RATIONALE OF STUDY
3. Rationale of study

A central problem in tuberculosis research is to explain why host immunity to \textit{M. tb} is unable to resolve infection and thereby stop the development of disease (Flynn and Chan 2001; Cooper and Khader 2008). In \textit{M. tb} infection cell-mediated immunity play a vital role. Initial wave of protective immunity involves the generation of (Th1) CD4$^+$ T cell which secrete interleukin 2 (IL-2) and gamma interferon (IFN-\(\gamma\)) (Falcone, Bassey et al. 1994; Thoma-Uszynski, Stenger et al. 2001; Kaushal, Schroeder et al. 2002). Protection offered by CD4$^+$ Th1 cells is almost entirely based on their ability to secrete IFN-\(\gamma\) and other Th1 cytokines and thus activate macrophages. IFN-\(\gamma\) may also be produced by CD8$^+$ cytotoxic T-cells. Hence presence of T cell in optimum number is crucial since they produce certain cytokines like IFN-\(\gamma\) that are essential to raise anti mycobacterial immune response.

Nitric oxide (Huang, Pan et al. 2006) is a potent soluble factor for T-cell suppression because it is known to inhibit T-cell proliferation (Albina, Abate et al. 1991; Lejeune, Lagadec et al. 1994; Young, Wright et al. 1996; Bingisser, Tilbrook et al. 1998; Bobe, Benihoud et al. 1999; Medot-Pirenne, Heilman et al. 1999; Angulo, de las Heras et al. 2000; Mazzoni, Bronte et al. 2002). Recently, it is illustrated that \textit{M. tb} infected iNOS knockout mouse strain (iNOS) exhibit significantly higher risk of dissemination and mortality compared with the wild type C57BL/6 mice demonstrating the protective role of NO in murine TB (Adams, Dinauer et al. 1997). Moreover, NO produced by mononuclear phagocyte has been reported to play an essential role in the killing of \textit{M. tb} in the murine model of TB, (Chan, Xing et al. 1992; Chan, Tanaka et al. 1995; MacMicking, North et al. 1997). It is well accepted that along with macrophages, MSCs produce substantial amount of nitric oxide. And above all, it is well documented that MSCs inhibit T cells by producing nitric oxide, helping the parasite.

Taking all the above facts into consideration i.e., lack of optimum number of antigen specific T cells, hike in nitric oxide production in diseased state of the host and nitric oxide mediated T cell suppression by MSCs lead us to think if at all they play any role in host immune response evasion of \textit{M. tb}. We further wanted to investigate how \textit{M. tb} is able to persist in the host even after a strong check by host immunity and whether there is any significant role played by MSCs in evasion of bacteria from host immune system. We even wanted to know if the coexistence of \textit{M. tb} along with the host is due to its ability to recruit certain inhibitory components of immune system which in turn facilitate pathogen survival within the host. Reduction in the number of \textit{M. tb}-specific T cells produced during course of infection may be one of the vital reasons for the persistence of the pathogen. It is yet not known whether failure to resolve infection is the result of the generation of too few \textit{M. tb}-specific Th1 cells which might be downregulated.
by certain soluble factors. One of the potent soluble factors could be nitric oxide which is also produced by MSCs only when it get two simultaneous signals, one from the pathogen as PAMP (Pathogen Associated Molecular Patterns) and other from T cell i.e., IFN-γ that inhibit T cell proliferation.

In mice, these anomalies might be correlated with a population of cells in the spleen that are capable of nonspecifically suppressing T cells proliferation. These cells have been poorly investigated and might be characterized as a heterogeneous population of cells that may belong to the monocyte/macrophage lineage. Many reports (Di Nicola, Carlo-Stella et al. 2002; Djouad, Plence et al. 2003; Krampera, Glennie et al. 2003; Tse, Pendleton et al. 2003; Maitra, Szekely et al. 2004; Meisel, Zibert et al. 2004; Aggarwal and Pittenger 2005; Beyth, Borovsky et al. 2005; Glennie, Soeiro et al. 2005; Groh, Maitra et al. 2005) have shown that MSCs suppress T-cell proliferation. Significant amount of nitric oxide is also produced by MSCs only when in direct interaction with T-cells, accompanied by a strong suppression of T-cell proliferation (Sato, Ozaki et al. 2007). MSCs from iNOS-/− mice were less effective than MSCs from wild-type mice at suppressing T-cell proliferation, suggesting that nitric oxide produced by MSCs is a major mediator of this (Sato, Ozaki et al. 2007).

In view of the above facts, it was of interest to monitor the role of MSCs during the tuberculosis progression. We tried to find the molecular components of _M. tb_ host interaction, dictating the strength and duration of its effect on the pathogen and other components of cellular immunity. We wanted to monitor their location within the infected organs and time dependent equilibrium shift of its effector functions in infected host.

Here we demonstrate that _M. tb_ suppresses T lymphocyte responses by recruiting MSCs to the site of infection. We found, in both mice and humans, that MSCs infiltrated tissues containing _M. tb_ and T lymphocytes. Studies in mice further demonstrated that MSCs suppressed T cell responses by producing nitric oxide. Our findings reveal a key role of MSCs in the capacity of _M. tb_ to evade host immune responses and identify these cells as new targets for therapeutic intervention in tuberculosis.