

## **TNF and Tuberculosis**

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*Mycobacterium tuberculosis*, responsible for 2 million deaths per year, can cause both primary disease and latent infections in humans. The factors responsible for control of *M. tuberculosis* include T cells, macrophages, and cytokines such as IFN- $\gamma$  and TNF. Formation of a granuloma, which consists of a spherical collection of macrophages and lymphocytes, is essential to the process of controlling infection and is a hallmark of tuberculosis. However, the mechanisms of granuloma formation and maintenance is not well understood. TNF is a major contributor to granuloma formation, in that mice deficient in TNF or TNF receptor 1 cannot form granulomas and do not control infection. Neutralization of TNF during chronic infection in mice leads to loss of granuloma structure and the mice succumb to the infection. The use of TNF inhibitors in humans with chronic inflammatory diseases has revealed an important role for TNF in control of latent *M. tuberculosis* infection. We are investigating the mechanisms by which TNF is important in granuloma formation and control of infection. TNF is induced by macrophages upon *M. tuberculosis* infection, and this is responsible in part for the strong induction of CXCR3- and CCR5-binding chemokines in vitro and in vivo. These chemokines may be important in the migration of cells within the lungs to form the granuloma. We have also used the murine and non-human primate models of TB to investigate the mechanisms by which the different TNF inhibitors used in humans have different effects on susceptibility to tuberculosis. These tools provide an opportunity to understand better the mechanisms by which TNF orchestrates the granulomatous response and controls infection.

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