pathophysiologic response to tissue dysfunction [74]. The composition of SASP, which is released by damaged or senescent fibroblasts, is known to support tumour growth [75]. Other research demonstrated that SASP may block the proliferation, as well as induce the growth arrest and apoptosis of cancer cells [76].

9. Comparison of Allogeneic and Autologous Sources of Mesenchymal Stem Cells

Debate over the benefit of allogeneic or autologous MSC therapy has been widely discussed [35][77], with the proposition that allogeneic MSCs are more advantageous than those harvested from autologous sources [77]. A higher quality of MSCs may be acquired from allogeneic sources because of the ability to control patients’ age and health status, cell potency, and absence of genetic and epigenetic abnormalities. The disadvantages of allogeneic MSCs have been shown with reports that these cells are not absolutely immune-privileged and despite low expression of MHC class I and II, can still be recognised by immune response and rejected after about 20 days in vivo [25].

The process of cryopreservation has important implications on the efficiency of clinical translation of MSC-based therapies. Application of allogeneic therapies will enable the production of ‘off-the shelf’ products, minimising the number of surgical interventions undertaken by the patient and maximising the number of therapeutic products that can be manufactured per tissue donor. For autologous applications, MSCs can be harvested from healthy tissues and

cryopreserved when required at a later date. To achieve this, more information is required regarding the impact of cryopreservation on the biological status of the cells, and by extension how both safety and efficacy is affected for both allogeneic and autologous applications [78]. It has been reported that cryopreservation of allogeneic MSCs can alter the survival of MSCs when recovered from cryopreservation in comparison to fresh MSCs in a model of normothermic machine perfusion to support transplant kidneys [79].

The age of the donor is also an important parameter that restricts the benefit of autologous MSCs transplantation. MSCs taken from older patients are known to have higher levels of replicative senescence, evidenced by significantly fewer CFU-Fs formed on derivation, reduced proliferation rate, reduced immunomodulatory properties, and an increased pro-inflammatory phenotype compared to those derived from younger donors [80][81][82].

Similarly, autologous MSCs derived from patients with autoimmune or autoinflammatory diseases may have a compromised genetic background that predisposes their stem cell compartment to immune disorders. An example of this is evident in juvenile idiopathic arthritis (JIA) where both HLA and non-HLA-related genes are heavily influential in predisposing disease susceptibility [83]. For these conditions, the use of allogeneic MSCs has been considered as a more preferable option for safe and effective treatment.

Considering the low expression of MHC class II antigens and the lack of the immune co-stimulatory receptors, allogeneic MSCs do not provoke a strong immune response and probably can be used for the treatment of diseases without complications. Many systemic intravascular delivery and intra-articular injections of autologous or allogenic MSCs have been performed over the last decade, without any serious complications, such as malformation or sepsis [70][84].

To summarise the results obtained from the preliminary analysis of studies of MSC transplantation, the potential risk may be defined from the allergic reactions in response to bovine proteins (safety of medium), ectopic tissue formation or malignant transformation, infection, aggregation of the cells, and embolisation. Nevertheless, in clinical trials in adult and paediatric populations, all complications of MSC therapy, except fever and adverse events at the administration site, did not correlate with cell transplantation [84]. A major step toward adoption of MSC therapies came in 2018 with the first allogeneic MSC product approved for use in the European Union [85].

10. Conclusions

The immunomodulatory and regenerative properties of MSCs, driven by direct cell contact or production of exosome secretions, place these cells as important candidates for potential clinical application in the treatment of autoimmune and autoinflammatory diseases. However, contemporary studies have shown that MSCs obtained from patients with these pathologies have impaired biology that restricts proliferative, differentiation, and immunomodulatory properties. Further research is required to form a comprehensive understanding of the contribution that MSCs make to the pathogenesis of autoimmune and autoinflammatory diseases and their application as therapeutics for moderating immune responses in clinical cases where standard therapeutic methods have proved ineffective.

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