Of Cavities and Catching Mycobacteria – Neutrophils as a Double-Edged Sword in Human TB

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Abstract
Tuberculosis (TB), a chronic infectious disease of global importance, is facing the emergence of drug-resistant strains with a paucity of new drugs to treat the infection. Pulmonary cavitation, the hallmark of established disease, is characterized by high bacillary burden. Cavitation is associated with delayed sputum culture conversion, emergence of drug resistance, and transmission of infection. The host immunological reaction to *M. tuberculosis* (*M.tb*) drives the development of pulmonary cavities. TB is characterized by a matrix degrading phenotype in which the activity of proteolytic Matrix Metalloproteinases (MMPs) are unopposed by their specific tissue inhibitors. The role of the neutrophil in TB will be explored and there are evidence that neutrophils play both a protective role as well as in host tissue destruction. Neutrophils secrete MMPs that drive tissue destruction in human TB. Neutrophil MMP concentrations are elevated in human TB and closely associate with clinical and radiological markers of tissue destruction and cavitation. Neutrophils line the circumference of human TB cavities. Neutrophil MMPs are tightly regulated by complex signalling paths. Neutrophil extracellular traps are produced when neutrophils are infected with *M.tb* and neutrophils phagocytose *M.tb* as part of the host defence. Consequently, immunomodulatory therapies in preclinical and clinical trials may be useful adjuncts in treating TB. Strategies targeting the neutrophil and MMPs have the potential to improve cure rates, reduce decrease transmission and decrease morbidity and mortality.

Selected Publications