European Respiratory Society
Annual Congress 2012

Title: The responses of multiple cytokines following incubation of whole blood from TB patients, latently infected individuals, and controls with the TB antigens ESAT-6, CFP-10, and TB7.7

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Body: Purpose: The development of clinically relevant biomarkers is important for diagnosing latent tuberculosis infection (LTBI) and active tuberculosis (TB) and predicting their prognoses. This study examined whether the responses of multiple cytokines can be used as a biomarker to distinguish the TB infection status and mycobacterial load. Methods: We analyzed the responses of multiple cytokines (IFN-γ, IL-2, IL-10, IL-13, IL-17, and TNF-α) in the supernatant from the QuantiFERON- TB Gold In-Tube assay following stimulation of whole-blood from TB group (n = 32), LTBI group (n = 19), and healthy controls (n = 30) with TB antigens (ESAT-6, CFP-10, and TB7.7). Results: The median responses of IFN-γ, IL-2, IL-10, and IL-13 were higher in the LTBI and active TB groups than in the non-TB control group (IFN-γ, $p < 0.001$; IL-2, $p < 0.001$; IL-10, $p = 0.012$; IL-13, $p < 0.001$). The median IL-2/IFN-γ ratio of the LTBI group was higher than that of the active TB group ($p = 0.014$) and differed significantly among LTBI, smear-negative TB, and smear-positive TB patients ($p = 0.027$). This difference was especially evident between the LTBI and smear-positive TB patients ($p = 0.047$). Conclusions: IFN-γ, IL-2, IL-10, and IL-13 can serve as biomarkers for distinguishing TB infection. In addition, the IL-2/IFN-γ ratio appears to be a biomarker for diagnosing LTBI and may be useful as a prognostic factor and for evaluating treatment responses.