

Stem cell therapy: an adjunct in the treatment of mdr tuberculosis

Abstract

Tuberculosis is a global health issue and a major cause of death worldwide. Emerging infectious disease as multidrug resistance and extensively drug resistance tuberculosis triggers the importance to improve the current therapy or else develop an innovative approach. Currently stem cell transplantation emerged as new therapeutic to overcome tuberculosis. Recent studies provide an opportunity to explore stem cell in treatment of drug resistant tuberculosis. This review is in concern with the regime, future effect and challenges of stem cell therapy in drug resistant patients.

Keywords: stem cell, multidrug-resistant, tuberculosis, transplantation

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Abbreviations: MDR, multidrug-resistant; TB, tuberculosis; XDR, extensively drug-resistant; LTBI, latent tuberculosis infection; WHO, world health organization; TLRs, toll-like receptors; CLRs, c-type lectin receptors; NLRs, nod-like receptors; MSCs, mesenchymal stromal cells; PRRs, pattern recognition receptors

Introduction

Tuberculosis (TB) is one of the most ancient diseases of mankind and has co-evolved with humans for several million years.¹ There are also evidences of the presence of the disease in pre-historic Asia, but it was only towards the end of 19th century that the peaks of incidence were observed in India and China.² Modern approach for diagnosis and treatment of TB is complicated. Specific perceptive of pathogenesis of TB is still unknown.³ Furthermore, HIV co-infection substantially increases the risk of progression from latent TB to active TB and is the leading cause of mortality in HIV infected person in India.^{4,5}

TB is an infectious disease with peculiar clinical and pathological features. It is pulmonary disease and progress to death of host if untreated. Immunity suppresses the causative bacteria and is often asymptomatic. TB is an organized aggregation of macrophages surrounding an area of caseous necrosis, thus avoiding the natural defense system in the patient's serum. The caseating granuloma is pathological feature in the humans. Infection with TB can result in two stages: asymptomatic latent tuberculosis infection (LTBI) or tuberculosis disease. If left untreated, the mortality rate with this disease is over 50%.

M. tuberculosis strains resistant to the two potent anti TB drugs, i.e., Isoniazid and Rifampicin, are termed as multidrug-resistant TB (MDR-TB) strains. Extensively drug-resistant TB (XDR-TB) is a form of TB caused by bacteria that are resistant to Isoniazid and Rifampicin alongwith any fluoroquinolone and any of the second-line anti-TB injectable drugs (amikacin, kanamycin or capreomycin). XDR-TB do not respond to the standard six-month treatment with first-line anti-TB drugs, since the disease requires the use of drugs that are less effective and more toxic, requiring treatment to be administered over longer periods and severely reducing the probability of success. The World Health Organization (WHO) estimates that almost 500,000 cases of MDR-TB emerged in 2006.⁶ Two high burden countries,

China and India have 240,680 cases which together account for 60% of all incident cases of MDR-TB globally. Both MDR-TB and XDR-TB are the emerging threats to anti-TB programs.⁷

In recent years, incomplete regimen and poor compliance with TB therapies resulted difficulties in controlling the emergence and spread of *M. tuberculosis* resistant strains representing a threat for global tuberculosis control. The World Health Organization estimates that in Eastern Europe, Asia and South Africa 450,000 people have MDR-TB, and around half of these will fail to respond to existing treatments. TB is a leading cause of death worldwide, especially in low-income and middle-income countries.⁸ India, estimated to have the highest number of MDR-TB cases among notified TB patient.⁷ TB bacteria trigger an inflammatory response in immune cells and surrounding lung tissue that can cause immune dysfunction and tissue damage.

Developing mechanisms entering human macrophages and innate immune recognition of *mycobacterium tuberculosis*

Tuberculosis has developed numerous mechanisms for entering human macrophages. It was found that macrophage receptors are involved in the uptake of *M. tuberculosis* and enter through a specific receptor-mediated pathway, including bacterial survival, phagosome trafficking, and activation of signal transduction pathways.⁹

Johanneke et al.¹⁰ studied the several classes of pattern recognition receptors (PRRs) involved in the recognition of *M. tuberculosis*, including Toll-like receptors (TLRs), C-type lectin receptors (CLRs) and Nod-like receptors (NLRs). Among TLR family, TLR2, TLR4 and TLR9 and their adaptor molecule MyD88 play most prominent role in the initiation of the immune response against tuberculosis. Moreover to TLRs, other PRRs such as NOD2, Dectin-1, Mannose receptor and DC-SIGN are also involved in the recognition of *M. tuberculosis*. Human epidemiological studies revealed that genetic variation in genes encoding for PRRs and downstream signaling products influence disease susceptibility, severity and outcome. An approach in PRRs combined with immunogenetic studies for recognition of mycobacteria in TB patients will lead to a better perceptive of the

pathogenesis of tuberculosis but also may contribute to the design of novel immunotherapeutic strategies.

Mesenchymal stromal cells (MSCs)

The novel therapeutic option: Stem cell transplantation holds as a promise for the treatment of many infectious and non-infectious diseases. Research advances increased the exploration of stem cell based treatment as an option for drug resistant tuberculosis treatment. Till date only little literature has been published pertaining to the short and long term therapeutic effect of stem cells in patients suffering from drug resistant tuberculosis.¹¹ The purpose of this review is to discuss the functional profile of mesenchymal stromal cells (MSCs) and their potential use for adjunct cellular therapy of multi-drug resistant TB, with the aim of limiting tissue damage, and to convert unproductive inflammatory responses into effective anti-pathogen directed immune responses.

Bone-marrow mesenchymal stromal cells (MSCs) are known to migrate to areas of lung injury and inflammation and repair damaged tissue. They modify the body's immune response and could boost the clearance of TB bacteria. Bone-marrow derived MSCs represent a mixture of different MSC populations and had been shown to be true for MSC from lung tissue.¹² Sabatini et al.¹³ showed that a plastic adherent cell population exists in human lungs isolated via BAL,¹⁴ or via tissue digestion.¹⁵ These cells are either long-lived or not mutually exclusive and have the capacity for renewal. Infact mesenchymal stromal cells support human stem cells in the bone marrow and broncho-alveolar stem cells, thus probability of these functions exist in adult life - and that enrichment of MSCs into damaged lung tissue may support to re-organize tissue and facilitate healing of chronic, unproductive inflammation associated with *M. tuberculosis* infection. MSCs have confirmed capacity to regenerate and repair with ability to change the activities of dendritic cells to regulate T cells, both *in vivo* and *in vitro*. The challenge still persists with merits and demerits of Autologous therapy/allogeneic therapy.

Recently, Skrahin et al.¹⁶ demonstrated Autologous mesenchymal stromal cell infusion as adjunct treatment in patients with multidrug and extensively drug-resistant tuberculosis: an open-label phase 1 safety trial. MSCs as an adjunct therapy are safe and can be further explored for the treatment of patients with MDR or XDR tuberculosis in combination with standard drug regimens. Adjunct treatment with MSCs needs to be evaluated in controlled phase 2 trials to assess effects on immune responses, clinical and microbiological outcomes.

MSCs dampen inflammation through an array of interactions with innate and adaptive immune cells thereby modulating immune responses. MSCs, which constitute ~0.001% of bone marrow mononuclear cells (proportion declines over age), can be easily expanded ex vivo in culture and when re-infused in patients they home to sites of injury and inflammation promoting tissue repair. The culture conditions, degree of expansion and the final MSCs preparations, may vary influencing clinical outcome.¹⁷

Kaufmann et al.¹⁸ studied adjuvant Autologous MSC therapy in South African patients with MDR/XDR-TB is establishing the safety in patients with MDR/XDR TB in Durban, King Dinuzulu Hospital Complex and is investigating immunological mechanisms of anti-TB responses and markers of a response to therapy. Specific efforts have been made to study responses to MSC treatment defined by HR-CT

imaging as well as to assess the best incremental value of this adjuvant therapy in the subset of patients who would benefit from this mode of cellular therapy, compared to other possible immune-interventions targeting the host immune response.¹⁸

Studies had been attempted to define the mycobacterial antigens using immunological techniques. An antigen, 65-kilodalton (kDa) protein, is present in a wide range of mycobacterial species and designated as 65K antigen or the cell wall protein a (CWP-a) antigen appears to co-purify with cell walls. It is one of the major immunoreactive proteins of the mycobacteria which contains epitopes that are unique to a given mycobacterial species can be blocked through stem cell activation to overcome tuberculosis.¹⁹

Joshi et al.²⁰ explored the therapeutic options available ranging from conservative treatment approaches to alternate adjunct therapies such as mesenchymal stromal cell (MSC) therapy interventions. TB drug resistance arises due to non-compliance of antibiotic therapy. They described the use of cells as drugs, in particular mesenchymal stem/stromal cells. 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 on scientific basis. The review examined 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.²⁰

Recently, Zumla et al.²¹ described treatment of multidrug-resistant tuberculosis (MDR-TB) as extremely challenging due to the virulence of the etiologic strains of *M. tb*, the aberrant host immune responses and the diminishing treatment options with TB drugs. New treatment regimens incorporating therapeutics targeting both *M. tb* and host factors are urgently needed to improve the clinical management outcomes of MDR-TB. Thus, new approach of Host-directed therapies (HDT) could avert destructive tuberculous lung pathology, facilitate eradication of TB, improve survival and prevent long-term functional disability.²¹

Conclusion

To overcome TB is a major priority worldwide. The role of stem cell therapy as MSCs have better prospect in tackling of infectious diseases with a focus on TB. Stem cell therapy can act as a potential novel therapeutic alternative for treatment of drug-resistance. MSCs can restore lung epithelium as it is a population of tissue-resident non-hematopoietic adult progenitor cells which resides in injured tissues and increases the proliferative potential of broncho-alveolar stem cells. MSCs are immuno-modulatory and anti-inflammatory mediated via cell-cell contacts in addition to soluble factors. Perhaps, cellular therapy suggests an alternate therapy options for drug-resistant TB patients. A promising development of adjunct host-directed therapies is projected to target pulmonary TB where inflammatory processes can be overcome immune exhaustion. Thus, stem cell approach is likely to shorten the extent of Anti-TB therapy with increase in clinically relevant anti-*M. Tuberculosis* directed immune responses.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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