MOI Project 15

The influence of immunopathology in human tuberculosis on immune cell functions and clinical immunological tests

(Supervising Investigator: Marc Jacobsen, Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie Universitätsklinikum Düsseldorf)

Immunological tests are of central importance in the diagnosis of tuberculosis. *Mycobacterium (M.) tuberculosis* sensitized T cells are detected *in vitro* due to secretion of the key cytokine, interferon (IFN)-γ, and this forms the basis for detection of *M. tuberculosis* infection. Previous studies have shown that the T-cell response is impaired in patients with acute tuberculosis, resulting in a decreased response to the mitogen, phytohemagglutinin (PHA). PHA serves as a 'positive control' of so-called IFN-γ release assays (IGRA), which frequently leads to false negative or unusable test results in patients with acute tuberculosis. The aims of this study are to investigate the underlying mechanisms of impaired T-cell response, to explore the possibilities of using alternative T-cell stimulants, as well as alternative cytokines, and to characterize the influence of plasma on the immune cell response in patients with acute tuberculosis. Part of this study will be performed in collaboration with partners at the Kumasi Center for Collaborative Research in Tropical Medicine (KCCR) in Kumasi/Ghana. Patients with presumptive pulmonary tuberculosis (n=800) and healthy contacts (n=100) will be recruited in a DFG-funded study in Kumasi/Ghana. For the sub-study planned here, the following groups [patients with confirmed pulmonary tuberculosis (n=30) and healthy contacts (n=30)] will be selected. To study the decreased PHA immune response, various T-cell activating agents will be used and tested *in vitro* on whole blood, as well as isolated immune cells from tuberculosis patients and controls. Selected candidate cytokines will be determined simultaneously in the supernatant after overnight stimulation by Cytometric Bead Assay. Functional implications of altered cytokine expression will be tested using an *in vitro* mycobacterial infection assay as well as by modulating expression key cytokines using lentiviral transduction of primary T cells. Furthermore, the role of the aberrant plasma milieu during acute tuberculosis in the induction of impaired T-cell functions will be tested. This study will provide insights into the nature of T-cell modulation by the plasma milieu in tuberculosis and a possible impact on T cell-mediated protection against the disease.