Title:

Neutrophils in Pulmonary Tuberculosis

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Abstract:

Tuberculosis (TB), due to Mycobacterium tuberculosis (M.tb) remains a substantial global health problem. TB kills 1-2 million people each year and is newly diagnosed in 8-9 million more patients. Severe immune deficiencies (genetic or acquired) are known risk factors for TB. However, most TB (80%) occurs in patients that are immunologically responsive to M.tb antigens and disease manifests specifically in the lungs. This discrepancy in patient profiles indicates that we do not know how disease develops in most TB patients. It is important to understand because these patients are sick and are contagious to others. Growing evidence shows that lung-damaging inflammation is associated with neutrophils and may contribute to pulmonary TB. However, discovering roles for neutrophils in TB has been hampered by two limitations. First, there have been technical challenges in generating sufficient numbers of unactivated neutrophils for in vitro and in vivo testing. Second, there may be a disconnect between the clinical situation and the experimental models: Human studies typically focus on sick patients with active TB while experimental studies typically focus on neutrophils prior to or during early M.tb infection when mice are not sick, or use immune deficient hosts, or derive data from gene association studies. Here, we show that the mouse experimental TB disease model can recapitulate features of pulmonary TB in humans, and that neutrophils are specifically associated with disease in mice. We can now produce ex vivo normal neutrophils that will be used in future studies to understand the mechanisms by which neutrophils alter immunity, or contribute to lung damage.