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Mesenchymal Stem Cells — Their Antimicrobial Effects and Their Promising Future Role as Novel Therapies of Infectious Complications in High Risk Patients

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Abstract

Mesenchymal stem cells (MSCs) are heterogeneous progenitor cells that have the capacity of self-renewal and multi-lineage differentiation. These adult stem cells can be derived from several sources including bone marrow (BM), peripheral blood, cord blood, placenta, amniotic fluid, skin and adipose tissue. They have certain distinguishing features and their immunomodulatory and immunosuppressive properties enable them to have several therapeutic and clinical applications. Recently, MSCs have gained enormous potential as they can potentially cure various intractable and chronic diseases and as they have shown effectiveness in the treatment of various infections in animal models and in early clinical trials. MSCs are essential constituents of the framework that supports organ integrity and tissue barriers. Suppression of both T and B cells allows them to be major players in the innate response to bacterial infection and in controlling inflammatory response. Human BM-MSCs possess direct antibacterial activity against Gram-negative bacilli and they have been shown to improve survival and reduce mortality in animal models having septic complications. BM-MSCs are effective in treating sepsis and acute respiratory distress syndrome in high-risk patients such as those with malignant hematological disorders, recipients of solid organ and hematopoietic stem cell transplantation (HSCT) and patients receiving advanced level of care in intensive care units. Additionally, human BM-MSCs can act as drug delivery vehicles by enhancing the effectiveness of conventional antimicrobials and thus they may prevent the evolution of drug-resistant microbes. MSCs contain a subset of interleukin-17+ that is capable of inhibiting the growth of

Candida albicans (*C. albicans*). Also, CD 271+ BM-MSCs may provide a long-term protective intracellular niche in the host where *Mycobacterium tuberculosis* (M.TB) organisms remain viable but in a dormant state. Two recent clinical trials in humans that included 57 patients have shown that autologous transplantation of MSCs can successfully treat multidrug resistant (MDR) strains of M.TB. Animal studies have demonstrated that MSCs enhance host defenses against malaria. MSC therapy improves liver function and promotes hepatocellular regeneration in patients with hepatic fibrosis caused by schistosomiasis. Transplantation of MSCs has been shown to reverse right ventricular dilatation, cardiomyopathy and advanced cardiac involvement caused by *Trypanosoma cruzi* infection.

Autologous MSC transfusion in patients having liver cirrhosis secondary to hepatitis B or C infection improves liver function tests. Transfusion of MSCs can confer resistance to human *immunodeficiency virus (HIV)* and may restore immune reconstitution in infected individuals. Also, MSCs obtained from Wharton's jelly of the umbilical cord may become a novel therapy to reverse immune deficiency in individuals infected with HIV_1, particularly immune non-responders. Additionally, recent studies have demonstrated that hematopoietic stem cell-based gene therapy may ultimately offer a curative therapeutic option for *HIV* disease. MSCs improve murine models of acute myocarditis induced by infection with *Coxsackie B_3 virus.*

There is low risk of transmission of human herpes viruses by transplantation of MSCs from healthy seropositive donors. Cytomegalovirus (*CMV*) infection impairs the immunosuppressive and antimicrobial effector functions of human MSCs, thus overt *CMV* infection in recipients of HSCT may undermine the clinical efficacy of MSCs in treating graft versus host disease (GVHD). The therapeutic applications of BM-MSCs in recipients of HSCT include: prevention and treatment of GVHD, induction of faster engraftment, immune reconstitution, healing of inflammation as well as prevention and treatment of various infectious complications.

Thus, taking into consideration the remarkable success in the utilization of MSCs in the treatment of various infections in animal models and in human clinical trials, it is reasonable to predict that MSCS may become very promising novel therapeutic modalities as they have the potential to control or even cure various infectious complications in high-risk patients. However, the field is still in its infancy and plenty of research and clinical trials are required to refine their therapeutic indications. Banking of MSCs is vital to make them available for use. Finally; strict guidelines, standardization techniques and quality control measures are urgently required for collection, cryopreservation and clinical utilization of MSCs.

1. Introduction

Mesenchymal stem cells (MSCs) - also called fibroblastoid cells, giant fat cells with blanket cells, spindle-shaped flattened cells or very small round cells - have an inherent ability of self-renewal, proliferation and differentiation toward mature tissues depending on the surrounding microenvironment [1, 2]. Such characteristic, intrinsic to stem cells, makes MSC very attractive for utilization in cell therapy and regenerative medicine [2]. The discovery of MSCs can be dated to the 1960s and can be credited to the work of AJ Friedenstein during which he observed that bone marrow (BM) is the source of MSCs in postnatal life [1].

MSCs comprise only a tiny fraction of BM and other tissues. BM-derived MSCs [BM-MSCs] constitute 0.0001% to 0.01% of all nucleated BM cells [2]. Adipose tissues contain 100, 000 MSCs in each gram of fat. Adipose tissue-derived MSCs (AT-MSCs) represent an attractive cell source for stem cell therapy. Transplantation of up to $2x10^8$ cells / kg of autologous human adipose tissue-derived MSCs may be safe when given by slow intravenous infusion [2]. The sources of MSCs, their distinguishing features and their therapeutic indications are included in Table 1 [1-4].

Sources of MSCs	Distinguishing features of MSCs	Therapeutic indications of MSCs
1- Bone marrow	(A) They must be plastic adherent	1- In stem cell transplantation:
2- Peripheral blood	(B) They must be capable of	- Prevention and treatment of graft versus
3- Blood of umbilical cord	differentiating into:	host disease
4- Placenta	osteoblasts, adipocytes	- Enhancement of engraftment
4- Amniotic fluid	and chondrocytes	2- In cardiology; treatment of:
5- Synovial fluid	(C) Findings on flowcytometry:	- Coronary artery disease
6- Dental tissues e.g. pulp	[1] positive surface molecules:	- Myocardial infarction
7- Palatal tonsil	- CD 105	- Dilated cardiomyopathy
8- Fallopian tubes	- CD 73	3- Critical limb ischemia
9- Fat: adipose tissue	- CD 90	4- Repair of skeletal tissues
10- Parathyroid glands	[2] negative surface molecules:	5- Non-healing chronic wounds
	- CD 45	6- Chronic spinal cord injuries
	- CD 34	7- Liver injury
	- CD 14	8- Regenerative medicine
	- CD 11	9- Osteogenesis imperfecta
	- CD 19	10- Amyotrophic lateral sclerosis
	- CD 79	11- Acute respiratory distress syndrome
	- HLA - DR	12- Severe autoimmune disorders: systemic
		lupus erythromatosis, rheumatoid arthritis,
		multiple sclerosis and systemic sclerosis

MSCs: mesenchymal stem cells

Table 1. Sources, basic features and therapeutic indications of MSCs

Study and year of publication	Type of MSCs, route of administration of MSCs and sepsis model	Results and proposed mechanism(s) of action
Hau SR et al 2013	- MSCs harvested from compact bone of mice - Intravenous injection of MSCs into tail veins of mice - CLP, in vivo method - Polymicrobial sepsis	- Increased survival of mice - Decreased organ injury - Increased neutrophil phagocytosis - Decreased circulating bacteria
Mei SHJ et al 2010	- Bone Marrow-MSCs - Intravenous administration - CLP - In vivo method	- Significant reduction in mortality in septic mice receiving appropriate anti-microbial therapy. - Significant increase in bacterial clearance partly due to increased phagocytic activity of host immune cells
Luo CT et al 2014	- Bone marrow-MSCs - Intravenous administration - CLP - Polymicrobial sepsis	- Decreased circulating bacteria - Alleviation of sepsis - related acute kidney injury - Improved survival of mice. - Inhibition of IL-17 secretion - After MSC therapy, the following interleukins and inflammatory mediators were reduced in kidney tissues: Il-6, IL-7, TNF-α, INF-γ, CXCL$_1$, CXCL2, CXCL5, CCL2 and CCL3
Gupta N et al 2012	- Bone marrow - MSCs - Intratracheal injection - Unstimulated mouse MSCs - *E. Coli* pneumonia - In vitro study	- Increased survival of mice - Inhibition of bacterial growth - Increased lipocalin-2 in bronchoalvealar lavage fluid. - Increased phagocytic activity
Nemeth K et al 2009	- Bone marrow - MSCs - Activated MSCs - CLP - In vivo study	- Reduced mortality of mice - Improved organ function - The beneficial effects of MSCs were eliminated by: macrophage depletion or pre-treat-IL-10 receptors. - MSCs reprogram macrophages by releasing postaglandin E2.
Gonzalez-Rey et al 2008	- Human and murine adipose tissue-MSCs - Intraperitoneal injection - CLP and endotoxin injection - Colitis and sepsis model, in vivo study	- Systemic infusion of adipose tissue-derived MSCs resulted in: increased survival of mice in addition to significant amelioration of severity of colitis and sepsis.
Chang C-L Et al 2012	- Apoptotic adipose tissue- MSCs - Rat model - Penile venous transfusion	- Protection of major organs from damage - Improved prognosis and reduced mortality of animals treated with MSCs.

Study and year of publication	Type of MSCs, route of administration of MSCs and sepsis model	Results and proposed mechanism(s) of action
	- CLP - Peritoneal sepsis, acute kidney injury	- Increased circulating levels of TNF-γ - Reduction in the numbers of: helper and cytotoxic T-cells, T-regulatory cells in peripheral blood and spleens of animals.
Yang R et al 2013	- IL-17 producing MSCs	- Inhibition of growth of *Candiada albicans* - Mechanism of action: stimulation of IL-17 production.
Sung P-H et al 2013	- Rat model - Adipose tissue - MSCs - CLP - Sepsis syndrome, kidney and lung injury	- Adipose tissue MSC therapy was superior to healthy adipose-derived MSC therapy in preventing major organ damage in rats treated with CLP-induced sepsis syndrome.

MSCs: mesenchymal stem cells; IL: interleukin

TNF: tumor necrosis factor; CLP: cecal ligation puncture

INF: interferon

Table 2. Studies using murine MSCs in infection or sepsis models

Study and year of publication	Type of MSCs, route of administration and sepsis model	Results and possible mechanism(s) of action
Meisel R et al 2011	- Human MSCs - Interferon –γ stimulated MSCs - In vitro study	- Inhibition of gram-positive bacteria - Inhibition of intracellular CMV and HSV-1 replication - Increased indoleamine -2,3- dioxygenase
Krasnodembskaya A et al 2010	- Human BM-MSCs murine model - Intravenous admin istration of MSCs - Intratracheal *E.coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* pneumonia	- Increased antimicrobial activity and decreased bacterial growth in bronchoalveolar lavage. - Decrease in lung bacterial load. - Inhibition of bacterial growth in vitro - IV MSCs + neutralizing antibodies to IL-37: reduced bacterial clearance.
Krasnodembskaya A et al 2012	- Human BM - MSCs - Intravenous administration - Murine Gram-negative peritoneal sepsis	- Increased survival due to increased clearance of bacteria from circulation. -Increased phagocytic activity of mononuclear cells in spleens of mice. - Marked reduction in circulating bacteria in the blood of treated mice. - Increased number of platelets inhibitor -1 (PAI-1) - No change in cytokine levels in plasma and peritoneal fluid.
Kim ES et al	- Human umbilical cord blood - MSCs	- Increased survival of treated mice - Reduced bacterial burden in pneumonia model.

Study and year of publication	Type of MSCs, route of administration and sepsis model	Results and possible mechanism(s) of action
2011	- Intrathecal administration - E. coli induced acute lung injury - In vivo study in mice	- Acute lung injury induced by *E.coli* was attenuated by: down-modulation of inflammatory process and enhancement of bacterial clearance - Anti-inflammatory mechanisms involved.
Casatella MA et al 2011	- Human MSCs - In vitro study	- Enhancement of neutrophil function - Proposed mechanisms: IL- 6, INF- β and GM-CSF
Maqbool M et al 2011	- Human MSCs - In vitro study	- Inhibition of neutrophil apoptosis - Unknown mechanism of action - No elucidation of molecular mechanisms that govern protection of neutrophils from serum-induced apoptosis
Rafaghello L et al 2008	- Human BM-MSCs and neutrophils - In vitro, MSC - conditioned media - Delivery method: co-culture - Effect of BM-MSCs on neutrophil survival and effector function.	- Inhibition of apoptosis of resting and IL-8 activated neutrophils with both MSCs and MSC-conditioned media - Recombinant IL-6 was found to protect neutrophils from apoptosis - Effect was mediated by IL-6
Lee JW et al 2013	- Human BM derived MSCs - Ex-vivo perfused human lung injured and intrabronchial *E. coli* delivery - Bacterial induction of acute lung injury * IV or intrabronchial injection of MSCs	- Increased macrophage phagocytosis - Reduced alveolar bacterial burden - Intrabronchial KGF-7 caused: increased alveolar macrophage phagocytosis and decreased bacterial load. - KGF duplicated most of the antimicrobial effects of MSCs. - In vitro: KGF-7 positive monocytes increased bacterial killing and monocyte survival and FGF-7 blocking antibodies nullified antimicrobial effects ex vivo and in vitro.

MSCs: mesenchymal stem cells; IV: intravenous

IL: interleukin; KGF: keratinocyte growth factor

IFN: interferon; GM-CSF: granulocyte monocyte-colony stimulating factor

Table 3. Studies using human MSCs in infection or sepsis models

Based on current clinical trials and irrespective of the treated disease condition or the mode of administration, MSC therapy appears relatively safe [3, 5]. Therapeutic applications of MSCs raise a series of concerns about the safety of culture-expanded MSCs for human use [4]. However, further large scale clinical trials with rigorous reporting of adverse events are required to further define the safety profile of MSCs [5]. Complications of MSC therapies include: (1) febrile reactions during or shortly after transfusion, (2) tumor modulation and malignant transformation, (3) increased risk of cancer, particularly hematologic malignancy, (4) genetic manipulation, induction of genetic instability and evolution of chromosomal

abnormalities, (5) increased incidence of infectious complications, particularly in recipients of hematopoietic stem cell transplantation (HSCT) having graft versus host disease (GVHD) treated with MSCs, and (6) persistence of human *Parvovirus B₁₉* in multipotent MSCs, expressing the erythrocyte P antigen, that are used to improve the outcome of HSCT and in regenerative medicine [1, 6-9]. Therefore, strict control and safety measures are needed in the production of MSCs for cell-based therapies in order to minimize or abolish the risk of malignant transformation [1]. It is also essential to establish standardized manufacture guidelines for the isolation, expansion, preservation and delivery of MSCs for safety evaluation and clinical applications [4].

2. MSCs and sepsis

Sepsis is the leading cause of death in the intensive care units and it ranks among the top 10 causes of death in the general population worldwide. Despite the advances in medical care, mortality rates from sepsis remain as high as 30%-50% in severe cases [10]. Sepsis is a systemic inflammatory response that is typically triggered by bacterial or other microbial infection and it involves a complex interaction between the microbial pathogen and the host immune system [11, 12]. The inflammatory response, designed to control infection, affects end-organ perfusion and exacerbates tissue injury leading to multi-organ failure [11]. In the early phase of sepsis, endogenous proinflammatory cytokines and coagulation pathways become hyperactive and their adverse effects cause multi-organ failure, collapse of the circulatory system and ultimately death of the affected individual [12].

Sepsis is associated with a surge of systemic signaling molecules including cytokines and growth factors that may become uncontrollable [11]. Stem cells have profound effects on the inflammatory response and coagulation cascade that are activated during sepsis [13]. Stem cells have been shown to modulate more than 3000 genes in experimental sepsis models. They enhance the clearance of pathogens and repair of injured tissues in sepsis. In addition, stem cells have been found to have an impact on cell leak that is encountered during sepsis [13].

2.1. MSCs in sepsis and experimental sepsis models

Mesenchymal stroma is an essential component of tissue barriers and it participates in protecting the body from infections. A breach in the integrity of tissue barriers such as trauma can lead to translocation of bacteria and colonization of vital organs, thus ultimately leading to multiple organ failure and sepsis [14]. Tissue injury compromises barrier function and increases the risk of infection and sepsis. Tissue injury can induce recruitment of MSCs from BM and promote their proliferation so as to reconstitute the integrity of injured tissues and mediate natural debridement [14]. MSCs can modulate systemic response to bacterial infection and support tissue repair in addition to healing after being recruited at the sites of tissue injury [14]. Sepsis is a devastating condition characterized by systemic activation of inflammatory and coagulation pathways in response to microbial invasion of sterile body organs or tissues [15]. Severe sepsis, sepsis with at least one dysfunctional organ, is a leading cause of death in

intensive care units (ICUs) as it is associated with mortality rates ranging between 30% and 50% [15].

The development of experimental sepsis models to elucidate the pathophysiology and progression of clinical sepsis spans over the last 8 decades. The following transitions in animal models took place since the 1930s: endotoxemia, bacteremia, ischemia and bowel perforation and finally cecal ligation puncture (CLP) and the colon ascends stent peritonitis (CASP) models [15]. Genetic differences in mice and possibly humans are associated with differences in the inflammatory process initiated in response to sepsis and that ultimately affect the outcome of sepsis. Hence, transgenic animal models have been extensively utilized in sepsis research [15]. Upon stimulation by endotoxins or proinflammatory mediators, activated neutrophils release a chromatin material composed of DNA and antimicrobial granular proteins in the form of neutrophil extra-cellular traps (NETs). The formation of NETs, NETOSIS, is an emerging field in sepsis research [15]. However, the presence of NETOSIS is distinct from that of necrosis and apoptosis. NETOSIS can be experimentally induced by endotoxins such as lipopolysaccharides (LPS), Gram-negative as well as Gram-positive bacteria, fungi and proinflammatory cytokines such as activated platelets and interleukin-8 (IL-8). NET formation has been found to cause host tissue and cellular damage [15]. LPS-induced endotoxemia in mice as well as plasma obtained from humans with severe sepsis were able to trigger NETOSIS. In vitro, NET formation resulted in endothelial cell damage while in vivo it caused hepatotoxicity in LPS-challenged mice [15]. In septic hosts, NETs can exacerbate sepsis by releasing high concentrations of potent proteases, forming a chromatin meshwork and trapping host cells (erythrocytes, leukocytes and platelets) that can potentiate inflammation, coagulation and ischemia in involved tissues [15].

Microparticles are a heterogenous population of small membrane-coated vesicles that are released by several cell lines upon activation or apoptosis [16]. Exosomes are a specialized category of microparticles with specific functions in immune response and protein sorting. Exosomes are released mainly from antigen presenting cells, although they have been identified after activation of platelets and mast cells and in body fluids such as urine or bronchoalveolar lavage [16]. Although the role of exosomes in sepsis remains deeply unexplored, accumulating data suggest that microparticles and exosomes play a role in the three pathways clearly involved in the pathogenesis of sepsis: inflammation, thrombosis and vascular dysfunction [16].

Human MSCs possess antimicrobial and immunosuppressive effects that are partly mediated by the tryptophan catalyzing enzyme indoleamine-2, 3-dioxygenase (IDO) [17]. Upon stimulation by inflammatory cytokines, MSCs exhibit broad spectrum antimicrobial effector functions directed against various clinically relevant pathogens and these effects are dependent on IDO and/or the antimicrobial peptide LL-37 [17]. MSCs have antiapoptotic, antifibrotic and angiogenic properties. Interferon γ (IFN-γ) primes MSC-mediated immunoregulatory effects and induces nitrous oxide (NO) production in MSCs. NO exerts antiapoptotic effects on cardiomyocytes and has antiviral properties [18].

The role of microparticles and exosomes in mediating vascular dysfunction suggests that they may represent novel pathways in paracrine transcellular signaling in vascular microenviron-

ment [16]. Further studies may aid in the clarification of their exact effects in sepsis and the development of additional interventional strategies for the prevention and treatment of sepsis [16]. Examples of experimental sepsis and infection models that utilized human as well as murine MSCs are shown in Tables 2 and 3 [19-35].

MSCs function at several levels of the inflammatory response, particularly in the early phase of sepsis, to regulate a wide panel of inflammatory cytokines and inhibit leukocyte infiltration into several target organs [12]. In an endotoxemic rat model, human AT-MSCs had the following beneficial effects: (1) modulation of host responses, (2) reduction of inflammatory cytokine levels in serum and lung, (3) reduction of alveolar inflammatory cell infiltration in the lung, (4) reduction of liver injury, and (5) improvement of tissue hypoperfusion [12]. As systemic administration of human-AT-MSCs at the onset of endotoxemia ameliorated the serological and histological signs of endotoxemia, they may become attractive candidates for cell therapy in the treatment of endotoxemia and septic shock [12].

Increasing evidence suggests that BM-MSCs secrete molecules that inhibit the effector function of immune cells [11]. AT-MSCs are a recently discovered cell population with much in common to their BM-derived counterparts. Both BM-MSCs and AT-MSCs have been shown to be effective in certain pre-clinical studies as they effectively inhibit the activation of T-cells [11].

Cellular immunotherapy for septic shock (CISS) trial is the first trial of stem cell therapy in humans [13]. It has 2 phases and the objectives of this Canadian trial are as follows: (1) in phase I, to establish safety and patient tolerability of stem cells and to find the optimal dose of stem cells to be administered, and (2) in phase II, to look at loose surrogates of efficacy for patients with septic shock [13]. The study has two arms: (1) an observational arm, where patients do not receive stem cells, and (2) an interventional arm, where patients receive stem cells with three different dose schedules [13]. The study is expected to address many aspects of stem cell therapy in patients having septic shock such as safety, tolerable dose and feasibility of use [13, 36].

In animal models of *Staphylococcal* toxic shock syndrome, MSCs have been shown to: (1) enhance bacterial clearance, and (2) suppress proinflammatory cytokine production, but they failed to prolong survival in experimental models [37, 38]. MSC therapy has also been shown to: (1) enhance antibiotic therapy in chronic *Staphylococcal* infections, and (2) enhance the effectiveness of conventional antibiotics in the treatment of antibiotic-resistant microbial infections [39, 40]. In patients with sepsis, the clinical application of MSC-based therapy is feasible, well tolerated and may be beneficial [36]. Studies have also shown that MSCs not only modulate the systemic inflammation, but also improve cardiac function in patients having endotoxemia [41]. Additionally, BM-MSCs can uptake and release antimicrobials, for example ciprofloxacin, into infected deep environment such as chronic osteomyelitis or deep seated abscesses [42]. Also, MSCs can act as drug delivery system for antibiotics or vehicles for targeted therapies in order to enhance effects of antimicrobials and other targeted therapies [42, 43].

2.2. Conclusions that can be drawn from experimental models

MSCs may be a potential new therapeutic modality in the prevention and reduction of sepsis-associated lung injury [21]. Decreased systemic and pulmonary cytokine levels may prevent acute lung injury and organ dysfunction. Genetic effects downregulate inflammation-related genes such as IL-10 and IL-6 and upregulate genes involved in the promotion of phagocytosis and bacterial killing [20]. The bacterial clearance effect could be party due to the upregulation of lipocalin -2 production by MSCs. However, lipocalin-2 antibodies have been found to block antimicrobial effects of MSCs [22].

In peritoneal sepsis models using murine MSCs; the following mechanisms were involved: down regulation of Th_1 inflammatory responses, reduced inflammatory cytokines and chemokines as well as increased IL-10 level and induction of IL-10 T-regulatory cells [24]. Apoptotic AT-MSCs represent an endogenous therapeutic strategy that may be enhanced for maximum clinical benefits [25]. Treatment with apoptotic AT-MSCs caused attenuation of sepsis syndrome induced lung and kidney parenchymal injury through suppression of inflammation, apoptosis and oxidative stress and enhancement of anti-oxidation and anti-apoptosis in rodent models [27].

Human BM-MSCs possess direct antimicrobial activity that is mediated by secretion of human cathelicidin hCAP-18/IL-37 [29]. Human MSCs participate in the innate response against Gram-negative bacteria through the secretion of the antimicrobial peptide IL-37 [29]. MSCs inhibit apoptosis of both resting and activated neutrophils and they increase the viability of resting and activated neutrophils in various culture serum concentrations [33]. MSCs can restore alveolar fluid clearance, reduce inflammation and exert antimicrobial activity party through keratinocyte growth factor (KGF) secretion [35]. Lastly, cultured or banked human BM-MSCs may be effective in treating sepsis in high-risk patients [23].

3. MSCs and viral infections

Fetal membrane derived MSCs [FM-MSCs] are susceptible to *herpes simplex virus-1* (*HSV-1*), *HSV-2*, *varicella zoster virus* and human *cytomegalovirus* (*CMV*) in vitro, while *Epstein-Barr virus* (*EBV*), human *herpes virus-7* (*HHV-7*) and *HHV-8* are capable of entering into FM-MSCs, but only limited gene expression occurs, thus resulting in non-productive infection. Therefore, FM-MSCs should be screened for the presence of herpes viruses before xenotransplantation [44]. Transcription factor nuclear factor (NF-kB) may affect the efficacy of *CMV* infection of MSCs. NF-kB inhibitors exacerbate the infection by the activation of human *CMV* in MSCs thus close attention should be given to human *CMV* infection once an NF-kB inhibitor is prescribed in clinical settings [45].

Human *CMV* is a leading cause of life-threatening complications in immunocompromised individuals, such as those with *acquired immune deficiency virus* (*AIDS*) and recipients of solid organ transplant (SOT) as well as HSCT [46]. Human *CMV* infects a wide range of cell types including fibroblasts, monocytes, granulocytes and BM cells such as myeloid progenitor cells

and MSCs. Following primary infection, human *CMV* establishes a lifelong latency in the host [46]. CD34+ progenitor cells have been recognized as the most likely reservoir for latent *CMV* infection in the BM, while CD34+ cells from the blood of healthy human *CMV* carriers have been demonstrated to contain the latent human *CMV*. The interaction between human *CMV* and BM-MSCs is complex and it is possible that BM-MSCs infected with human *CMV* may play a role in the development of human *CMV*-associated pathology [46]. Frequent virus reactivation in BM cells and subsequent productive human *CMV* infection of MSCs may be the underlying cause of various pathological processes [46]. *CMV*-infected MSCs lose their cytokine-induced immunosuppressive capacity and become no longer able to restrict micro-bial growth [17]. IDO expression is substantially impaired following *CMV* infection of MSCs and the interaction between *CMV* infection of MSCs and IDO expression critically depends upon (1) having an intact virus, (2) the number of infected MSCs, and (3) the viral load [17]. It is recommended that patients scheduled for MSC therapy should undergo thorough evalua-tion for an active *CMV* infection and receive *CMV*-directed therapy prior to the administration of MSCs as overt *CMV* infection in recipients of MSCs may undermine the clinical efficacy of MSC therapy [17].

MSCs could express receptors that permit their infection by *human immunodeficiency virus* (*HIV*)-1 [47]. Highly active antiretroviral therapy (HAART) significantly decreases mortali-ty and morbidity in patients with *HIV*-1 infection, but immune non-responders (INRs) with full viral suppression still fail to reverse the immune deficiency state [48]. In a pilot prospective controlled clinical trial that had enrolled 13 patients with *HIV*-1 infection, it was found that umbilical cord or more precisely Wharton's jelly derived-MSC transfu-sions were not only well tolerated, but also found to efficiently improve immune reconsti-tution in INR patients, suggesting that MSC therapy may be used as a novel therapeutic approach to reverse immune deficiency in INR-*HIV*-1 infected individuals [48]. Another study suggested that *HIV*-1 infected individuals could be cured if the HAART therapy is administered before the virus is able to establish its reservoir in the body [49]. Human *T-lymphotropic virus* (*HTLV*)-1 could infect and replicate in human BM-MSCs possibly by involvement or infiltration of CD4+ T-lymphocytes [50].

Although pre-clinical studies have shown that MSC therapy can induce anti-inflammatory effects and enhance repair of the injured lung and despite the clinical and pathological similarities between acute lung injury and severe influenza infection, it was found that MSC therapy may not be effective for the prevention and/or treatment of acute severe influenza [51]. It is well established that MSCs can be infected by *adenoviruses* and that these viruses are widely used as gene transfer vectors [52]. Recent studies revealed that the cationic polymer polybrene can potentiate *Adenovirus*-mediated transgene delivery into MSCs and should be routinely used as a safe, effective and inexpensive augmenting agent for *Adenovirus*-mediated gene transfer in MSCs [52].

Coxsackie virusB₃ (*CVB₃*) causes myocarditis not only by immune mediated mechanisms but also by inducing direct cardiomyocyte injury [18]. MSCs improve murine acute *CVB₃*-induced myocarditis via antiapoptotic and immunomodulatory mechanisms that occur in a NO-dependent manner and require priming with IFN-γ [18]. MSCs have the potential to treat acute

CVB_3-induced myocarditis since MSCs (1) cannot be infected with CVB_3, (2) have antiapoptotic and antiviral effects, and (3) improve cardiac function in experimental models of acute CVB_3-induced myocarditis [18].

Several lines of evidence indicate that human BM-MSCs can maintain *hepatitis B virus* (*HBV*) infection in vitro and support the replication of *HBV*-DNA. Human BM-MSCs may be a useful tool for investigating the *HBV* life-cycle and the mechanism of initial virus-cell infection [53].

4. MSCs and *Mycobacterium tuberculosis*

Persisters are a small fraction of quiescent bacterial cells that survive lethal antibiotics or stresses but are capable of reactivation under certain circumstances. Despite the discovery of persisters more than 70 years ago, the mechanisms of persistence are still poorly understood [54]. A number of pathways and genetic abnormalities have recently been identified and they may explain the mechanisms of persistence. These pathways include: DNA repair or protection, toxin-antitoxin modules, phosphate metabolism, antioxidative defense, efflux and macromolecule degradation [54]. However, more sensitive techniques are required to have a better understanding of the mechanisms of persistence. Once the underlying mechanisms are elucidated, cellular therapies, vaccination and targeted treatments are likely to make significant improvements in the management of persistent infections [54].

Bacterial persistence is the hallmark of tuberculosis (TB). The remarkable success of *Mycobacterium TB* (*M.TB*) as a human pathogen is attributed to its ability to program itself into entering prolonged periods of dormancy thus resulting in a latent TB infection [55]. Thus, *M.TB* can successfully evade the host immune system to establish a persistent infection [56, 57]. *M.TB* suppresses T-lymphocyte responses by recruiting MSCs into the site of infection and these cells can inhibit T-lymphocyte responses further by producing NO [56, 57]. Recruitment of MSCs into the tuberculous granuloma plays a vital role in the pathogenesis of *M.TB* infection as these MSCs infiltrate into the sites of infection and position themselves between the harbored pathogen and the effector T-cells [56, 57]. Targeting MSCs or NO is a feasible strategy to design future therapeutic and preventive interventions against *M.TB* infections [56, 57]. Macrophage apoptosis is a rather essential process in the development and maintenance of immunity as its augments the adaptive immune response through dendritic cell activation and subsequent antigen presentation and also reduces bacterial viability [58]. CD_4+T-cells play a crucial role in host defense against *M.TB* infections [59]. Animal studies have shown that isoniazid (INH) treatment causes dramatic reduction in *M.TB* antigen-specific immune responses and the induction of apoptosis in activated CD_4+ cells thus rendering treated animals vulnerable to TB reactivation and reinfection [59]. The finding that anti-TB treatment may be associated with further immune impairment should be taken into consideration in designing new anti-TB therapies [59].

Studies have shown that (1) *M.TB* may maintain long-term intracellular viability in BM-derived CD_{271}+/CD_{45}-MSC population in vitro, and (2) viable *M.TB* organisms have been detected in CD_{271}+/CD_{45}-MSCs isolated from individuals who had successfully completed

months of anti-TB chemotherapy [57, 60, 61]. Thus, CD_{271}+BM-MSCs are capable of providing an antimicrobial protective intracellular niche in the host in which dormant *M.TB* can reside for long periods of time [57, 60, 61].

4.1. The role of autologous MSC transplantation in the treatment of TB

Recently, autologous transplantation of MSCs has successfully been utilized in the treatment of infections caused by multi-drug resistant TB (MDR-TB) and even extensively drug resistant TB (XDR-TB) [57, 62, 63]. In one study, 27 patients in whom previous anti-TB drug therapy had been unsuccessful were included and they received autologous MSC transplantation [62]. Positive clinical responses were obtained in all patients, bacterial discharge from lung was abolished in 20 patients and resolution of tissue damage and lung cavitation were achieved in 11 patients 4 months after MSC infusion [62]. Also, persistent remission of the tuberculous process was obtained in 56% of patients who had follow-up for 2 years post MSC transplantation [62]. In a second phase 1 clinical trial, 30 patients with MDR and XDR-TB received autologous MSC transplantation after 4 weeks of starting anti-TB therapy [63]. Six months post-autologous MSC transplantation (1) no major adverse events were encountered and (2) 70% of patients showed radiological improvement, while 16.7% of patients showed stable radiological appearances [63]. Eighteen months post-MSC transplantation, 53% of the patients were cured while 10% of transplanted patients had evidence of treatment failure [63]. Therefore, combining standard anti-TB chemotherapy with autologous MSCT may become a promising maneuver to enhance the efficacy of treatment in patients with drug-resistant pulmonary TB [57, 62, 63].

5. MSCs and parasites

Plasmodium berghei infection in mice leads to massive recruitment of MSCs in secondary lymphoid organs [64, 65]. Also, infusion of MSCs into naive mice can confer host resistance against malaria by (1) augmentation of IL-12 production, (2) suppression of IL-10 production, (3) inhibition of hemozoin, and (4) dramatic reduction in regulatory T-cells in spleens of animals [64, 65]. *Leishmania* parasites can survive in different tissues and organs for decades even after treatment [66]. Several studies have shown that intracellular parasites can persist and remain viable in fibroblasts in latent, inactive or dormant forms [66, 67]. Also, *Leishmania* parasites could remain viable in inactive forms in AT-MSCs in vitro [66]. Therefore, screening for leishmaniasis is essential in recipients of HSCT living in areas that are endemic for leishmaniasis [66].

MSCs ameliorate liver injury and reduce fibrosis in mouse models of *Schistosoma japonicum* (*S. japonicum*). When combined with praziquantel, the preceding effects are enhanced [68, 69]. Infusion of MSCs in mice infected with *S. mansoni* caused (1) reduction of hepatic fibrosis, (2) amelioration of liver injury by induction of liver regeneration, thus ultimately leading to (3) improvement in liver function tests [70]. IFN-γ activated murine MSCs (1) could not inhibit the growth of a highly virulent strain of *Toxoplasma gondii* (BK), (2) strongly inhibited the

growth of a type II strain of *Toxoplasma gondii* (ME4a), and (3) inhibited the growth of *Neospora caninum* [71].

5.1. MSCs in Chagas disease

Chagas disease is caused by infection with *Trypanosoma cruzi* (*T. cruzi*) [72, 73]. Up to 30% of infected individuals develop cardiac symptoms related to a chronic chagasic dilated form of cardiomyopathy (CMP) [72]. Cardiac manifestations of Chagas disease include congestive cardiac failure, arrhythmias, heart block, thromboembolism, stroke and sudden death [73]. Available therapies include treatment of heart failure and arrhythmias, antiparasitic therapy, resynchronization treatment, heart transplantation and stem cell therapies [73].

The use of cell therapies to improve cardiac function has been attempted experimentally for more than two decades [72]. The use of BM-derived cells to treat cardiac diseases gained impulse based on the observation that stromal BM cells could be induced to differentiate into cardiomyocytes in vitro and when transplanted into cryoinjured rat hearts improved myocardial function and promoted angiogenesis [72, 74, 75]. Another significant development was that hematopoietic stem cells (HSCs) obtained from transgenic mice expressing enhanced green fluorescent protein, when transplanted into infarcted hearts of syngenic mice, differentiated into cardiac muscle and vascular cells [72, 76]. Since then, many laboratories reported that HSCs and stromal cells derived from BM improved myocardial function in animal models of both cryoinjured and ischemic heart lesions [72]. In one study, cardiac MSCs were isolated from hearts of green fluorescent protein transgenic mice then injected into left ventricular (LV) walls of mice chronically infected with *T. cruzi* [77]. Results of the study showed (1) cardiac MSCs demonstrated adipogenic, osteogenic and differentiation potentials, (2) histological analysis showed that mice treated with cardiac MSCs had a significant reduction in inflammatory cells but no reduction in fibrotic areas, and (3) molecular studies showed that cell therapy significantly decreased TNF-α expression and increased transforming growth factor-beta in heart samples [77]. The results clearly demonstrated that cardiac MSCs exert a protective effect in cardiac chagasic CMP primarily by immunomodulation [77]. In another model of chagasic CMP, direct LV injection of co-cultured skeletal myoblasts and stromal BM-derived cells improved heart function in chronically infected chagasic rats as measured by echocardiography [72, 78]. Injection of the co-cultured cells increased ejection fraction and decreased diastolic and end-systolic volumes [72, 78]. Intraperitoneal administration of MSCs into a mouse model of chronic chagasic CMP reduced inflammation and fibrosis in hearts of mice but had no effect on cardiac function as shown by another study involving an experimental animal model [79].

After the encouraging results in animal models, a clinical trial examining the feasibility and safety of intracoronary injection of autologous BM cell transplantation in patients with congestive cardiac failure due to chronic chagasic CMP was performed [72, 80]. Results of the trial showed that the procedure was safe and effective as cell therapy induced small but rather significant improvements in both ejection fraction and quality of life in patients included in the study [72, 80]. In an experimental cardiac ischemia model, the administration of granulocyte-colony stimulating factor (G-CSF) had beneficial effects on cardiac structure and function

[81]. Repeated administration of G-CSF in another experimental model of chronic chagasic CMP, which closely resembled human disease, induced beneficial effects on (1) cardiac structure as inflammation and fibrosis were reduced, and (2) cardiac function [81].

Based on the promising results of the previous safety trial, a larger multicenter, randomized, double-blinded and placebo-controlled trial was designed to test the efficacy of intra-coronary injection of BM-derived mononuclear cells (MNCs) in patients with chronic chagasic CMP [72, 82]. Although no serious adverse events were observed, this efficacy trial showed no additional benefit of intracoronary injection of BM- MNCs in chagasic patients with low ejection fraction, that is, intracoronary injection of BM-MNCs neither improved LV function nor improved quality of life in patient with chronic chagasic CMP [72, 82]. After the initial homing experiments, it was demonstrated that BM MNCs from non-chagasic syngeneic donors significantly reduced cardiac inflammation and fibrosis in mice with chronic *T. cruzi* infection. This improvement was maintained for up to 6 months after cell therapy [72, 83]. Using magnetic resonance imaging (MRI), it was demonstrated that BM-MNCs prevented and reversed the right ventricular dilatation induced by *T. cruzi* infection. Thus, histological improvement achieved by BM-MNC transplantation was paralleled by a functional correlate [72, 84].

One of the most striking observations after cell therapy in mice, chronically infected with *T. cruzi*, was related to the pattern of gene expression examined by microarray [72, 85]. While chagasic mice had 1702 out of 9390 (18%) cardiac genes with expression altered by infection after BM-MNC therapy, 96% of these genes were restored to normal levels although additional 109 genes had their expression altered by therapy [72, 85]. Transplantation of BM-MNCs in experimental mice showed immunomodulatory effects in chronic chagasic CMP and caused reversion of gene expression alterations in hearts of mice infected with *T. cruzi* [85]. In a chicken model of Chagas disease, the genetic alterations resulting from kDNA integration in the host genome caused an autoimmune-mediated destruction of heart tissues even in the absence of *T. cruzi* parasites [86]. In animal models of Chagas disease, microarrays were used to analyze global gene expression [87]. Eight distinct categories of mRNAs were found to be differentially regulated during infection and the dysregulation of several key genes was identified. These findings provide insights into the pathogenesis of chagasic CMP and provide new targets for intervention [87].

It is expected that within a few years, scientists will be able to find the (1) best animal model, (2) appropriate stem cell dose, (3) appropriate stem cell type, (4) injection route, and (5) disease status that will result in benefits for chronic chagasic CMP patients [72]. Despite the success of stem cell therapy in animals, preclinical models of Chagas disease have not translated into successful human studies [88]. Addressing the challenges associated with future research and providing solutions to have acceptable levels of safety and strict quality controls would enable successful clinical applications of stem cell therapies in chagasic CMP [88].

Ultimately, transplantation of BM-derived cells may prove to be an important therapeutic modality in the treatment of end-stage chagasic heart disease [89]. Identifying which cell type(s) is responsible for the effects observed in both animal studies and preliminary human experiments will be an important step in further improving this treatment [89]. Since the percentage of stem cells (either hematopoeitic or mesenchymal) is minimal in the mononuclear

fraction, use of purified stem cell population has the potential to significantly increase the therapeutic benefit of cell therapy in chagasic CMP [89].

6. MSCS and fungal infections

Despite the availability of new antifungal agents, mortality and morbidity related to invasive fungal infections is still high, particularly in patients with hematological malignancies and in recipients of SOT and HSCT [90, 91]. The recent advances in the immunopathogenesis of invasive aspergillosis have provided critical information to augment host immunity against fungal pathogens [90, 91]. Potential approaches for enhancement of the host immune system to combat invasive fungal infections include (1) administration of effector and regulatory cells such as granulocytes, antigen-specific T-cells, natural killer cells and dendritic cells, and (2) administration of cytokines, interferons and growth factors such as INF-γ, G-CSF and granulocyte monocyte-colony stimulating factor (GM-CSF) [90, 91]. Although promising results have been obtained from animal studies, limited data are available to draw conclusions on risks and benefits in clinical settings [90, 91]. So, appropriately designed, multicenter and international clinical trials are needed in order to improve the outcome of invasive fungal infections in immunocompromised individuals [90, 91]. MSC therapy in HSCT recipients has been found to facilitate faster control of invasive fungal infections [92].

Studies have shown that human cathelicidin LL-37 and its fragments LL13-37 and LL 17-37 exhibit similar potencies in inhibiting the growth of *Candida albicans* (*C. albicans*) [93]. However, death of (*C. albicans*) cells may not solely be due to increased permeability caused by LL13-37, but can also be due to certain intracellular targets [93]. In patients with severe refractory neutrophilic bronchial asthma, administration of MSCs appears to play a significant role in decreasing inflammation and ameliorating disease manifestations by mediating *Aspergillus*-induced inflammation through inhibition of the Th_{17} signaling pathway [94].

7. MSCs and wound healing

Chronic non-healing wounds are a serious medical problem [95]. Biofilms, which are bacterial communities attached to a surface and become protected by a polysaccharide coating, are believed to contribute significantly to the persistence of chronic wounds by altering the host immune response. Current treatment options are ineffective and do not significantly target biofilms [95]. It has been shown that the paracrine factors secreted by reprogrammed MSCs accelerate wound healing and reduce bacterial growth in biofilm-infected wounds in mice [95]. Therefore, clinical studies are needed to test the efficacy of these paracrine factors in the eradication of biofilms in patients with non-healing wounds [95].

In an in vitro study, MSCs have recently been shown to exert measurable antimicrobial activities in a synovial fluid setting, suggesting that they may have future application as adjunct therapy for peri-prosthetic joint infections [96]. Also, AT-MSCs have been shown to

enhance closure of enterocutaneous fistula and aided in the recovery and healing of wounds in a rat model [97].

8. MSCs and lung injury

Melatonin, the chief secretary product of the pineal gland, is an indirect antioxidant that acts to stabilize cell membranes thereby making them less susceptible to oxidative insults and ultimately suppressing inflammatory reactions [98]. Combined melatonin and apoptotic AT-MSCs treatment has been found to be superior to either regimen alone in ameliorating lung injury in the setting of CLP-induced sepsis in a rodent model [98]. Also, adult tissue-derived MSCs have been shown to have antimicrobial effects that inhibit bacterial growth in lung tissues [96].

BM-derived MSCs have unlimited potential clinical applications in acute lung injury, due to various pulmonary disorders and they exert their effects by various mechanisms [99]. *Vibrio vulnificus* sepsis can induce acute lung damage and pulmonary edema. BM-derived MSCs can downregulate inflammatory cytokines and reduce lung injury caused by *Vibrio vulnificus* sepsis in mice [100]. BM-MNCs were able to diminish pulmonary inflammation, lung elastance, lung modeling and fibrosis resulting in lower mortality in acute respiratory distress syndrome (ARDS) experimental models [101]. However, the benefits of BM-MNCs depend on several factors including the type of initial insult as they were shown to exert different effects on endothelial cell activation and adhesion molecules. Therefore, further studies are needed to clarify their mechanisms and to examine this novel therapy in clinical trials [101].

Multipotent MSCs have shown remarkable therapeutic effects in preclinical models of both ARDS and sepsis [102]. Initial research focused on the ability of MSCs to engraft at sites of tissue injury [102]. Recent literature shows increasing evidence suggesting that MSCs exert their therapeutic effects through mechanisms that are unrelated to long-term incorporation into tissues of the host [102]. One of the most compelling pathways is their capacity to interact with injured tissue through the release of soluble bioactive factors [102].

9. MSCs and neutrophils

MSCs participate in the regulation of inflammation and innate immunity by responding to pathogen-derived signals and by regulating the function of innate immune cells [103]. MSCs derived from the BM and peripheral tissues share common basic cell-biological functions [103]. MSCs contribute to the resolution of infection and inflammation by promoting the antimicrobial activity of polymorphonuclear leukocytes, a property that is exhibited by MSCs derived from either BM or peripheral glandular tissues [103]. MSCs rescue neutrophils from nutrient- or serum-deprived cell death. Whether this effect is exerted through a specific signaling pathway or confining neutrophils in a resting state by MSCs requires further evaluation [33].

Both multipotent adult progenitor cells (MAPCs) and MSCs are adult stem cells that can be derived from BM and are currently utilized in tissue engineering due to their immunomodulatory and trophic effects [104]. The use of stem-cell-based immunotherapy is very promising as in vitro studies have shown comparable suppressive effects of both human MSCs and human MAPCs [104]. However, the broader expansion capacities of human MAPCs make them more attractive than human MSCs for clinical use [104]. Neutrophils release many lysis-inducing factors and cause local tissue damage. Conversely, neutrophils themselves could become a target in controlling sepsis [105].

10. Antimicrobial effects of MSCs

Multipotent, BM-MSCs (MP-BM-MSCs) are culture-expanded, nonhematopoietic stromal cells with immunomodulatory properties that are currently being investigated as novel cellular therapies in the prevention and treatment of clinical diseases that are associated with immune dysfunction [106]. Preclinical studies suggest that MP-BM-MSCs may protect against infectious challenge through direct or indirect pathways [106]. Direct effects exerted by MP-BM-MSCs on the pathogen are manifested by reduction of pathogen burden by inhibition of growth through soluble factors and enhancement of antimicrobial function of immune cells [106]. Indirect effects exerted by MP-BM-MSCs on the host include: (1) attenuation of proinflammatory cytokine and chemokine induction, (2) reduction of proinflammatory cells immigration into the sites of tissue injury or infection, and (3) reduction of immunoregulatory soluble and cellular factors that preserve organ function. These preclinical studies provide insights into the future therapeutic applications of MP-BM-MSCs [106].

Through toll-like receptor (TLR) signaling and immune crosstalk between MSCs and immune effector cells, MSCs become capable of maintaining a critical balance between (1) promotion of pathogen clearance during the initial phase of inflammatory response, and (2) suppression of inflammation to preserve host integrity and to facilitate tissue repair [106]. The presumed or suggested roles of MP-BM-MSCs during infection can be divided into five phases as shown in Table 4 [106].

Human BM-MSCs have direct antimicrobial activity, against Gram-positive as well as Gram-negative bacteria, which is mediated in part through the secretion of human cathelicidin hCAP-LL-37 [107]. Also, evidences suggest that MSCs position themselves between the acid fast bacilli harbored in the BM and the host protective T-cells. Hence MSCs can be a potential target for the treatment of latent TB [108]. Targeting MSCs is not expected to lead to the evolution of new resistance in the pathogen as MSCs do not need to be directly targeted and as the host immune response needs to be manipulated [108]. Upon stimulation of inflammatory cytokines, human MSCs exhibit broad-spectrum antimicrobial effector function directed against a range of clinically relevant bacteria, protozoal parasites and viruses [28]. Human MSCs act as immunosuppressants that concurrently exhibit potent antimicrobial effector function thus encouraging further evaluation in clinical trials [28]. Human multipotent MSCs exhibit broad-spectrum antimicrobial activity mediated by IDO [28].

Phase	Main effect / mechanism	Details and explanations
1	Detection of pathogens and damage signals	- Engagement of TLR-mediated signaling pathways - Recruitment of MSCs at the sites of infection
2	Activation of host immune response	- Maintenance of quiescent HSC pool - BM emigration of activated HSCs - Mobilization and emigration of immune effector cells from BM. - Thymic development to augment response of immune effector cells
3	Elimination of pathogens	- Production of microbiocidal soluble factors - Containment of infectious pathogen within micro-environment (pathogen phagocytosis)
4	Induction of proinflammatory gradients	- Antioxident soluble factor (HO-1) - Antiinflammatory soluble factors such as: IDO, PGFZ, IL-10, TGF-B, TGF-6, HLA-G5 and Galectin-1
5	Modulation of proinflammatory host immune response	- Activation of function, differentiation and migration of immune effector cells. - Augmentation of wound healing - Enhancement of revascularization - Inhibition of tissue toxicity - Modulation of inflammation and organ dysfunction.

TLR: toll-like receptor; HSC: hematopoietic stem cell; IL: interleukin; IDO: indoleamine-2, 4-dioxygenase

Table 4. Accepted roles MSCs during infection

Human gut microbial communities reside in an open ecosystem subject to disruptions ranging from dietary change to toxin exposure and pathogen invasion [109]. Host inflammatory mechanisms to remove harmful organisms and restrict bacteria to gut lumen commonly target conserved molecular patterns found on pathogens and commensals alike, yet healthy gut microbial communities can remain stable for years in humans [109]. A delicate balance between microbial resilience and host tolerance thus allows for commensal persistence throughout a diverse range of perturbations while preventing commensal overgrowth or depletion, either of which could have deleterious effects on the host [109]. Thus, antimicrobial peptide resistance mediates the resilience of prominent gut commensals during inflammation [109]. Stem cell differentiation can be regulated by TLR activation. Activation of TLRs on MSCs increases osteogenesis and decreases adipogenesis [110]. Upon exposure to microbial legends, stem cells change their differentiation to help the initial immune response [110]. Microbial ligands can influence stem cell fate via pattern recognition receptors. Microbial ligands such as LPS and lipoproteins can alter: proliferation, differentiation, migration and the function of stem cells. In mice stem cell proliferation is stimulated by TLR activation, while in humans most TLR activity does not seem to affect stem cell proliferation [110]. TLR activation alters stem cell differentiation, cytokine production of stem cells and immunosuppressive functions of MSCs

[110]. However, cytokine production can also be influenced by microenvironment, co-stimulatory molecules as well as downstream signaling pathways [110]. The immunosuppressive function of MSCs can be stimulated or inhibited by TLR activation depending on the type of signaling pathways that are activated [110]. With the identification of innate immune receptors on stem cells and the finding that microbial ligands can influence stem cell fate, a new era of stem cell research has begun [110].

11. MSCs and HSCT

Recent studies revealed that, during pathogen exposure, hematopoiesis may yield progeny in magnitudes that are different from those produced under routine or stable hemostatic circumstances [111]. HSCs not only sustain blood cell formation following bleeding, BM damage or chemotherapeutic ablation, but also respond directly to microbial products as well as inflammatory cytokines thus permitting real-time alterations in the direction of hematopoiesis in response to exposure to a certain burden of pathogenic organisms [111].

Various evidences from experimental models and clinical studies suggest the implication of bacterial and fungal infections in the pathogenesis of acute GVHD [112]. Appropriate treatment or prophylaxis of bacterial infections during the early post-HSCT period might be beneficial in reducing not only infection-related but also GVHD-related mortality [112]. To eliminate the systemic proinflammatory cytokine surge induced by bacterial infection, the following are needed: (1) specific antimicrobial strategies, (2) therapies targeting the pathways of innate immunity, and (3) nutritional interventions that might help in reducing the risk of acute GVHD. These issues should be evaluated prospectively in clinical trials[112]. In a retrospective cohort study that evaluated the risk factors for pneumonia-related death following HSCT and that included 691 patients, meta-analysis showed that the following were the risk factors that contributed to death: (1) acute GVHD grades II - IV, (2) CMV infection, and (3) receiving MSCs. Additionally, bacteremia and mold infections contributed to pneumonia-related deaths [113].

MSC therapy in HSCT recipients has been found to have the following advantages: (1) prevention and treatment of GVHD, (2) immune reconstitution, (3) induction of faster engraftment, (4) healing of infections and inflammatory disorders, and (5) reduction in the incidence of various infectious complications [92, 103, 104, 114, 115]. Studies have shown that administration of human BM-derived MSCs given during allogeneic bone marrow transplantation or human umbilical cord blood-derived MSCs in the post-transplant period, in patients with bone marrow failure, is safe and advantageous [92, 114]. In recipients of unrelated allogeneic HSCT following non-myeloablative conditioning therapy, co-infusion of MSCs did not show any pulmonary deterioration for up to 1 year post–transplant [115]. Additionally, in recipients of haploidentical HSCT, infusion of umbilical cord–derived MSCs did not increase the incidence of pulmonary infections [116].

12. Nanotechnology in stem cell research and therapy

Stem cell tracking using modern imaging modalities offers new insights into understanding the biology and achieving the full therapeutic potentials of stem cell therapies [117]. Currently used standard methods for tracking stem cells in vivo include: (1) MRI, (2) bioluminescence imaging, (3) positron emission tomography, (4) fluorescence imaging, (5) single-photon emission tomography, (6) X-ray computed microtomography, (7) Raman or surface enhanced Raman spectroscopy-based imaging, and (8) photoacoustic imaging [117-119]. The selection of the imaging modality and stem cell tracer or label should take into consideration: the clinical condition of the patient, the primary disease and the comorbid medical conditions [120].

Nanotechnology offers valuable information on migration, homing, survival, differentiation, function and the engraftment of transplanted stem cells [117, 121, 122]. The delivery of nanomaterials enables a personalized approach and individualized tailoring of nanotechnology and materials used to the specific needs of each patient [120]. To be of most use, tracking methods should ideally be non-invasive, high resolution and allow tracking in three dimensions [121]. To identify transplanted stem cells from the host tissue, optically active probes are usually used to label stem cells before their administration [117]. Nanofibers have recently gained substantial interest for their potential application in tissue engineering [123]. Nanofibers accommodate: (1) the survival and proliferation of human MSCs, and (2) the continuous differentiation of human MSCs into obsteoblasts and chondrocytes [123].

13. Homing and migration of MSCs

An important property of MSCs is their capacity for migration and homing in or around the zones damaged by trauma, inflammation, ischemia or tumor infiltration [124]. Intravenous administration of MSCs causes their migration, in substantial numbers, into areas of tissue damage [124]. Therefore, it is essential to understand the mechanisms involved in the homing and migration of MSCs. In addition, MSCs derived from various sources express different patterns of chemokines and their receptors [124]. Hence, the possibility to modulate the migration ability of MSCs opens a new era for the development of directed migration of greater numbers of MSCs injected intravenously into the sites of injury [124].

14. Banking of MSCs

MSCs hold great potential for developing effective cellular therapies and current trends indicate that their clinical applications will continue to rise markedly [125]. There has been considerable success in manufacturing and cryopreserving MSCs at laboratory level, but these successes have not translated into technologies developed at industrial scale [125]. The development of cost-effective and advanced technologies for the production and cryopreservation of MSCs is a crucial step in the process of successful clinical cell therapy [125]. Also, it

is essential to have simple and appropriate but validated protocols for cell and tissue processing under good manufacturing conditions in order to develop a cost-effective banking of MSCs such as those obtained from umbilical cord blood [126].

15. Conclusions and future directions

MSCs are heterogeneous progenitor cells that have the capacity of self-renewal and multi-lineage differentiation. Their distinguished immunomodulation and immunosuppressive properties allowed MSCs to have several therapeutic applications. MSCs are essential constituents of the framework that supports organ integrity and tissue barriers. Suppression of both T and B cells enables them to be major players in controlling inflammatory response and in the innate response to bacterial infection. Human BM-MSCs possess direct antibacterial activity against Gram-negative bacilli and they have been shown to improve survival and reduce mortality in animal models having septic complications. Also, human BM-MSCs can act as drug delivery vehicles, enhance the effectiveness of conventional antimicrobials and may prevent the evolution of drug–resistant microbes. MSCs contain a subset of IL-17$^+$ that is capable of inhibiting the growth of *C. albicans*. CD 271$^+$ BM-MSCs may provide a long-term protective intracellular niche in the host where *M.TB* organisms remain viable but in a dormant state. Two recent clinical trials in humans have shown that autologous transplantation of MSCs can successfully treat MDR strains of *M.TB*. Animal studies have demonstrated that MSCs enhance host defenses against malaria. MSC therapy improves liver function and promotes hepatocellular regeneration in patients with hepatic fibrosis caused by schistosomiasis. Transplantation of MSCs has been shown to reverse right ventricular dilatation, cardiomyopathy and advanced heart involvement in *T. cruzi* infection. Transfusion of MSCs can confer resistance to HIV and may restore immune reconstitution in infected individuals. Autologous MSC transfusion in patients having liver cirrhosis secondary to hepatitis B or C infection improves liver function tests. MSCs improve murine models of acute myocarditis caused by CVB_3 infection. However, MSCs are not effective in the prevention or treatment of severe *Influenza virus* infections. There is low risk of transmission of human herpes viruses by transplantation of MSCs from healthy seropositive donors. *CMV* infection impairs the immunosuppressive and antimicrobial effector functions of human MSCs, thus overt *CMV* infection in recipients of HSCT may undermine the clinical efficacy of MSCs in treating GVHD. MSC therapy in patients with severe GVHD is associated with increased mortality related to *Adenovirus* infections. Therapeutic applications of BM-MSCs in recipients of HSCT include prevention and treatment of GVHD, induction of faster engraftment, immune reconstitution, healing of inflammation as well as treatment and prevention of various infectious complications. Also, cultured or banked human BM-MSCs may be effective in treating sepsis in high-risk patients.

Taking into consideration the remarkable success in the utilization of MSCs in the treatment of various infections in animal models and the few published clinical trials in humans with MDR infections, such as those caused by *M.TB*, and with the advancements in technology and medical care, it is reasonable to predict a similar success in the use of MSC therapy in humans

in the near future. However, complications of this form of cellular therapy should never be underestimated. Also, it is essential to have banking facilities for these stem cells in addition to guidelines and protocols for their use in high risk individuals, particularly those with *HIV*, MDR-TB, hematological malignancy, recipients of SOT and HSCT as well as patients receiving advanced level of care in ICUs.

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