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Epidemiology, diagnosis and treatment of tuberculosis

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Tuberculosis (TB) remains a major cause of morbidity and mortality and represents the most frequent cause of death by a single infectious agent worldwide[1]. While the incidence of TB is slowly decreasing in Europe due to active case finding and targeted therapies, the emergence of multi-drug-resistant and extensive-drug resistant strains of *Mycobacterium tuberculosis* (Mtb) are a great concern for the control of tuberculosis worldwide[2-5].

In approximately 90% of individuals infected with Mtb, a successful T cell-mediated immune response is established, effectively arresting Mtb growth within granulomas[6]. *M. tuberculosis* can survive for a lifetime inside such granulomas (latent tuberculosis infection: LTBI) but may escape from the host's immune response, if granulomas break down[6,7].

The clinical diagnosis of LTBI relies on immunological methods which show that the T cell arm of adaptive immunity has developed a memory of a previous contact with mycobacterial antigens. For the past 100 years the induration that occurs following the intracutaneous injection of purified protein derivate (PPD) in the tuberculin skin test (TST), developed by Felix Mendel and Charles Mantoux, has been used as a marker for an immunological memory towards Mtb antigens. However, the positive predictive value of the TST in the diagnosis of tuberculosis or LTBI depends on the sensitivity and the specificity of the test as well as on the prevalence of the infection in the population tested.

The specificity of the TST is decreased by cross-reactions with non-tuberculous mycobacteria, common in developing countries, and previous BCG vaccination, common in developing countries and parts of Europe. The sensitivity of the test is reduced by wrong (e.g. subdermal) application and false measuring of the skin induration. Most importantly, however, false negative responses in persons with immunosuppression are frequent. Recently, a new generation of tests that measure the interferon-γ release by MTB-specific T cells in the blood has been developed as an ELISPOT- (T-SPOT.*TB*; Oxford Immunotec, Abingdon, UK) and ELISA (QuantiFERON-TB Gold in tube; Cellestis, Carnegie, Australia). These T cell interferon-γ release assays (TIGRAs) measure T cell responses against Mtb-specific antigens which are not part of PPD (for reviews see[8,9]). The antigens used in the tests are the early secretory antigenic target-6 (ESAT-6) and the cultured-filtrate-protein-10 (CFP-10) which are encoded in the RD-1 region of Mtb, *M. bovis* (but not the BCG vaccine strains derived from *M. bovis*), *M. szulgai*, *M. kansasii* and *M. marinum*. There are some cross-reactions with proteins from *M. leprae*. For the diagnosis of LTBI in contact tracing both tests perform irrespectively of prior BCG vaccination and test results show a better

correlation with the exposure to the index case than the TST[10,11]. Both tests are more specific than the TST. In a recent subanalysis of patients with immunosuppression, the sensitivity for the diagnosis of active tuberculosis was 34.5% with the TST, 62.1% with the ELISA , but 96.6 % with the ELISPOT[12].

When antigen-specific T cells are stimulated, they clonally expand and are recruited to the site of infection from the blood and lymphatic organs. TIGRAs are routinely performed on whole blood (ELISA) or peripheral blood mononuclear cells (ELISPOT), but can also be employed with non-sanguinous fluids if these contain T lymphocytes. Very recently, counting the frequency of Mtb-specific T cells by ELISPOT in pleural fluid and bronchioalveolar lavages has thus been successfully explored for the diagnosis of tuberculous pleuritis, and in smear-negative pulmonary tuberculosis[13,14]

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