Review article

Tuberculosis treatment --new approach to an old problem

Lakshmi Kiran Chelluri[1], Prasad C E[2], Murthy K J R[3], Ratnakar K S[4]

[1] *Transplant Biology & Stem Cell, Global Hospitals, Lakdi-ka-Pool, Hyderabad* - 500004, *India*
[2] *A. P. Chest Hospital, Irrumnuma, Hyderabad* - 500036, *India*
[3] *Bhagwan Mahavir Hospital & Research Centre, Masab Tank, Hyderabad* - 500004, *India*
[4] *Global Medical Education & Research Centre, Global Hospitals, Lakdi-ka-Pool, Hyderabad* - 500004, *India*

Abstract

Chronic mycobacterium infections are major causes of disease burden of 20% in a tropical country like India. The inflammatory cascade following these bacterial infections often leads to tissue damage and perpetuates necrosis, fibrosis and the disease process. Pulmonary tuberculosis, multi-drug resistant tuberculosis not only affects individuals but society at large. Current remedial measures using various technology platforms singularly did not produce effective and appreciable reduction in global disease burden. On the contrary, the conventional chemotherapeutic chemical moieties have demonstrated variable pharmacogenomic expression, increased drug resistance, non compliance of strict prolonged drug regimens with debilitating side effects and contraindications. Furthermore, secreted inflammatory cytokines results in chronic infection, immune deviation, and immunopathology in the lungs. Hence, identification of immune escape mechanisms leading to chronic mycobacterial infections is crucial for development of new treatments. The review would dwell into the basic pathogenic mechanism and the newer approaches that may need to be considered for developing novel therapeutic strategies.

Keywords: Tuberculosis; Multi-drug resistant tuberculosis; Treatment

INTRODUCTION

Tuberculosis (TB) and multi-drug resistant tuberculosis (M. tuberculosis) with ever increasing disease burden worldwide and in particular third world countries, is setting tone for the epidemic outburst. India constitutes 20% of the global Tb prevalence, which is the highest as per 2006 revised national TB control programme (RNTCP), Indian statistics[1]. Various treatment strategies are being pursued to combat this dreaded ailment. Some of the treatment strategies include directly observed treatment short-course (DOTS), DOTS-Plus, recombinant human-interleukin2 (rhu-IL2) by aerosol treatment, recombinant interferon-gamma, improvised bacille Calmette-Guérin (BCG) etc., with various degree of success[2]. It is a proven fact that the host immune profile plays a vital role in the disease susceptibility. Numerous studies have documented the role of inflammatory cytokines in the depressed immune profile of the host. With many theories, there exists the ongoing debate whether there is any implication of associated Th phenotype in triggering the innate host immune profile to external stimuli. The controversy still persists as far as the immunologists are concerned and the clinical implication of the modern therapy, often leading to skepticism amongst clinical scientists. The ability of mesenchymal stem cells (MSCs) to regulate the immune system, coupled with their capacity for tissue regeneration, opens ex-

Correspondence to: Lakshmi Kiran Chelluri, Ph. D, Head, Transplant Biology & Stem Cell, Global Hospitals, Lakdi-ka-Pool, Hyderabad - 500 004, India.
E-mail: apparusu@ hotmail. com; lkiran@ globalhospital. net.
Tel: +91-40-30244501 Fax: +91-40-23244455

citing possibilities for treating both the underlying cause of immune-mediated diseases and correcting damage resulting from these diseases. Despite all the controversies and progress, newer treatment modalities with proven efficacies would be a welcome change to alleviate the disease burden. Reports from various studies concur on singular point that the overall immune response to mycobacterial antigens decreases in TB, and the inflammatory cytokines play a major role in perpetuating pulmonary tissue damage[3].

Mesenchymal Stem cell therapy

The first use of employing one's own tissues for treatment was introduced by Paul Niehans in treating woman whose parathyroid glands had failed after an unsuccessful operation in 1931[4]. One´s own immune responses to variety of pathogens has been attributed to primary cause i. e., bacterium, followed by host genetic susceptibility, environmental factors[5]. All of these or individual reasons have enormous implications on the primary targets such as mucosal layer, epithelial layer leading to tissue damage, fibrosis and necrosis with permanent scar formation[6]. The structural deformity compounds the functional integrity thereby necessitating the repair process. There is a considerable amount of debate of new treatment modalities. Currently, the use of autologous adult stem cells for cell therapy definitely seems promising owing to distinctive advantages over conventional therapies[7]. Of particular interest are the mesenchymal stem cells. They have already been successfully employed in the tissue regeneration of the affected organs such as myocardium, spine, and neurodegenerative disorders[8]. The most important use is its immunomodulatory property. This has been widely explored and ill understood. The cell-cell interactions of various genre demonstrated some beneficial role in restoring functional integrity by way of releasing tropic, stimulatory factors constitutively to become more tolerant/stimulate the immune responses favorable to host resistance & down regulate host susceptibility. Mesenchymal stem cells constitutively express soluble immunomodulatory factors such as macrophage stimulating factor, prostaglandinE2 (PGE2), hepatocyte growth factor (HGF) along with IL-10. IL-10 is a dichotomous functional cytokine with immunosuppressive/immunostimulatory properties[9].

Th1/The paradigm in TB infection

Various reports concur that there exists depressed immune responses of host to the invading pathogen such as Mycobacterium tuberculosis. Protective immunity is associated with Th1 cytokine mediated macrophage activation and granuloma formation but a superimposed Th2 response elicits tissue destroying delayed hypersensitivity reactions[10]. This crucial difference in immune reactivity is related to the cytokine regulated effect of tumor necrosis factor alpha (TNF-alpha) on the tissues at the site of the lesions. If granulomas can provide protection to host, the other side of the coin could be that they have the potential for pathological damage through caseous necrosis and fibrosis. Erosion by the granuloma into the airways provides the route of transmission for M. tuberculosis and maintenance of TB infection within the population[11]. Either ways, tissue regeneration through immune function modulation secreted by mesenchymal stem cells is warranted in order to develop intact airway epithelium and improve the quality of life. Th1 and Th2 paradigm is still elusive as the stage of infection plays a crucial role in the alteration/balance of Th1 and Th2 phenotype[12]. Th1/Th2 counterregulation is important for the prevention of infection-associated immunopathology The complex interplay of the various pro-inflammatory (IL-10 in particular) holds the key in skewing the host immune responses to Th2[13]. The current understanding puts dendritic cells (DCs) ahead of T cells in defining the ultimate Th phenotype. It is therefore to be seen if there are alternate mechanisms to switch the phenotype of DC to Th1 type of response in Tb infection.

Proposed mechanism of action

Current reports have shown that tissue specific mesenchymal cells can modify dendritic cell function demonstrated by an altered capacity to interact with T cells and induce tolerance or T cell unresponsiveness[14]. Mycobacteria may use this as a subversion strategy that includes promoting immune deviation

towards less effective T cell responses. There is a need to understand the underlying mechanisms of host responses and it's influence on DC activation to mycobacteria and the following differentiation of effector T cell functions. This will serve as a base for the design of new therapeutical interventions and vaccines to combat mycobacterial infections such as Pulmonary TB[15]. Also, the constitutive secretion of soluble immunomodulators by MSC's is an added advantage to counter single cytokine strategies for therapy such as anti-TNF-alpha, rhu IL-2, Interferon-gammal (IFN-gamma) etc. They address the local inflammatory milieu in totality countering the anti-inflammatory cytokine secretions to balance the Th1/Th2 responses.

Hypothesis

It is therefore hypothesized that mesenchymal stem cell released IL-10 along with macrophage stimulatory factors, PGE2, HGF would antagonize the IL-12, TNF-alpha secretions by M. Tb and may modify the DC function to become more tolerant/stimulate the immune responses favourable to host resistance and downregulate host susceptibility. It is expected that the macrophage stimulating factor produced by mesenchymal stem cells would either increase the healthy macrophages or enhance the property of phagocytosis by the activated macrophage in the infection stage itself rather than progressing towards inflammation and subsequent tissue damage. Further, the process may help develop the tolerant phenotype. The outcome of such studies would open a new window in the treatment protocols and wider clinical implications i. e., autologous cell based therapy to skew immune compromised state to immune competent state as an adjunct to the existing chemotherapy. In vitro model needs to be developed to evaluate the Th paradigm of TB and to see if there is any discernable differential Th changes prior to the chemotherapy and subsequently follow up studies at 2months, 4 months and completion of the treatment with MSCs as immunomodulators. The MSC-T cell, MSC-DC1 & DC2 interactions would help us understand the T cell mediated pathways in mycobacterium infection.

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