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Chapter

The Rising Role of Mesenchymal Stem Cells in the Treatment of Various Infectious Complications

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Abstract

Mesenchymal stem cells are heterogenous adult multipotent stromal cells that can be isolated from various sources including: bone marrow, peripheral blood, umbilical cord blood, dental pulp, and adipose tissue. They have certain immuno-modulatory, immunosuppressive, and antimicrobial properties that enable them to have several therapeutic and clinical applications including: treatment of autoimmune disorders, role in hematopoietic stem cell transplantation and regenerative medicine, as well as treatment of various infections and their associated complications such as septic shock and acute respiratory distress syndrome. Although more success has been achieved in preclinical trials on the use of mesenchymal stem cells in animal models than in human clinical trials, particularly in septic shock and Chagas disease, more progress has been made in both disorders after the recent use of specific sources and certain doses of mesenchymal stem cells. Nevertheless, the utilization of this type of stem cells has shown remarkable progress in the treatment of few infections such as tuberculosis. The clinical application of mesenchymal stem cells in the treatment of several diseases still faces real challenges that need to be resolved. The following book chapter will be an updated review on the role of mesenchymal stem cells in various infections and their complications.

Keywords: mesenchymal stem cells, host immunity, antimicrobial properties, septic shock, *Mycobacterium tuberculosis*, Chagas disease, human immunodeficiency virus

1. Introduction to mesenchymal stem cells

Mesenchymal stem cells (MSCs), which were first described by Alexander Fridenstein in the 1960s, are heterogeneous, non-hematopoietic, adult multipotent stromal progenitor cells that are capable of self-renewal as well as differentiation into multiple lineages and various cell types [1–8]. They can be isolated from several sources including bone marrow (BM), peripheral blood (PB), umbilical cord blood (UCB), amniotic fluid, placenta, adipose tissue (AT), and dental pulp as shown in **Table 1** [1–8]. Although the BM is the main source of MSCs, these stromal cells constitute only a small fraction of the total number of cells populating the BM [2, 4–6].

MSCs have the following distinguishing features: (1) ability to adhere to the plastic vessel under optimal culture conditions; (2) capability to differentiate into osteoblasts, adipocytes, and chondrocytes; and (3) having characteristic immunophenotypic profile on flow cytometry [1–3, 5, 6, 8, 9]. MSCs are characteristically positive for: CD 105, CD 73, and CD 90 and characteristically negative for the following surface

1	Bone marrow
2	Peripheral blood
3	Umbilical cord blood: Wharton's jelly
4	Placenta: chorionic villi of placenta
5	Amniotic fluid
6	Menstrual blood
7	Fallopian tubes and cervical tissue
8	Breast milk
9	Adipose tissues: fat
10	Dental pulp, periodontal ligaments, and exfoliated deciduous teeth
11	Palatal tonsils
12	Salivary glands
13	Skeletal muscle tissues
14	Dermal tissues
15	Lung tissues and alveolar epithelium
16	Liver tissues: fetal liver
17	Synovial membrane and fluid
18	Parathyroid glands

Table 1.
Sources of mesenchymal stem cells.

	Positive		Negative
Characteristic surface markers	**CD 105**		**CD 45**
	CD 73		**CD 34**
	CD 90		**CD 14**
			CD 11b
			CD 19
			CD 79a
			HLA-DR
Other surface markers that may/may not be expressed	CD 117	CD 33	CD 31
	CD 166	CD 49b	CD 33
	CD 29	CD 71	CD 133
	CD 44	CD 164	
	CD 106	CD 271	
	CD 9	HLA-class I	
	CD 10	Stro-1	
	CD 13	SSEA-4	
	CD 28	ITGA-11	

MSCs, mesenchymal stem cells; HLA, human leukocyte antigen.
The bold values are to differentiate characteristic from non-characteristic surface markers.

Table 2.
Surface markers of MSCs on Flow cytometry.

markers: CD 45, CD 34, CD 11b, CD 14, CD 19, CD 79a, and HLA-DR. However, certain types of MSCs can occasionally show positivity or negativity for specific surface markers as shown in **Table 2** [1–3, 5, 6, 8–14]. Also, MSCs can differentiate into other cell types including: myocytes, cardiomyocytes, and neurons [5].

Several studies have shown that MSCs obtained from BM, AT, and other sources do express CD 34 surface markers [4, 15–18]. MSCs can be seen in abundant numbers in the circulation under the following circumstances: stem cell mobilization with growth factors, tissue injuries, stroke, hypoxia, and inflammatory conditions [4, 19–24]. Despite the efforts displayed over the last five decades including identification of nine transcriptional factors, little is known about the molecular basis underlying the stemness of MSCs and it is still unclear whether these recently discovered genes regulate stemness or only differentiation of MSCs [7].

2. Functions, properties, and therapeutic indications of MSCs

MSCs have immunomodulatory and immunosuppressive properties that enable them to have several therapeutic and clinical applications including: hematopoietic stem cell transplantation (HSCT), autoimmune disorders, regenerative medicine and tissue repair, neurological diseases, bone and cartilage disorders, as well as treatment of several infections and acute respiratory distress syndrome (ARDS). Details are shown in **Table 3** [1, 2, 6, 8, 25–29]. MSCs are major constituents of the BM microenvironment and the HSC niche and apparently they are the masters of

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1. Hematopoietic stem cell transplantation:
    a. Enhancement of engraftment
    b. Prevention of graft versus host disease (GVHD)
    c. Treatment of GVHD
2. Treatment of autoimmune diseases:
    a. Systemic lupus erythromatosus
    b. Rheumatoid arthritis
    c. Systemic sclerosis
    d. Type 1 diabetes mellitus
    e. Multiple sclerosis
    f. Crohn's disease
3. Regenerative medicine and tissue repair:
    a. Myocardial ischemia
    b. Cardiac dysfunction
    c. Chronic non-healing wounds
    d. Liver injury
    e. Myocardial infarction
    f. Dilated cardiomyopathy
    g. Critical limb ischemia
    h. Spinal cord injuries
4. Treatment of various infections:
    a. Bacterial infections including sepsis and its associated acute respiratory distress syndrome
    b. Viral infections such as human immunodeficiency virus, hepatitis B and C viruses
    c. Parasitic infections such as Chagas disease, schistosomiasis, and malaria
    d. Mycobacterial infections such as tuberculosis
5. Other indications:
    a. Macular degeneration, corneal reconstruction and transplantation
    b. Bones and joints: osteogenesis imperfecta, osteoarthritis, and osteoporosis
    c. Cancer gene therapy
    d. Amyotrophic lateral sclerosis
    e. Liver cirrhosis

Table 3.
Current and potential therapeutic indications for mesenchymal stem cells.

survival and clonality [30–32]. The main functions of MSCs include: formation of hematopoietic microenvironment, modulation of the activity of the immune system, and regulating cell trafficking [33].

3. Role of MSCs in host defense and infections

The putative roles of BM-MSCs during infection are: (1) detection of pathogens, (2) activation of host immune responses, (3) elimination of pathogens, (4) induction of proinflammatory gradients, and (5) modulation of proinflammatory host immune response due to having specific immunoregulatory properties of MSCs including: inhibition of differentiation of monocytes to dendritic cells (DCs), alteration of cytokine profile of DCs, induction of tolerant phenotypes of naïve and effector T-cells, inhibition of antibody production by B-cells, and suppression of natural killer (NK) cell proliferation and NK-mediated cytotoxicity [1, 2, 28, 34]. BM-MSCs may augment antimicrobial responses, abridge proinflammatory and damage responses, and ameliorate associated tissue injury and they appear to function as a critical fulcrum providing balance by promoting pathogen clearance during the initial inflammatory response, and suppressing inflammation to preserve integrity of the host and facilitate tissue repair [1, 2, 34].

The immunomodulatory properties of MSCs are mediated by cell-to-cell interaction and the secreted cytokines [35–37]. MSCs could potentially be involved at multiple levels in host defense by mobilizing immune effector cells and modulation of proinflammatory immune responses to minimize tissue damage [1, 37]. BM-MSCs may protect against infectious challenge by direct effects on the pathogens or through indirect effects on the host [1]. However, placenta-derived MSCs and fetal membrane-derived MSCs are highly susceptible to herpes viruses including varicella zoster virus (VZV) [2, 38]. Several types of stem cells including BM-MSCs and neural stem cells can cross the blood brain barrier and reach not only brain tumors but also ischemic and injured tissues caused by certain infections in the brain and engraft there. Consequently, MSCs can be utilized as means of cellular carriers to deliver therapeutic agents to sites of brain injury in order to exert their therapeutic and tissue regenerative effects in the brain [39–43].

4. Antimicrobial properties of MSCs

MSCs have been shown to exhibit the following antimicrobial properties: (1) capacity to enhance antibacterial activity by interaction with the host innate immune system in order to increase antibiotic sensitivity, increase bacterial killing, and slow bacterial growth; (2) capacity to enhance bacterial clearance in preclinical models of sepsis, cystic fibrosis, and ARDS; and (3) secretion of antimicrobial peptides such as: interleukin (IL)-17, indoleamine 2,3-dioxygenase (IDO), β-defensins, lipocalin-2, and cathelicidin LL-37 [44–46]. Members of the chemokine family have been found to have antimicrobial peptide activity although the role of chemokines in immunity during infection is rather complicated [47].

5. MSCs in sepsis, ARDS, and chronic bacterial infections

5.1 MSCs in sepsis syndrome and septic shock

Sepsis syndrome and septic shock represent major health problems worldwide and they are leading causes of death in hospitalized patients due to their association with

high rates of morbidity and mortality in the absence of effective therapy [48–51]. Sepsis is a potentially lethal syndrome that can develop following an infection in which a breakdown in the immune homeostasis results in both proinflammatory and anti-inflammatory mechanisms that become uncoupled from normal regulation [50]. The inflammatory-driven maladaptive response induces disruption of endothelial and epithelial barriers, thus resulting in organ dysfunction. However, the host responds to sepsis by stimulating the proliferation of HSCs in the BM or by activating emergency hematopoiesis in an attempt to counteract the effects of sepsis on the function of multiple body organs [51]. Septic shock is a devastating complication of uncontrolled bacterial infection that carries a mortality rate of 20–50% [50, 52]. Currently, there is no specific treatment for septic shock and the management of this devastating complication of serious infections remains supportive. However, the following measures should be taken into consideration: early identification, fluid resuscitation, prompt institution of antibiotic therapy, control of the source of infection, circulatory support, and lung protection by mechanical ventilation [48, 49, 52, 53].

Based on numerous preclinical studies, cell-based therapies are potentially beneficial in the treatment of septic shock and ARDS. However, various types of stem cells including embryonic stem cells, MSCs, and induced pluripotent stem cells have been used in the treatment of sepsis and ARDS, but MSCs are the most commonly used stem cells in septic shock [53]. In patients with septic shock complicated by acute lung injury (ALI) and ARDS, the paracrine factors secreted by MSCs can: mediate endothelial and epithelial permeability, and increase alveolar fluid clearance in addition to other mechanisms that reduce the complications of septic shock [54].

In a mouse model of sepsis, lipopolysaccharide-preconditioned MSC transplantation has been shown to: ameliorate survival rate after transplantation, protect cells from apoptosis and organ damage, and have immunomodulatory therapeutic properties [55]. Also, transplanted MSC can secrete Toll-like receptor-4, which plays a seminal role in attenuating in vivo *Escherichia coli*-induced pneumonia and ALI through anti-inflammatory and antibacterial effects [56]. In experimental animal models of sepsis, the effectiveness of BM-MSCs was compared to that of Wharton's jelly (WJ) of umbilical cord; both sources of MSCs regulated leukocyte trafficking and reduced organ dysfunction but only WJ-MSCs were able to improve bacterial clearance and survival [57]. In animal models of Staphylococcal toxic shock syndrome, MSCs; particularly AT derived MSCs; were able to suppress cytokine production and attenuate sepsis but they failed to improve survival [58, 59].

Several preclinical sepsis studies have suggested that MSCs are capable of: modulating inflammation, enhancing clearance of pathogens as well as tissue repair, thus resulting in improvement in symptoms and reduction in organ damage and finally improvement in survival and reduction in mortality rates [48–50, 52]. A meta-analysis that evaluated the preclinical use of MSCs in animal models of septic shock demonstrated that MSC treatment significantly reduced mortality rates and the results of this survey supported the decision to proceed to clinical trials that test the effectiveness of MSCs in treating infections causing sepsis in humans [60].

In a phase I clinical trial that included patients admitted to the intensive care unit (ICU) with septic shock, infusion of freshly cultured allogeneic BM-MSCs in doses up to 3 million cells/kg into these ICU patients was shown to be safe as this dose of stem cells did not exacerbate the elevated cytokine levels in the plasma of patients with septic shock [52, 61].

5.2 MSCs in ALI and ARDS

Bacterial pneumonia and sepsis from non-pulmonary causes are the most common etiologies of ALI and ARDS that are associated with mortality rates ranging

between 25 and 50% [62–65]. Management of ARDS is mainly supportive with: protective ventilation, fluid conservation, and antimicrobial therapy [62, 64]. In patients with bacterial pneumonia and sepsis, MSCs can attenuate inflammatory process and enhance bacterial clearance [63, 65]. MSCs secrete paracrine factors that can regulate lung permeability and decrease inflammation and this makes MSCs a potentially attractive therapeutic modality for ALI [62]. In patients with ARDS, MSCs can exert beneficial effects by secreting paracrine factors, microvesicles, and transfer of mitochondria. These secretory products have: (1) anti-inflammatory properties that participate in resolving injuries to lung endothelium and alveolar epithelium; (2) regulatory effects on alveolar fluid clearance, thus reducing lung edema; (3) antimicrobial effects mediated by release of antimicrobial factors; and (4) upregulation of monocyte/macrophage phagocytosis [66]. In *Escherichia coli*-injured human lungs, MSCs were able to: restore alveolar fluid clearance, reduce inflammation, and exert antimicrobial activity partly through secretion of keratinocyte growth factor [62].

In patients with bacterial pneumonia causing ALI and ARDS, MSCs could become a promising novel therapeutic modality and an ideal candidate for future cellular therapy due to the following reasons: (1) MSCs are able to differentiate into various cell types, (2) MSCs can secrete multiple bioactive molecules that are capable of stimulating recovery of injured cells and inhibiting inflammation, (3) MSCs lack immunogenicity, and (4) MSCs can perform immunomodulatory functions [62, 63, 65, 67]. In a phase I clinical trial, Jennifer Wilson et al. showed safety of allogeneic BM-MSCs administered to patients with ARDS [56, 68]. However, the role of MSCs in ARDS patients should be carefully evaluated by well-designed multicenter randomized clinical trials [68].

5.3 MSCs in severe and chronic infections

Chronic implant and wound infections that are characterized by biofilm formation are often difficult to treat and they usually require continuous antibiotic therapy for weeks to months. However, alternative therapies for chronically infected wounds include: use of antibiotic impregnated implant materials or biological scaffolds, administration of biofilm disrupting agents, and combining cellular immunotherapy with antibiotics [44].

In patients with very severe aplastic anemia (VSAA), prolonged neutropenia results in refractory and overwhelming bacterial infections as well as invasive fungal infections that are associated with significant morbidity and mortality in these severely immunocompromised individuals [69]. In patients with VSAA lacking human leukocyte antigen identical sibling donors and having refractory infections, co-transplantation of haploidentical HSCs and allogeneic BM-MSCs has been shown to be a safe and a promising therapeutic modality [69].

Studies have shown that: (1) secretion of cathelicidin LL-37 by MSCs could enhance bacterial products indicating that MSCs can upregulate antimicrobial activity in the presence of infection and (2) activated MSCs, when administered intravenously and in combination with conventional antibiotics, can potentially suppress and eradicate chronic *Staphylococcus aureus* biofilm infection in difficult-to-treat locations. Thus, treatment with activated MSCs represents a novel therapeutic option for patients having highly drug-resistant infections [44].

5.4 MSCs in bone, joint, and dental infections

The multidirectional differentiation potential of BM-MSCs is essential for tissue repair after local injury of bones, joints, and medullary adipose tissue. Additionally,

the regulation of multiple differentiation potentials of MSCs by various antimicrobial agents affects the recovery from bone and joint infectious diseases [70]. Minocycline induces the following favorable changes in MSCs: migratory capacity, proliferation, gene expression, and growth factor release, ultimately resulting in enhancement of angiogenesis. Also, the triple antimicrobial-loaded hydrogels reduce bacterial bioburden and preserve viability of MSCs in the presence of bacteria [71].

Gingival MSCs encapsulated in silver lactate-containing alginate hydrogel have successfully differentiated into osteogenic tissue and have shown promise for bone tissue engineering with antimicrobial properties against peri-implantitis caused by gram negative bacterial infections [72]. Synthesized antibiotic-containing scaffolds have been shown to possess significantly lower effects on proliferation and viability of human dental pulp stem cells when compared to the saturated ciprofloxacin/ metronidazole solution [73].

6. MSCs in viral infections

Studies have shown that: (1) MSCs are susceptible to infection by members of the herpes group of viruses such as: cytomegalovirus, Epstein-Barr virus, herpes simplex virus (HSV) type 1, HSV-2, and VZV, and MSCs become functionally defective following infection with herpes viruses; (2) AT-MSCs can differentiate into functional hepatocyte-like cells but AT-MSCs undergoing hepatic differentiation are not susceptible to infection by hepatitis B virus in vitro; (3) human MSCs are permissive to the highly pathogenic avian influenza A/H5N1 infection and infection of MSCs can cause apoptosis and loss of their immunomodulatory activity; and (4) MSCs can significantly reduce the impairment of alveolar fluid clearance induced by influenza A/H5N1 infection in vitro and prevent or reduce influenza A/H5N1-associated ALI in vivo [28, 34, 74]. The extracellular vesicles (ECVs) secreted by MSCs have anti-inflammatory and anti-influenza properties. Hence, they can be used as cell-free therapy for influenza in humans [75]. Infection of MSCs by respiratory syncytial virus (RSV) alters their immunoregulatory functions by upregulating interferon (IFN)-β and IDO, thus accounting for the lack of protective RSV immunity and for the chronicity of RSV-associated lung diseases such as bronchial asthma and chronic obstructive airway disease [76]. In mice models, treatment with MSCs alleviates inflammation and mortality associated with Japanese encephalitis virus, which is a leading cause of viral encephalitis in Asia [77]. Zika virus infection of human MSCs promotes differential expression of proteins that are linked to several neurological disorders such as Alzheimer's disease, Parkinson's disease, autism, and amyotrophic lateral sclerosis [78].

MSCs exhibit immunomodulatory, anti-inflammatory, and pro-angiogenic properties, and therefore have the potential to improve the outcome of allogeneic HSCT in patients with AA. In a multicenter study that included 75 patients with AA, the combination of HSCs obtained from BM and PB sources as well as MSCs has resulted in amelioration of acute graft versus host disease (GVHD) and viremia resulting ultimately in an improved survival benefit [79].

6.1 MSCs in HIV infection and AIDS

Acquired immunodeficiency syndrome (AIDS), which is caused by human immunodeficiency virus (HIV), poses a real threat to human life [80]. Despite the advent of highly active antiretroviral therapy (HAART) that suppresses plasma viral load but does not cure disease, HIV-1 persists in latent tissue reservoirs, mainly

in macrophages and T-helper lymphocytes, and this poses significant challenge to long-term cure [2, 80–82]. HIV-1 predominantly infects HSCs such as macrophages, monocytes, and T-helper lymphocytes [82]. Non-immune responders (NIRs) do respond to HAART, which effectively suppresses HIV replication, but do not show any improvement in their immune status as reflected by an increase in CD4+ T-cell counts [83]. More than 20% of HAART-treated HIV-infected individuals exhibit NIR phenotype and these individuals are at risk of opportunistic infections, cancer, and reduced life expectancy [83].

Coexposure to MSC-conditioned media can enhance the latency-reactivation efficacy of the approved latency reversing drugs vorinostat and panobinostat [81]. Undifferentiated AT resident MSCs are not permissive to HIV-1 infection despite that HIV-1 exposure may increase the expression of some hematopoietic lineage related genes [82]. It has been reported that transfusions of UCB-MSC or more specifically WJ are well tolerated and can efficiently improve immune reconstitution in HIV-infected individuals who are NIRs [83, 84]. Memory CD4 T cells are the key cells organizing all immune actions against HIV while being the targets of HIV infection [85]. MSCs can express receptors that permit their infection by HIV-1. Additionally, human T-lymphotropic virus (HTLV)-1 could infect and replicate in human BM-MSCs possibly by involvement or infiltration of CD4+ lymphocytes [2, 86, 87].

7. MSCs in parasitic infections

Recently, MSCs have been introduced to treat parasitic infections associated with tissue damage in the form of granuloma formation or organ fibrosis such as: schistosomiasis, malaria, and Chagas disease [88, 89]. Studies have shown that MSCs can: (1) ameliorate liver injury and hepatic fibrosis induced by Schistosoma japonicum, particularly when combined with conventional therapies such as praziquantel and (2) play an important role in improving host protective immune responses against malaria by modulating regulatory T cells [88, 89].

7.1 MSCs in Chagas disease

Chagas disease, which is caused by the protozoan *Trypanosoma cruzi*, is endemic in Central and Latin America. However, incidence of the disease has recently increased in the United States of America, Canada, Japan, Australia, and Europe due to migratory movements [2, 90–93]. The disease has acute and chronic phases [90–92]. The acute phase is characterized by intense parasitemia with no or few symptoms while the chronic phase, which extends over indeterminate period of time that may span over years or decades, is characterized by the evolution of cardiac as well as gastrointestinal manifestations reflecting disease complications [90, 91]. Pathogenesis of chronic Chagas cardiomyopathy (CMP) is still debatable but the following have been proposed to be the main pathological mechanisms involved: parasite persistence, microcirculatory alterations, autoimmune mechanisms, and autonomic dysfunction [90, 94]. The cardiac complications of Chagas disease include: myocarditis, dilated CMP, heart failure, arrhythmias, heart block, thromboembolism, stroke, and sudden death [2, 90, 91, 94].

The available and future therapies of Chagas disease include: treatment of arrhythmias and heart failure, antiparasitic therapy, resynchronization treatment, heart transplantation, and stem cell therapies [2, 90, 91, 93, 95]. In patients with chronic Chagas CMP and cardiac failure, conventional pharmacologic therapies are limited by being not always effective, thus rendering the disease incurable [90, 91, 96].

Heart transplantation may occasionally be needed but the procedure has a number of problems including: shortage of donors, high costs, and complications of long-term immunosuppressive therapies administered to recipients of heart transplants [90, 95].

Different stem cell types and delivery approaches have been used in both pre-clinical models as well as clinical trials with the aim of improving cardiac function and reversing complications [95]. In animal models, stem cell therapies have shown reductions in: right ventricular dilatation, and inflammatory infiltrates as well as fibrosis [91, 93]. Stem cell therapy with BM-MSCs has emerged as a novel therapeutic option for Chagas CMP and heart failure [91, 93]. In a murine model of Chagas disease, cotransplantation of autologous BM-MSCs and skeletal myoblasts has been shown to be effective in reversing ventricular dysfunction [94]. Also, in an animal model of chronic Chagas disease, genetic modification of MSCs mobilized by granulocyte colony stimulating factor has increased the immunomodulatory actions and paracrine functions of MSCs by recruitment of suppressor cells such as regulatory T-cells and myeloid-derived suppressor cells [97].

Transplantation of MSCs has shown clinical efficacy in animal or mouse models but studies in humans have not shown equivalent success due to a number of challenges that need to be overcome [2, 91, 93, 95, 98]. In animal models of chronic Chagas CMP, cardiac MSCs have been shown to exert protective effects by decreasing the degrees of fibrosis and inflammatory infiltrates in the affected myocardium [99]. The beneficial effects of MSC therapy in Chagas mice models may be an indirect action of the cells on the heart rather than a direct action of the large numbers of transplanted MSCs on the myocardium [91, 96]. Tracking of infused BM-MSCs in animal models has shown migration of these cells to the heart and their participation in tissue repair or regeneration [91–93]. Although an early clinical trial of intracoronary injection of autologous BM-cells in patients with chronic Chagas CMP and heart failure showed safety and feasibility, a large multicenter, randomized double-blind, placebo-controlled trial using intracoronary infusion of BM-mononuclear cells showed no improvement in cardiac function or in quality of life in patients with chronic Chagas CMP [2, 99, 100].

8. MSCs in tuberculosis

Mycobacterium tuberculosis (MTB) remains a leading cause of morbidity and mortality due to infectious diseases in humans [101]. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, mainly caused by non-adherence to antimicrobial therapy, are recognized health problems in: Eastern Europe, South Africa, and South East Asia [101–103]. Therapeutic strategies that are employed in the management of MDR/XDR TB include: directly observed treatment (DOTS), DOTS-Plus, recombinant human IL-2 by aerosol therapy, and recombinant IFN-γ [102].

Despite the strong host immune response in humans, MTB organisms are capable of persisting or staying dormant for prolonged periods of time, thus resulting in latent infection [104–106]. Hypoxia or hypoxemic microenvironment may favor dormancy of MTB and subsequent evolution of drug resistance [106]. MSCs play a crucial role in the ability of MTB to evade the potent host immune responses and cause TB. Hence, targeting MSCs or nitrous oxide (NO) seems a plausible therapeutic intervention for the design of new effective preventive strategies against TB [107]. Studies have shown that MSCs are recruited into the tuberculous granulomas and they position themselves between the harbored pathogen and the effector T-cells [107–109]. CD271+ BM-MSCs can provide an antimicrobial protective intracellular niche in the host in which dormant MTB can reside for prolonged periods of

time [106, 109–111]. MTB infects and persists in a dormant form inside BM-MSCs even after successful antimicrobial therapy [112]. Virulent mycobacteria can manipulate Toll-like receptors and certain signaling pathways including nuclear factor kappa-light-chain-enhancer of activated B cells in order to survive inside the BM stem cells [112]. MSCs can increase NO production in *Mycobacterium abscessus*-infected macrophages through activation of tumor necrosis factor (TNF)-α in the presence of IFN-γ [113]. The cellular crosstalk between TNF-α and prostaglandin-E2 is essential for the increased production of NO in macrophages [113]. Consequently, MSCs may become an ideal choice as adjunct therapy in MDR and XDR TB particularly in individuals with comorbid medical conditions [102, 103, 114]. There are three main clinical trials on the use of MSCs in the treatment of MDR/XDR TB [115–117]. In the first trial, 27 patients with MDR/XDR TB who had been unsuccessfully treated with conventional anti-TB chemotherapy received autologous MSCs, the following results were obtained: all patients showed positive responses to MSC therapy, bacterial discharge from lungs was abolished in 20 patients, tissue damage and lung cavitation resolved in 11 patients, and persistent remission of TB was encountered in 56% of patients after 2 years of autologous MSC transplantation [115]. In the second study, a phase I clinical trial, 36 patients with MDR/XDR TB received anti-TB chemotherapy for 4 weeks; then, they were subjected to autologous MSC transplantation [116]. Six months after autologous transplantation of MSCs: no major adverse events were reported, 70% of patients showed radiological improvement, while 16.7% of patients showed stable radiological appearances. Eighteen months after autologous transplantation of MSCs: 53% of patients were cured, while 10% of patients showed evidence of treatment failure [116]. In the third study, a randomized clinical trial, 72 patients with MDR/XDR TB were included: 36 patients (control group) received conventional anti-TB chemotherapy only, and the other 36 patients (study group) received anti-TB chemotherapy and autologous MSC transplantation [117]. Successful outcomes were encountered in 81% of the study group and 40% of the control group. So, the addition of autologous MSC transplantation to conventional anti-TB chemotherapy significantly enhanced the response rates in patients with MDR/XDR TB [117]. Therefore, combining standard anti-TB chemotherapy with autologous MSC transplantation may ultimately become valuable in increasing the efficacy of anti-TB treatment in patients with MDR-TB [2, 102, 115, 116].

9. MSCs in fungal infections

Administration of human MSCs does not have negative impact on host response against Aspergillus fumigatus [118, 119]. Also, Aspergillus fumigatus does not stimulate MSCs to secrete cytokines that play a major role in the pathogenesis of GVHD indicating that Aspergillus fumigatus is not involved in the pathogenesis of GVHD following HSCT. In an animal model, infusion of BM-MSCs into mice infected with Paracoccidioides brasiliensis failed to induce any antimicrobial effects.

10. Conclusions and future directions

Since their first description in the 1960s, the history of MSCs has witnessed steady progress that ultimately resulted in their clinical application in the treatment of many disorders including several infectious diseases. Although the success has not been uniform with regard to various infections and despite the gap between the achievements in animal studies and results of clinical trials in humans, plenty of

efforts have been made to resolve the remaining challenges in the clinical applications of MSCs in several diseases.

Some of the remaining challenges facing the utilization of MSCs in the clinical arena include: (1) encountering failure of treatment or resistance to therapy; (2) the need to have quality control and safety measures; (3) implementation of guidelines and design of specific protocols for: preparation and manufacture, banking and cryopreservation of MSC products, administration and therapeutic use of each type and source of MSCs, and finally tracing of infused MSCs; and (4) performing large prospective multicenter clinical trials on the use of specific MSCs in certain diseases in order to test their uniform efficacy and verify their long-term safety.

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