

Understanding the Role of Mesenchymal Stem Cells in Infectious Diseases: Focus on Tuberculosis, Malaria, Sepsis and HIV

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Review Article

Abstract

The mesenchymal stem cells (MSCs) are endowed with multi lineage differentiation potentials and self-renewal properties, which qualify them as potential sources for cell transplantation and gene therapy. Numerous studies have shown that MSCs can be recruited to sites of inflammation, where they exert potent immune-suppressive activities that can be exploited for the development of immunotherapies. MSCs from several origins, including bone marrow and adipose tissue, have been well described. Adipose tissue derived MSCs (ASCs), like bone marrow derived (BM-MSCs), have the capacity to differentiate along multiple lineages at clonal levels. Now a day scientists have isolated and cultured MSC or MSCs like cells from various sites or organs of body other than bone marrow, including adipose tissue, amniotic fluid fetal tissues etc. with different phenotypic heterogeneity. They can differentiate into neurons, cardiomyocytes, chondrocytes, osteocytes, and adipocytes. Thus MSCs are of great interest in the area of tissue regeneration. Apart from these, MSCs like cells are also found from pathological tissues such as rheumatoid arthritic joint, lung granuloma of tuberculosis, splenomegaly of malaria etc. from human or rodent with bone morphogenetic protein receptors. And it has been reported that, MSCs have immunosuppressive effect by which it suppress T-cell proliferation and cytokine production showing immunomodulatory effect on MSCs or immune enhancement effect which is generated by chemokine-mediated immune cell aggregation in the absence of immunosuppressive effector molecules.

Therefore, MSCs plays an important role in non-infectious and infectious diseases. Here in this review we are mainly focusing on the role of Mesenchymal stem cells in some infectious diseases.

Keywords: Mesenchymal Stem Cells (MSCs), Mycobacterium tuberculosis, Malaria, Sepsis, HIV.

1. Introduction

Mesenchymal stem cells (MSCs) are non-hematopoietic stem cells which are usually present within the bone marrow stromal compartment and represent a very small fraction (0.001–0.01%) of total population of nucleated cells [1]. This multipotent stromal precursor cells were first identified by Friedenstein on the basis of studies showing that bone-marrow-derived stromal cells are common precursor cell type of mesenchymal tissues. MSCs have capability to differentiate into mesenchymal tissues such as bone, cartilage, tendon, muscles and adipose tissues. Recently, several other studies have reported that multipotential stromal precursor cells have also capability to differentiate into unrelated germline lineages by trans differentiation process [2]. Initially due to their self-renewal and differentiation capacity, they were considered as stem cells and named mesenchymal stem cells by Caplan [3]. However, the rare stromal cells provide heterogeneous population of cells, that contain a mixture of progenitors at different stages of commitment to the mesodermal lineage and constitute a small fraction of multipotent self-renewing stem cells with CD146 expression (MCAM) [4]. It is now accepted that most bone-marrow-derived progenitor

stromal cells can only be considered as MSCs after *in vitro* proliferation [5]. Thus MSCs are of great interest in the area of tissue regeneration. Other than tissue repair, recently it has been reported that MSCs possess potent anti-proliferative, anti-inflammatory as well as immunomodulatory activity. Due to these properties many clinical trials are being conducted with transplantation of MSCs in treating various diseases which arise from immunological abuses. These cells have specific capacity of homing and thus can repair infection induced injuries of various organs of body.

1.1 Phenotype and characteristics

Colter et al., isolated Human MSCs (h-MSCs) by density gradient centrifugation from mononuclear layer of the bone marrow [6]. When mononuclear cells are cultured in medium with 10% fetal calf serum, the non-adherent cells washed away, leaving adherent, nonphagocytic, fibroblast-like cells. After initial lag phase, these cells started dividing as colony like structure, the doubling time of these cells varies and it depends on the donor and the initial plating density [7-10]. Apart from these, MSCs like cells are also have been isolated from pathological tissues such as rheumatoid arthritic joint, lung granuloma of tuberculosis, splenomegaly of malaria etc. from human or rodent with bone morphogenetic protein receptors [11-13]. Previously, it has been reported that post natal organs also contains the cells similar to that of MSCs. MSCs have been isolated and cultured from many other species including mice, rats, cats, dogs, rabbits, pigs, and baboons, albeit with varying success [14]. Blanck and Ringde clearly demonstrated in different experimental model that, MSCs are not only regenerated tissues of mesenchymal lineages, such as intervertebral disc cartilage [15], bone [16,17], cardiomyocytes [18] and knee joint repair following meniscectomy [19] but also differentiated into the cells derived from other embryonic layers, including neurons [20], and epithelial layer, lung, liver, intestine, kidney and spleen [21-23]. Due to the lack of definitive marker and scarcity of cell types in bone marrow, MSCs culture used to be expanded *in vitro* several fold consecutively to get proper amount of cells for experiment [1,24].

There is a general consensus that human MSCs do not express the haematopoietic markers CD45, CD34, CD14, CD11 or the co-stimulatory molecules CD80, CD86 and CD40, or the adhesion molecules CD31 (platelet/endothelial cell adhesion molecule [PECAM]-1), CD18 (leukocyte function-associated antigen-1 [LFA-1]), or CD56 (neuronal cell adhesion molecule-1), however they express variable levels of CD105 (also known as endoglin), CD73 (ecto-5'-nucleotidase), CD44, CD90 (THY1), CD71

(transferring receptor), the ganglioside GD2 and CD271 (low-affinity nerve growth factor receptor), and they are recognized by the monoclonal antibody STRO-1 as well as the adhesion molecules CD106 (vascular cell adhesion molecule [VCAM]-1), CD166 (activated leukocyte cell adhesion molecule [ALCAM]), intercellular adhesion molecule (ICAM)-1, and CD29 [1,25-27]. The variability of expression level of these markers depends on the species differences, tissue source and culture conditions.

Previously it has been reported that MSCs express intermediate level of major histocompatibility complex (MHC) class I but do not express human leukocyte antigen (HLA) class II on their cell surface [28]. The expression of HLA varies from fetal to adult [29]. In the adult, HLAII come out at cell surface by the induction of interferon- γ for at least 1 hour to 2 Days [28] whereas, in fetal condition there is lower level of surface HLA class I as well as HLA II in either intracellularly or in cell surface of fetal liver MSCs [29], suggesting that there are changes of human MHCs expression from fetal condition to adult.

1.2 Role of MSCs

Mesenchymal stem cells have some unique characteristics like differentiation in different mesodermal origin and that make promising for the research and clinical trial of tissue endogenous repair and gene therapy, which represents a powerful new arms for treating human diseases. From systemic administration of MSCs as an intravenous treatment to the delivery of their molecular secretions by extracorporeal devices, groups around the globe are focusing their attentions on this cell, seeking to harness its full therapeutic potential. Previously it has been reported that MSCs has immunosuppressive effect, by which it suppress T- cell proliferation and cytokine production showing immunomodulatory effect of MSCs [30,31] or immune enhancement effect which is generated by chemokine-mediated immune cell aggregation in the absence of immunosuppressive effector molecules [32]. Therefore, MSCs play pivotal role in both non infectious or infectious disease.

1.3 Infectious disease

Any disease caused by the entrance, growth and multiplication of micro-organism in the body, are called infectious disease, where pathogens modulate host's response and manage to survive. As mesenchymal stem cells have capability of infuse within the injured region, regenerate the cells, and modulate the immune response, that is why it is believed that it has great role in infectious diseases. There are various infectious diseases but we mainly focus on life threatening and globally challenged diseases.

1.4 Tuberculosis

Tuberculosis (TB) is the cause of 2 million deaths each year, which is the second highest cause of mortality from a single infectious disease worldwide, after HIV/AIDS [33]. One third of the global population is latently infected with *M. tb*, waiting for the opportunity of perturbations of the immune response, such as HIV infection for reactivation. Thus, the vast reservoir of TB disease is alarming, and its epidemic is becoming a global public health emergency. Unfortunately, even after 100 years of discovery of its pathogen *Mycobacterium tuberculosis*, no therapeutics has been discovered for total eradication of this bacterial pathogen. Bacillus Calmette Guerin (BCG) is the only TB vaccine presently available, has been widely used throughout the world since its inception in 1921, and an estimated three billion people have received it [34]. But, its efficacy in adult pulmonary tuberculosis is under satisfactory [35]. BCG is effective against disseminated and meningeal tuberculosis in young children. However, its efficacy against adult pulmonary tuberculosis varied dramatically 0-80% in different populations depending on the ethnicity, and geographical locations [36]. *Mycobacterium tuberculosis* infects humans through aerial route and thus lungs are the primary organ for its infection. Subsequently, infection spreads over other organs of body such as spleen and lymph nodes.

Granulomas are the hall marks of tuberculosis infection. These are the site of infection with inflammation where infected bacteria are surrounded by macrophages, lymphocytes, neutrophils, eosinophils, fibroblasts and collagen. It is considered that within the granuloma, immune responses are concentrated and that eradicate the pathogen, but, it has been reported that MSCs has important role in providing niche to these pathogens or conversely these pathogens impose on MSCs for their niche [37]. Infection to the macrophages leads to secretion of several types of chemokines and cytokines which attract lymphocytes and neutrophils at the site of infection. These cells are able to hold these pathogens inside granuloma, thus preventing the spread of bacilli to other parts of body and further inflammation. Recognition of pathogen associated molecular patterns leads to activation of T cells which secrete IFN- γ , which is known to provide protective immunity against tuberculosis.

Despite the generation of robust host immune responses, *Mycobacterium tuberculosis* (*M. tb*) successfully evades host immunity and establishes a persistent infection. The mechanism(s) by which *M. tb* manages to persist in the face of potent host immune responses remain(s) incompletely understood. Therefore, the optimal strategy for the treatment of

latent and/or persistent TB infection is not clear. We, for the first time demonstrated that *M. tb* suppresses T-lymphocyte responses by recruiting mesenchymal stem cells (MSCs) to the site of infection [12]. We found that MSCs infiltrate tissues containing *M. tb* organisms and T lymphocytes. We further demonstrated that MSCs suppress T-cell responses by producing nitric oxide [12]. Our findings reveal the role of MSCs in *M. tb* evasion from host immune responses and identify these cells as unique targets for therapeutic intervention in tuberculosis. MSCs contribute to the delicate balance within granulomas that contains the pathogenic microorganisms but does not completely eliminate them. *M. tb* might have exploited this mechanism to promote the establishment of latent infection [12]. Recently Das, B et al, further put some light in MSCs in tuberculosis and demonstrated that in *in vitro* studies of human BM-MSCs, where CD271⁺ BM-MSCs from patients with pulmonary TB are a cellular niche for *M. tb* that may be important for the maintenance of the non-replicating phase of *M. tb* in humans. CD271⁺ BM-MSCs have many features that could be potentially advantageous for *M. tb* persistence including their ability to self-renew, expression of the ABCG2 drug efflux pump, and the immune-privileged nature of the BM stem cell niche. They concluded that human BM-MSCs may participate in TB pathogenesis with potentially important clinical implications [37].

1.5 Sepsis

In sepsis syndrome, invading pathogen such as lipopolysaccharide (LPS) interacts with toll like receptors to produce proinflammatory cytokine, with elevated level of interleukins, chemokines and endothelial cell adhesion molecules, which induce inflammation [38]. These exorbitant inflammatory response activates number of pathways that include host immune dysfunction, dysregulation of the coagulation cascade, and endothelial dysfunction in response to systemic hypotension, end-organ ischemia, and multi-organ dysfunction [39,40]. Inflammation followed by a subsequent anti-inflammatory phase characterized by further immune dysregulation, cytokine alteration which eventually lead to organ damage by cellular apoptotic pathways [41]. Due to short falls of current therapeutics and morbidity / mortality of sepsis, recently scientists have turned towards novel cell based therapy of sepsis. As Mesenchymal stem cells are capable of differentiating into multiple cell types it is one of the choice for use in damaged tissue repair. Intravenous or intra peritoneal delivery of these cells are effective because of its ability of chemotactic migration to the injured tissues such as lung, myocardium, brain, liver and kidney [42-46]. Recently it has been observed that MSCs promote the regeneration of

injured tissue, prevent loss of threatened tissues and improve overall functions of the tissues affected by ischemia or bacterial function [23,47-49]. MSCs protect the bacterial induced aggressive proinflammatory cytokines secretion, organ damage by inflammation through overall reduction of local and systemic inflammation by balanced decrease of proinflammatory cytokines with the help of an increase in anti-inflammatory cytokines production [50-52]. Most important anti-inflammatory cytokines produced by MSCs are TGF β , IL-10, IL13 and TNF α [47,53]. Rather than these cytokines, it has been also observed that prostaglandin E2 (PGE2) secreted by MSCs inhibits inflammatory cytokines [54]. These findings were confirmed when human adipose-derived MSCs were injected to septic mice, its inflammatory response was decreased and anti-inflammatory cytokine IL10 was increased [51]. In the second phase of sepsis, wide-spread of cell death occur due to apoptosis which is thought to be due to the cytokines such as TNF mediated activation of caspase systems. In several studies it has been found that MSCs can alter this apoptotic signaling. Several myocardial infarction/reperfusion studies, demonstrated that MSCs are capable of promoting the survival of threatened cells along the border of the myocardial infarct zone [47,55-57]. Recently, Yagi et al. showed that in endo-toxicemic rats bone marrow MSCs significantly reduced the apoptotic cells of lungs and kidney [58]. Similarly, Mei et al. revealed the capacity of MSCs to prevent apoptotic cell death as well as bacterial burden in the lung and kidneys of mice after cecal ligation and puncture [59].

1.6 Malaria

Plasmodium sp., the causative agent of malaria which invades within the host erythrocytes leads to extreme destruction of red blood cells causes' anaemia. For surviving and replication, malarial parasite suppresses the host immune responses [60]. Earlier it has been demonstrated that malarial parasites induces Treg cells, which inhibit host protective immune responses against malaria [61-63]. In the blood stage, malarial parasites and/or components of parasite from the ruptured erythrocytes activate macrophages to produce the inflammatory cytokines tumor necrosis factor (TNF)- α and interleukin (IL)-1 β [64,65] which are responsible for the pathological symptoms. It has been also established that during malarial infection, host requires both humoral and cell mediated immunity for protection [66]. After activation of PAMP, proinflammatory cytokines are produced. NK cells produce huge amount of IFN- γ acting as a bridge between innate and adaptive immunity [67]. NKT cells migrate to the spleen and induce pathogen specific antibody productions, result splenomegaly [68], indicating resistance to malarial parasite.

Recently it has been reported that accumulation of MSCs (Sca1⁺CD44⁺CD29⁺CD34⁻) to the site of malaria parasite infection is a novel protective immune mechanism employed by the host [13]. MSCs alter host immune responses by producing proinflammatory cytokines which restrict malarial parasitic growth. Furthermore, MSCs also inhibit the accumulation of Treg cells, which are generally induced by malaria parasites as an immune evasion mechanism. Recruitment of MSCs is one of the immune protection mechanisms employed by the host to encounter malaria infection [13]. Another group has identified an atypical myelo-lymphoid progenitor cells derived cell lineage from malaria infected mice which also has been shown to provide protective immunity against malaria [69].

1.7 HIV

Stem cell therapy for treatment of HIV is under intensive investigation in recent times.

Scientists are trying to reconstitute HIV-resistant lymphoid and myeloid systems in experimental mice model to combat HIV infections [66,70]. HIV patients treated with anti-retroviral drugs show some age related problems with complications including cardiovascular, liver, brain and bone diseases [71]. These complications are resulted from both HIV infection and antiretroviral treatment, in addition to aging and immune dysfunction. In such case adipose tissue showed lipodystrophy syndrome with subcutaneous lipoatrophy and visceral fat hypertrophy [72-74]. Bones show loss of minerals, leading to the development of osteopenia and osteoporosis [75]. This increased risk of premature osteoporosis is the result of both combination antiretroviral therapy and HIV infection itself [71,76]. Sandra J. Hernandez-Vallejo et al. have hypothesized that HIV protease inhibitors drug could induce premature aging of osteoblast precursors, human bone marrow mesenchymal stem cells (MSCs), and affect their capacity to differentiate into osteoblasts. They also have evaluated the capacity of HIV protease inhibitors-treated MSCs to differentiate into adipocyte [71] which is similar with the normal aging. Cotter, et al. hypothesized that MSC function can be altered both by exposure to and infection by HIV-1 and the combined effects leading to a changed clonogenic potential and altered cell phenotypes [77]. In *in vivo* system adipogenic potential of MSCs in HIV-1 infection may not lead directly to increased fat mass, but potentially may reduce the availability of osteoblast precursors. Other than this, our group found that infiltration of MSCs in the site of TB-granuloma of HIV-coinfected patients is significantly high (unpublished data).

2. Conclusion

It is highly likely that many infectious agents' use

MSCs as a reservoir during lag period because (1) MSCs are mild phagocytic cells which facilitate entry with ease (2) MSCs don't express MHC class I and thereby avoid killing by cytotoxic T cells; (3) MSCs don't possess phagolysosomal killing machineries; and (4) MSCs expresses abundant drug efflux pump. In fact a recent years study came out suggests that HIV can infect MSCs [77]. Therefore, it is highly anticipated that MSCs play critical role in different types of infections. And by manipulating or targeting MSCs we can develop future therapeutic agent against different infectious agent.

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