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REVIEW

Mesenchymal Stromal Cell Therapy in MDR/XDR Tuberculosis: A Concise Review

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Abstract Multi-drug-resistant (MDR) tuberculosis is a major public health problem worldwide. Drug resistance arises due to non-compliance of antibiotic therapy. Herein, we explored the therapeutic options available ranging from conservative treatment approaches to alternate adjunct therapies such as mesenchymal stromal cell (MSC) therapy interventions. It is attractive to understand the scientific rationale of using cells as drugs, in particular mesenchymal stem/stromal cells. The review dwells and attempts to analyze the mechanistic approaches of the current treatment modalities to modern therapies. MSCs have demonstrated profound capacity to regenerate and repair. They appear to modulate that the activities of dendritic cells regulate T cells, both in vivo and in vitro. While there seems to be some benefit of such therapies, its use warrants further research. The merits and de-merits of autologous therapy/allogeneic therapy are ill understood. The challenges of requirement of large number of cells for infusion, the route of administration, choice of timing are complex issues that need to be addressed. Furthermore, the host immune responses, environmental factors and epigenetic mechanisms compound the problem. Although, clinical studies are being performed using autologous MSCs in different inflammatory models, it is important that such an intervention should be based on sound scientific rationale. The current review examines the immunomodulatory properties of MSCs, its interactions with other cell types, in assessing the basis for autologous/allogeneic cell-based therapies in the treatment of XDR/MDR tuberculosis.

Keywords Mesenchymal stem cell therapy · Immunomodulation · Clinical trials · Adjunct therapy

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Epidemiology

Mycobacterium tuberculosis continues to be one of the leading causes of mortality and morbidity in humans among infectious diseases. In 2013, an estimated nine million people developed tuberculosis (TB) and 1.5 million died from the disease (WHO 2014). One-third of the world population is latently infected with *M. tuberculosis* and 10 % of these may develop the active TB during their lifetime and majority of them remain asymptomatic until host immune responses are active (Lin and Flynn 2010). The current treatment of TB is implemented by DOTS (directly observed treatment, short-course) program, and the therapy consists of multiple antibiotics for an extended period of time depending on the form of the disease. The continuous intake of these drugs may result in the risk of developing drug resistance. TB can be resistant to one or more chemotherapeutic agents. Multidrug-resistant (MDR)-TB is defined as resistance to at least the first-line drugs Isoniazid and Rifampin. Extensively drug-resistant (XDR)-TB is defined as MDR plus resistance to any fluoroquinolone, and at least one of the second line injectable drugs, Capreomycin, Kanamycin or Amikacin. Hence the continued spread of MDR-TB and XDR-TB poses a major threat to global tuberculosis control (Uhlin et al. 2012). In

2013, an estimated 480,000 people worldwide developed MDR-TB. It is estimated that about 9 % of these cases were XDR-TB (WHO 2014). It was also found that the number of cases of MDR-TB is alarmingly increasing worldwide, with MDR detected up to 35 % of newly diagnosed cases and in 76.5 % of patients who had previously been treated for tuberculosis. XDR-TB was identified in 14 % of patients with MDR (Skrahina et al. 2012). Totally or extremely drug-resistant TB, or XDR-TB, refers to strains that are resistant to all the first-line drugs as well as all the second-line TB drugs (Migliori et al. 2007).

Mechanism of Drug Resistance

Drug resistance in *M. tuberculosis* occurs due to genetic factors related to previous anti-TB treatment and other factors. MDR-TB develops when patients suffering from TB fail to comply with their course of drugs. This causes the TB bacteria to develop resistance towards the drugs. The bacterial resistance thus developed impedes the effectiveness of the two potent drugs, i.e., Isoniazid and Rifampicin. However, in MDR-TB, the bacterium develops resistance towards them, making treatment of TB extremely difficult. XDR-TB is a less common form of multidrug-resistant TB in which TB bacteria have changed enough to circumvent the two best antibiotics, i.e., INH (isonicotinylhydrazine) and RIF (rifampicin), as well as the most of the alternative drugs used against MDR-TB. The route and speed of transmission of MDR/XDR-TB and other forms of TB are similar (Salam 2010). Treatment of MDR and XDR tuberculosis has become complex, toxic and expensive. Various factors like, poor treatment outcomes, slow progress in development and evaluation of new tuberculosis drugs and drug regimens for drug-resistant tuberculosis have given rise to the development of several immunotherapies for potential use as adjuncts to conventional treatment. The new approach of using the patient's own bone-marrow stromal cells has found to be safe and could help to overcome the body's excessive inflammatory response, repair and regenerate (Skrahina et al. 2014). Currently, mesenchymal stromal cells (MSCs) are the widely used cell type in cell-based therapy in clinical trials (Rai et al. 2011).

Immunomodulatory Properties of Mesenchymal Stromal/Stem Cells in Chronic Inflammation

MSCs are multi-potent progenitors constituting a small proportion (0.01 %) of the bone marrow and are present in both adult and fetal tissues (Herzog et al. 2003; Prockop et al. 2003), including adipose tissue, umbilical cord blood, and amniotic fluid and fetal lung (Erices et al. 2000; Gronthos et al. 2001; in't Anker et al. 2003a, b). They were first characterized by Friedenstein and colleagues more than 30 years ago, and were described as fibroblast-like cells with the property of adhering to plastic when cultured (Friedenstein et al. 1968; Friedenstein 1976). These cells possess remarkable immunosuppressive properties and can inhibit the proliferation and function of the major immune cell populations, including T cells, B cells and natural killer (NK) cells; modulate the activities of dendritic cells (DCs); and induce regulatory T cells both in vivo and in vitro. These unique properties make MSCs ideal candidates for clinical application as immunosuppressants. The immunomodulatory effect of MSCs is mediated by a non-specific anti-proliferative action of these cells. Growing understanding of their role in the modulation of host immune response has made them an important cell type for regenerative medicine and immunotherapy. Although there are no exclusive markers for MSCs, they are characterized by their ability to differentiate into different kinds of cells mentioned above and by the combined surface expressions of $CD29^{+}CD44^{+}Sca\text{-}1^{+}CD45^{-}CD11b^{-}CD11c^{-}Gr\text{-}1^{-}F4/80^{-}MHC\text{-}II^{-}MHC\text{-}I^{low}$ (Ren et al. 2008, 2010).

MSCs Modulate T Cell Proliferation and Function

Numerous studies have demonstrated that MSCs can suppress the T lymphocyte proliferation induced by alloantigens, mitogens, anti-CD3, anti-CD28 antibodies in in vitro baboons and mice. MSCs have a similar effect on memory and naive T cells (Krampera et al. 2003), as well as $CD4^{+}$ and $CD8^{+}$ T cells (Glennie et al. 2005), of a murine model. MSCs are profoundly influenced by microenvironmental factors and can respond to some inflammatory cytokines such as interleukin (IL)-1β (Groh et al. 2005), IL-17 (Huang et al. 2006) and interferon (IFN)-γ, all capable of significantly affecting their function. Inhibition of T cell proliferation by MSCs appears to be mediated by both cell–cell interaction (Jiang et al. 2005; Sotiropoulou et al. 2006) and release of soluble factors such as IFN-γ and IL-1β (Groh et al. 2005; Krampera et al. 2006). IFN-γ also appears to enhance the immunosuppressive activity of human MSC. The suppression is due to cell cycle arrest at G0/G1 stage of T cells (Glennie et al. 2005). They induce Th2 cells to produce IL-4 and also inhibit the production of IFN-γ, thus creating an anti-inflammatory state.

Some studies have indicated that soluble factors are essential for enhancing the suppressive effect of human MSCs. Transforming growth factor (TGF)-1, hepatocyte growth factor (HGF) (Di Nicola et al. 2002), indoleamine 2,3-dioxygenase (IDO) (Meisel et al. 2004) and

prostaglandin E2 (PGE2) (Aggarwal and Pittenger 2005) represent MSC-derived molecules that are believed to have immunomodulatory activity on T cell responses. Neutralizing antibodies against TGF-β and HGF can restore the MSC-induced suppression of T cell proliferation (Glennie et al. 2005).

Co-culturing T cells with MSCs resulted in elevated levels of PGE2, and treatment with inhibitors of PGE2 production mitigated the MSC-mediated immune modulation (Aggarwal and Pittenger 2005). Chelluri et al. (2010a, b) have demonstrated the TNF-α and IFN-γ levels in the co-culture experiments of MSCs and the T cell subsets of pulmonary tuberculosis were MSC dose-dependent. The production of nitric oxide (NO) by MSCs has also been implicated as a potential mechanism by which MSCs inhibit T cell proliferation (Sato et al. 2007). NO inhibits the proliferation of T cells by suppressing the phosphorylation of signal transducer and activator of transcription-5 (STAT5), a transcription factor crucial for T cell activation and proliferation (Bingisser et al. 1998). The immune responses appear to modulate based on the cell number that interacts with other cell types.

MSCs do not express MHC class II and co-stimulatory molecules such as CD80, CD86 or CD40 (Deans and Moseley 2000), and it is believed that T cell activity may result in anergy, which is reflected as immune tolerance. Le Blanc et al. (2003a) reported that when MSCs are treated with IFN-γ, which is upregulated in inflammation, they express MHC class II. Immunosuppression by human MSCs is not intrinsic, but perhaps, induced by inflammatory cytokines which is chemokine-dependent. It is believed that the mechanisms underlying the suppressive effect of MSCs may differ by species. Ren et al. (2009) demonstrated that mouse MSCs and human MSCs utilize different effector molecules in suppressing immune reactions. The degree of the suppressive effect depends on the concentration of the MSCs.

MSCs Modulate B Cell Proliferation and Function

In humans, MSCs have also been shown to inhibit the proliferation of B cells activated with anti-immunoglobulin antibodies, anti-CD40L antibody and cytokines (IL-2 and IL-4). In addition, the B cell functions of antibody production and secretion of the chemokine receptors CXCR4, CXCR5 and CCR7, which are responsible for chemotaxis to CXCL12 and CXCL13, are impaired by MSCs. However, the expression of B cell co-stimulatory molecules and cytokine production do not get affected by MSCs (Corcione et al. 2006). MSCs inhibit the proliferation of B cells only in the presence of IFN-γ, which probably implies that IFN-γ causes MSCs to produce IDO, which in turn suppresses the proliferation of effector cells through the tryptophan pathway (Glennie et al. 2005). The major mechanism of B cell suppression by MSCs is attributed partly to the physical contact between MSCs and B cells and in part to the soluble factors released by MSCs. This leads to the blocking of B cell proliferation in the G0/G1 phase of the cell cycle with no apoptosis (Augello et al. 2005; Corcione et al. 2006; Glennie et al. 2005), unlike the case with T cells.

MSCs Modulate the Functions of NK Cells

Several studies have shown that MSCs suppress NK cell proliferation and IFN-γ production which is supposedly driven by IL-2 or IL-15 and partially inhibits the proliferation of activated NK cells (Aggarwal and Pittenger 2005; Maccario et al. 2005; Rasmusson et al. 2003; Ryan et al. 2007). Soluble factors such as TGF-β1 and PGE2 are believed to play a role in the MSC-mediated suppression of NK cell proliferation (Friedenstein et al. 1968).

Interaction Between MSCs and DCs

MSCs impair the differentiation of monocytes or $CD34^+$ hematopoietic stem cells into DCs by inhibiting the response of the monocytes to maturation signals, reducing the expression of co-stimulatory molecules and hampering the ability of the former to stimulate naive T cell proliferation and IL-12 secretion (Nauta et al. 2006; Zhang et al. 2004). Ramasamy et al. (2007) reported that the cell cycle in DCs was arrested in the G0/G1 phase upon interaction with MSCs. A recent study reported that MSCs isolated from human adipose tissue were more potent immunomodulators for the differentiation of human DCs than MSCs derived from the bone marrow (Ivanova-Todorova et al. 2009).

Tregs Induced by MSCs

MSCs may also modulate immune responses via the induction of Tregs. MSC can induce the generation of $CD4^+CD25^+$ cells displaying a regulatory phenotype ($FoxP3^+$) in mitogen-stimulated cultures of peripheral blood mononuclear cells (Meisel et al. 2004; Rasmusson et al. 2003). The induction of Tregs by MSCs involves not only direct contact between MSCs and $CD4^+$ cells, but also the secretion of soluble factors such as PGE2 and TGF-β (English et al. 2009).

MSCs and Immunosuppression

MSCs are immuno-suppressive in nature and they exert their effect only when they are stimulated. Unstimulated MSCs are not capable of performing this effect (Shi et al. 2010). MSCs have been shown to prevent rejection of allogenic skin grafts (Xu et al. 2007), graft-versus-host disease (Le Blanc and Ringdén 2006) and, therefore, are helpful in treating auto-immune disorders. They are able to alter function of T cells, B cells, DCs and NK cells as discussed in the above sections (Ren et al. 2010).

Thus, immunosuppression is due to cytokines secreted by MSCs and through direct cell–cell contact. MSCs produce number of cytokines, signaling molecules and growth factors which can suppress inflammatory response and may also lead to trophic effects (Caplan and Dennis 2006; Lin et al. 2011). Their regulatory effect on immune system, such as anti-proliferative (Sudres et al. 2006) and anti-inflammatory roles, makes them an important cell candidate for therapy.

Scientific Basis for the Consideration of MSC Therapy

Mesenchymal stem cells have ability to create a microenvironment which helps in engraftment. They are hypoimmunogenic lacking the HLA class II and costimulatory molecules such as CD40, CD80 and CD86 (Krampera et al. 2003). Low level MHC-I expression can still activate T cells, but they become anergic as there are no secondary signals or co-stimulation (Javazon et al. 2004). Also low level expression of MHC-I prevents these cells from being destroyed by NK cells (Wong 2011). They generally do not express MHC-II molecules on their surface but could be immunogenic in certain circumstances (Le Blanc et al. 2003b; Moretta et al. 2001). Suppression of T and B cell proliferation and their activation makes them a candidate cell in the treatment debilitating chronic inflammatory, autoimmune disorders. These cells have ability to migrate specifically to the site of injury. This has been shown in many of the diseases involving injury of tissues and cartilages (Stagg et al. 2006).

Effector Molecules of MSCs

The molecules that play key role in the immunosuppression is mainly NO, IDO and PGE2 (Krampera et al. 2003). Three NO synthases catalyze the synthesis of NO, leading to immune-suppressive effect. It affects the phenotype of T cells and impairs its proliferation and function affecting T cell receptor mediated signaling (Hoffman et al. 2002). MSCs have been shown to express many chemokine receptors such as CCR1, CCR4, CCR5 and CCR10, in response to many of the cytokines, to move in the desired destination (Von Lüttichau et al. 2005).

Autologous vs Allogeneic MSC Therapy

In the autologous therapy, the host mesenchymal stem cells from different tissue sources are widely explored for the clinical applications. They are primarily for the tissue regeneration. There are various routes of administration that are being attempted, of which infusion is the most common route based on the body mass. This entails the use of large number of cells that get administered. The chief limitation of autologous therapy would be the continuous supply of large number of cells owing to multiple doses and time frame. Several reports have demonstrable efficacy for 6 months. Beyond that, multiple infusions are advised to treat the disease. Many clinical trials using autologous MSCs in Phase I/II have migrated to allogeneic in Phase III/IV. This is made possible owing to hypoimmunogenic nature of MSCs and the safety profile. The other challenges encountered in allogeneic therapy include the xenogenic materials that are used in the propagation of the cells to the desired numbers, lack of uniform protocols for expansion and non-availability of reliable potency assays. There are several other technical challenges attributed to the ex vivo expansion of allogeneic MSCs to the desired numbers for cell transplants. It is dependent on the primary volume of the bone marrow aspirate, amount of primary tissue source. Another school of thought is that MSCs evade host immunity and persist in latent state as $CD271^{+}$ MSC-positive cells. As briefed in the previous sections, MSC interaction with host cells is predominantly based on the premise of immunosuppression. Augmenting the immune suppression may lead to susceptibility of the host to other bacterial infections.

Skrahina et al. (2012) recently have used autologous MSCs of bone marrow in cases of MDR-TB. They have shown that systemic transplantation of the autologous MSCs mitigated the bacterial discharge, and the lung tissue cavities were resolved in TB patients infected with resistant forms of *M. tuberculosis* (Skrahina et al. 2012).

The MSC ability to avoid allogenic rejection has been traced to three main factors, (a) they are hypoimmunogenic by lacking MHC-II (do have MHC-I expression that helps prevent NK cell deletion) and co-stimulator molecule expression including CD40, CD40L, CD80 or CD86, which are necessary for effector T cell induction; (b) the cells prevent T cell response through indirect modulation of antigen-presenting cells such as DCs by directing them into a suppressor or inhibitory state and direct disruption of

NK, $CD4^+$ and $CD8^+$ cell functions. Specifically, MSCs reduce DC secretion of proinflammatory cytokines IFN-γ, IL-12 and TNF-α, while increasing the production of suppressive cytokine IL-10 (Erokhin et al. 2008), (c) they create a suppressive local microenvironment through the creation of bioactive products including prostaglandins, like PGE2 that suppresses B cell activation and induction of regulatory T cells; IL-10, which inhibits T cells; HGF, which has been shown to induce mitogenic and apoptotic activity and has a role in wound repair; as well as by the expression of IDO, which depletes the local milieu of tryptophan which in turn inhibits allogenic T cell responses (Le Blanc and Ringdén 2007; Ryan et al. 2005). This ability of MSCs to create an immune-depleted healing environment has been shown in multiple in vitro studies of co-cultured or mixed lymphocyte reactions by the lack of a T cell response to the co-culturing of cells from two different individuals (Ryan et al. 2005).

TB bacteria can trigger an inflammatory response in immune cells and surrounding lung tissue that can cause immune dysfunction and tissue damage. Bone marrow MSCs are known to migrate to areas of lung injury and inflammation and repair damaged tissue. They also modify the host immune response and could boost the clearance of TB bacteria.

Another study by Erokhin et al. (2008) examined the effect of systemic transplantation of autologous MSC. They studied 27 patients with pulmonary tuberculosis, including 15 patients with multidrug-resistant pulmonary tuberculosis and 12 with extensive drug resistance of *M. tuberculosis*. All the patients were bacteria-discharging persons with disseminated destructive processes in lung tissue; most ($n = 17$) of them had chronic fibrocavernous tuberculosis. In all the patients, previous long specific anti-tuberculous treatment was ineffective or inadequately effective. After systemic MSC transplantation, 16 patients were followed up for 1.5–2 years or more and the remaining 11 patients for at least 6 months. After MSC administration, a positive clinical effect was observed in all 27 cases; bacterial discharge stopped in 20 patients after 3–4 months; resolution of sustained lung tissue cavities further occurred in 11 patients. They have observed that inclusion of transplantation of the autologous MSCs may be a promising procedure for enhancing the efficiency of therapy in patients with resistant forms of pulmonary tuberculosis (Erokhin et al. 2008; Rush 2010).

Furthermore, another study of the Phase 1 clinical trial (Skrahina et al. 2014) tested autologous MSCs as an adjunct treatment to regress the inflammation associated with MDR-TB in the lungs and accelerate clearance of the pathogenic bacteria. Nine patients with MDR-TB were enrolled in a study to evaluate this approach; all received individualized therapy after drug-susceptibility testing, in accordance with World Health Organization standards. The patients were infused with bone marrow-derived MSCs and followed clinically and experimentally for 6 months. Five patients were cured, and four patients showed disease stabilization. The researchers note that the immune response can damage tissues in ways that sequester bacteria from antibiotics. MSCs are non-hematopoietic in bone marrow but repair damage to other tissues, especially in ravaged lungs. Therefore, the goal of deploying a patient's own MSCs was transforming chronic inflammation into productive immune responses (Skrahina et al. 2014).

Disadvantages of the MSC Therapy in TB

The major risks of MSC therapy are that they play a critical role in *M. tuberculosis*-induced immunosuppression but are limited to the infected organs. The findings by Raghuvanshi et al. (2010) suggest that MSCs contribute to the delicate balance within granulomas that contain the pathogenic microorganisms but do not completely eliminate them. This mechanism avoids general immunosuppression and, instead, limits immune suppression to the zone of infection within infected organs (Raghuvanshi et al. 2010).

Conclusion

The current treatment modalities for MDR-TB and XDR-TB are costly and ineffective. Hence it has become essential for studying alternate approaches of effective therapy. The transplantation of autologous MSCs into the course of drug-resistant anti-tuberculous therapy may be one of the competent therapies. In conclusion, the MSCs can be used as potential targets for therapeutic intervention in tuberculosis. More data emanating from the clinical trials are key to look forward to such alternate routes of medical management of the indomitable MDR/XDR-TB.

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Conflict of interest None of the authors of this paper have any conflict of interests.

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