1.1 Introduction

All infections are the result of a pathogen’s ability to circumvent, overcome, or even exploit innate immune defenses, therefore, chronic infections pose additional challenge because of their ability to evade or exploit adaptive immune responses. *Mycobacterium tuberculosis* (*M.tb*), which infects, on an average of one of three individuals in the human population, is an outstanding example of a pathogen that successfully evades adaptive immune responses. The past two decades have yielded considerable insight into the pathogenesis of tuberculosis (TB), the mechanisms of protective immunity and the ways by which *M. tuberculosis* induces innate and adaptive immune responses and evades elimination by them. In addition, recent studies have provided substantial knowledge of regulation of adaptive immunity in TB, including context and mechanisms in which immune responses contribute to tissue injury, morbidity, and even transmission of bacteria to new hosts (O’Garra et al 2013, Phillips and Ernst 2012). Although host defense mechanisms against mycobacterium, on the whole, are poorly understood, cytokines have been firmly established to have a major role in determining the outcome of infection with these important intracellular pathogens. The critical evidences are derived from studies in experimental models as well as observations on patients with genetic or drug-induced deficiencies in cytokines or their signaling pathways, particularly, tumor necrosis factor (TNF) and interferon (IFN)-γ signaling, where host resistance to *Mycobacterium tuberculosis* is well documented. Cytokines have an important role in the adaptive immune response as both effectors and regulators of mycobacterial immunity. Their expression profile in CD4⁺T cells clearly delineates the dominant Th1-like response that is associated with the control of infection.

A number of animal models have been tested for their ability to study the immune responses to *Mycobacterium tuberculosis* infection and its pathogenesis. The most popular model is the inbred mouse, which has provided large amount of information related to pathogenicity and mechanisms of immunity that are
subsequently shown to be operative in humans also. The pathogenesis of tuberculosis is the product of the interaction between bacterial virulence and host resistance, which are two distinct and independent variables. The availability of targeted gene disrupted mice has provided a powerful tool to decipher the importance of key molecules in the host response. In recent years, plethora of work has been done in several laboratories in the mouse model and has firmly established the importance of the Th1 pathway in the expression of protective immunity against *M. tuberculosis* (Nunes-Alves et al 2014). Following activation of macrophages by T cell cytokines, the mouse model has been used to demonstrate changes in the intracellular environment as well as production of antimicrobial molecules, notably nitric oxide. A diverse T cell response allows the host to recognize a wider range of mycobacterial antigens presented by different families of antigen-presenting molecules and, thus, greater ability to detect the pathogen. Macrophages are key antigen presenting cells for T cells, and *M. tuberculosis* survives and persists in this central immune cell. This may likely be an important factor in generating the T cell diversity. The effect or mechanisms used by T cells to control *M. tuberculosis* are still not fully understood. Several cytokines, like TNF-α, IFN-γ, IL-10, IL-12, IL-18 etc., are known to play distinct role in mounting the appropriate immune response against the pathogen.

Among these cytokines, Interferon -gamma (IFN-γ) is believed to play a key role. IFN-γ is an effective inducer of antimicrobial mechanisms and inhibits the growth of mycobacterium *in-vitro* and *in-vivo*. It is well established that development of IFN-γ dominant host response is an essential pre-requisite for the containment of *M. tuberculosis* infection. The importance of IFN-γ biased immune response in TB is evidenced from several reports/investigations (Cooper et al 1993; Flynn et al 1993). Mutations in genes encoding IFN-γ and its receptor confer susceptibility to development of severe mycobacterial infection. Signaling defects of IFN-γ pathway also impairs host immune response to *M. tuberculosis* and their subsequent clearance.

The improved comprehension of the role of the innate response in inducing, maintaining, and regulating the acquired response suggests that modulation of innate arm of the immune system could aid in the control of *M.tb* disease. In addition to this, there is a dynamic crosstalk between host and pathogens. In response to *M.tb*
infection, there occurs dramatic change in gene expression program in the host tissues. Therefore, a comprehensive understanding on the host factors involved in acquired or innate immune response to \textit{M.tb} is essential. In a pursuit to understand mechanism of adaptive immunity in tuberculosis, we studied the role of one such host protein SMAR1, which was identified from mouse double positive thymocytes, as nuclear matrix associated protein that interacts with \textit{cis} regulatory matrix attachment regions (MARs) present in the genome. SMAR1 functions as negative regulator of T cell receptor beta (TCR\textgreek{B}) locus; it represses transcription from E\textbeta enhancer and regulates V(D)J recombination process, critical for T cell diversity and response. Transgenic mice constitutively expressing SMAR1 in tissue independent manner exhibit perturbed immune response with splenomegaly and lymphadenopathy.

Given the phenotype of transgenic mice, observed in the previous studies (Kaul-Ghanekar et al 2005), here we demonstrate the response of SMAR1 transgenic mice from two different genetic backgrounds (BALB/c and C57BL/6) to \textit{M. tuberculosis} infection \textit{in-vivo}. We further extended our studies in human macrophages, where we performed gene expression studies after \textit{M.tb} infection, and found that SMAR1 expression is highly reduced upon infection. This observation is also reproducible in TB patients. Further, we also highlight the potential role of nuclear matrix associated chromatin remodeling protein SMAR1 in regulating immune responses upon infection.

\subsection*{1.2 Objectives of the thesis}

The present thesis was designed to understand the host and pathogen interactions during \textit{M.tb} infection. To achieve this aim, following objectives were put forth to investigate, in detail, using a mice model for tuberculosis:

1. To study the modulation of Th1 type of immune response during \textit{Mycobacterium tuberculosis} infection using SMAR1 transgenic mice as model.
2. To study the regulation of Interferon-\textgreek{Y} gene by SMAR1.
3. To study the role of \textit{M. tuberculosis} secretory antigen ESAT-6 in modulating the host immune response.