7. Summary

*M. tb* with its unique lipid rich cell wall, a generation time of close to 18-54 hours (Gill, Harek et al. 2009), an arsenal of almost 4000 genes and its ability to spread through aerosol infection represents a unequaled pathogen. *M. tb* infection can generate a strong host immune response which can contain it but cannot consume it. *M. tb* therefore exist in a perfect equilibrium with its host resulting in a latent infection and represent the pinnacle of evolution of host pathogen interaction. What makes it a successful pathogen remains to be understood. Resistance of these organisms to drugs has emerged as an important health concern. Alternate approaches to the prevention and treatment of tuberculosis are therefore urgently needed.

In humans granulomas are pathological hallmark of tuberculosis where T cells, B cells, macrophages and fibroblast aggregate to form the granuloma. Macrophages harboring the pathogen are surrounded by the lymphocytes. Within the granuloma, T lymphocytes secrete cytokines such as IFN-γ, which activates the macrophages to destroy the bacteria with which they are infected (Kaufmann et al. 2002). Perforin and granulysin secreted by cytotoxic T cells can directly kill infected cells (Houben, Nguyen et al. 2006). Despite the generation of robust host immune responses, *M. tb* 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.

On the other hand it is well supported that MSCs can modulate many T cell function including cell activation (Bartholomew, Sturgeon et al. 2002; Di Nicola, Carlo-Stella et al. 2002) which appears to be independent of MHC matching between MSCs and T cells. MSCs can also produce a variety of growth factors, cytokines, chemokines and proteases that are likely to play a role either in their immunomodulatory or in its migratory function (Kim, Yoo et al. 2005; Lee, Seo et al. 2006). The immunomodulatory properties of MSCs impair the maturation and function of dendritic cells. It has also been well documented that hMSCs inhibit *in vitro* human B cell proliferation, differentiation and chemotaxis (Aggarwal and Pittenger et al. 2005; Beyth, Borosky et al. 2005; Jiang, Ma et al. 2005; Corcione, Benvenuto et al. 2002).

Keeping these observations in perspective we went on to explore the role of MSCs in persistence of *M. tb* during disease progression. Here we demonstrate that *M. tb* suppresses T lymphocyte responses by recruiting MSCs to the site of infection. We found that large number of MSCs infiltrate to the site of tuberculosis infection and position themselves between the harbored pathogens and effector T cells that
target the pathogens. We have shown that MSCs induce strikingly suppressive effect on T cell proliferation with the help of effector molecule like Nitric oxide (Huang, Pan et al.), Indolamine 2, 3-dioxygenases (IDO), Transforming growth factor-β1 (TGF-β1), Hepatocyte growth factor, IL-10 etc. Hence MSCS suppresses cellular immune responses, which contributes to the establishment of persistent M. tb infection. Our finding suggest that the harbored pathogen recruits MSCs to aid in its persistence in the host beside robust immune response. These findings also identify MSCs as potential targets that can be instrumental in therapeutic intervention in tuberculosis.