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Using Cytokines as Markers to Improve Diagnostic Evaluation of Tuberculosis Infections

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Thanks to the use of qualitative medicine for tuberculosis, patients suffering from tuberculosis have decreased in Japan. There are, however, still many patients with the disease. This phenomenon is probably due to immigration of infected foreigners into Japan and also existence of drug-resistant tuberculosis strains that are difficult to cure and eradicate. It is especially important to diagnose tuberculosis immediately and accurately because the symptoms may resemble those of other bacterial or viral infections that would be treated without quarantine, which would result in spread of an actual tuberculosis infection. More importantly, we should not forget that a *Mycobacterium tuberculosis* infection may not manifest any apparent symptoms, i.e., a latent tuberculosis infection (LTBI). LTBI patients may later develop the disease or even spread the microbe without being aware. Thus, our guideline for LTBI states clearly that they must be administered anti-tuberculosis therapy. Even though education and monitoring of patients are thought to improve adherence to treatment, in the absence of symptoms LTBI patients may discontinue treatment. In addition, anti-tuberculosis drugs may cause serious adverse effects including neuropathy, pruritis, rash, hepatitis and hypersensitivity. For that reason, unnecessary treatment should be avoided, and evaluation of the efficacy of anti-tuberculosis treatments is very important. Therefore, existence of an easy-to-perform, rapid-diagnosis and accurate tool for detecting active tuberculosis and monitoring therapeutic efficacy would be very impactful, especially in settings where the culture technique and medical supplies are not fully available.

Knowing that blood samples are convenient for measurement and that antigens derived from the microbe would react specifically with *Mycobacterium tuberculosis*, we hypothesized that mediators in the plasma of tuberculosis antigen-stimulated blood would be useful for accurate diagnosis of tuberculosis infection. Additionally, if we could identify from LTBI a mediator responsible for active tuberculosis, that mediator might provide us with clues for elucidating the differences between the immunological pathogenesis of active tuberculosis and LTBI.

To that end, we assayed for 27 cytokines in QuantiFERON® -TB Gold in-Tube test (QFT-3G) supernatants of specific antigen-stimulated blood samples (TBAg) and negative-control samples (Nil) from 31 active tuberculosis patients, 29 LTBI patients and 10 healthy control subjects [1]. For the TBAg-Nil supernatants, we found that IL-10, IFN-γ, MCP-1 and IL-1RA showed high AUCs for distinguishing active tuberculosis from LTBI. In addition to that, combinations of these cytokines were even more effective in differentiating active tuberculosis from LTBI. Based on our previous data as well as data from other groups showing the potency of mediators in QFT-3G supernatants, we believe that not only IFN-γ but also other mediators or even combinations of mediators in QFT-3G supernatants may be useful for diagnosis of active tuberculosis. We are now prospectively recruiting patients with active tuberculosis and LTBI, as well as healthy control subjects, to generate further data in support of our hypothesis.

We have now extended our clinical research from using plasma from QFT-3G samples to using plasma from QuantiFERON® -TB Gold-Plus (QFT-plus) samples for multiple cytokine analysis. In QFT-plus, two sets of antigen tubes are employed: TB1 tube with ESAT-6 and CFP-10, and TB2 tube with ESAT-6, CFP-10 and a short peptide that specifically activates $CD8^+$ cells to produce IFN-γ. With the idea that these different antigen tubes may yield different results due to the different cell types stimulated in each tube, we conducted a clinical study similar to our previous study. By using samples from 83 active tuberculosis patients and 70 healthy control subjects, we found that mediator release in the QFT-plus tubes was lower compared to that of QFT-3G [2]. With QFT-plus, the levels of most of the cytokines were higher in TB1 compared to TB2, except for the level of PDGF-BB, which was higher in TB2 compared to TB1 [2].

Among the cytokines measured, IP-10 was the best cytokine for diagnosis of active tuberculosis [2].

IP-10 is a well-known cytokine in the field of tuberculosis, since many reports have shown it to play an important role in diagnosing tuberculosis infections. For example, IP-10 has been suggested as a potent marker for diagnosis of tuberculosis [3, 4], for differentiating active tuberculosis from LTBI [5] and for monitoring the efficacy of tuberculosis treatment [6, 7]. IP-10 is able to recruit activated T cells, macrophages and natural killer cells to tissue sites infected with *Mycobacterium tuberculosis* [8], and it may thus be important for defense against tuberculosis. That said, IP-10 is not specific for tuberculosis since serum IP-10 levels are reported to be increased in patients with other diseases, including cancer, autoimmune diseases and infections. Nevertheless, utilizing QFT-plus supernatants may enable efficient detection of tuberculosis-specific inflammatory cells in the blood.

Our identification of cytokines that are useful for diagnosis of active tuberculosis may lead to new information regarding the mechanisms underlying development of active tuberculosis. These cytokines may reflect the underlying molecular mechanisms in individuals infected with *Mycobacterium tuberculosis* and provide clues as to why *Mycobacterium tuberculosis* is able to infect some, but not all, individuals. However, to elucidate those mechanisms, we need to perform further basic microbial research with a precise understanding of human immunology against infection by *Mycobacterium*.

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Conflicts of interest

The authors have no conflicts to disclose.

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