

## Cytokines and Chemokines as Biomarkers of Tuberculosis

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### Abstract

Tuberculosis (TB) is an old disease representing a major public health problem globally. The current widely used tools are very long time since licensed and are inefficient in diagnosing and prognosing of tuberculosis infection and disease. A new diagnostic test which is sensitive, specific and rapid is urgently needed for timely detection, appropriated treatment response and control. Biomarkers are crucial to the development of new diagnostic and prognostic tools, drugs and vaccines against tuberculosis and could be instrumental in reducing morbidity and mortality and curtailing spread of tuberculosis. In this review we shall highlight the progress of biomarkers focusing on cytokines and chemokines as biomarkers of tuberculosis infection and reactivation; tuberculosis disease and tuberculosis cure.

**Keywords:** Biomarkers; Sputum culture; HIV/AIDS; Cytokines; Antigens

### Background

Tuberculosis (TB) is the world's second most common cause of death from all infectious diseases, next to HIV/AIDS. In 1993 the World Health Organization (WHO) declared TB as a 'global emergency' [1], however, this did not change the situation significantly. Every year, 40 million individuals become infected with *M. tuberculosis* and near to 10 million fall ill. It has been estimated that up to 2 billion individuals are currently infected with *M. tuberculosis* [2].

The current widely used diagnostic technique; therapeutic drugs and vaccine are very long time since licensed and are inefficient in detecting, treating or protecting against tuberculosis respectively. The lack of reliable biomarkers to indicate or predict the different clinical outcomes of *M. tuberculosis* infection has been given as a key reason for the failure of developing new diagnostic and prognostic tools, drugs and vaccines against tuberculosis.

A biological marker, or biomarker, is a characteristic that is objectively measured and evaluated as an indicator of a normal physiological or pathological process or pharmacological response(s) to a therapeutic intervention. Host or pathogen specific TB biomarkers provide prognostic information, either for individual patients or study cohorts, about health status and can advance knowledge of disease pathogenesis in predicting reactivation and cure, and indicating vaccine-induced protection [3]. Cytokines and chemokines, as key molecules that regulate immunological responses, have been extensively studied in relation with their potential as diagnostic and prognostic biomarker of tuberculosis. In this review we shall highlight the recent findings in relation with cytokines and chemokines as biomarkers of TB infection reactivation, disease and cure.

### Cytokines and chemokines and their role in *M. tuberculosis* immune response

Cytokines and chemokines are small protein molecules that regulate immunological responses at cellular level. They stimulate and recruit wide range of cells involved in immunity and inflammation. The actions of cytokines could be pleiotropic where one cytokine has the ability to act on different cell types or redundant where multiple cytokines have the same functional effect. Other cytokines have a cascade effect in which one cytokine manipulate the manufacture and actions of other cytokines. They may also have antagonistic action where the effect of

one cytokine opposes the action of others or synergistic effects where two different cytokines work together.

The actions of chemokines could be homeostatic where they guide cells during immune surveillance for pathogens by interacting with antigen presenting cells residing in these tissues. Some chemokines have roles in promoting angiogenesis or guide cells to tissues that provide specific signals critical for cellular maturation. Other chemokines are inflammatory and they function mainly as chemo attractants for leukocytes from the blood to sites of infection or tissue damage.

The protective response to *M. tuberculosis* is complex and multifaceted involving many components of the immune system, mainly the result of productive cooperation between macrophages and T-cell populations. Different animal and human studies have firmly established that cytokines and chemokines have a major role in determining the outcome of infection with *M. tuberculosis* [4,5].

Studies in mice and human showed that IFN- $\gamma$ , TNF- $\alpha$  and IL-12 are the key cytokines involved in the control of *M. tuberculosis* infections [6-10]. *M. tuberculosis* induced elevated levels of a variety of chemokines, including IL-8 (CXCL-8), monocyte chemoattractant protein 1 (MCP-1) (CCL-2), MCP-3 (CCL-7), MCP-5 (CCL-12), regulated on activation normal T cell expressed and secreted (RANTES/CCL-5), MIP1- $\alpha$  (CCL-3), MIP1- $\beta$  (CCL-4), MIP-2 (CXCL-2) and IFN  $\gamma$ -inducible protein-10 (IP-10/CXCL-10) [11] and their receptor such as CCR5 and CXCR4 [12].

### Cytokines and chemokines as biomarkers of tuberculosis infection and reactivation

Extensive research has been carried out on biomarkers that result from the immune response to *M. tuberculosis* infection. Tests that indicate exposure to the pathogen have been developed based on *in*

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*vitro* T cell based immuno assays which measures IFN gamma (IFN- $\gamma$ ) response against *M. tuberculosis* specific antigens, early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10). The two T-cell-based Interferon Gamma Release Assays (IGRAs) are commercially available and widely used for diagnostic and research purposes: QuantiFERON TB-GOLD In-Tube (QFT-G-IT) (Cellestis Ltd., Carnegie, Australia) which uses enzyme-linked immunosorbent assays (ELISAs) to measure differences in the concentration of IFN- $\gamma$  and T-SPOT.TB (Oxford Immunotec, Abingdon, UK) which measures differences in the number of cells that produce IFN- $\gamma$ , after incubation of whole blood or peripheral blood mononuclear cells (PBMCs) with *Mtb* antigens. The sensitivity of these two FDA approved IGRAs is less than ideal, and typically no better than the sensitivity of the TST particularly in immunocompromised individuals and children.

Currently a number of investigations are ongoing for biomarkers that might be used to indicate *M. tuberculosis* infection and there are studies reporting IP-10 may be a better alternative marker for latent TB infection diagnosis among immunocompromised individuals and children [13-15]. Others reported measurement of IL-2, IL-6, IP-10, and MIP-1 $\beta$  may improve diagnostic sensitivity for *M. tuberculosis* infection compared with assessment of IFN- $\gamma$  alone [16]. The increase of IP-10, MCP-1, MCP-2, MCP-3, and IL-1RA in supernatants from whole blood stimulated with *Mycobacterium tuberculosis*-specific antigens was also reported to be a marker of tuberculosis infection [17]. A multicenter study also showed that IP-10 as a novel diagnostic marker for infection with *M. tuberculosis* and its level was less influenced by infections other than TB [18]. The decreased ratio of IL-4 to IL-4 $\delta$ 2 in chronic or long time latently infected individuals reported predicting low risk of reactivation [19] where as lower IFN- $\gamma$ /IL-4 and IL-4 $\delta$ 2/IL-4 mRNA ratios predict high risk of *M. tuberculosis* infection and reactivation [20].

### Cytokines and chemokines as biomarkers of tuberculosis disease

The paucity of knowledge regarding specific biomarkers for active TB is a major barrier to the development of point of care diagnostic tests. Biomarker discovery and validation studies are urgently needed to define combinations of markers that might eventually assist case finding and accelerate access to treatment. A century old sputum smear microscopy is the most widely used test in high endemic countries and this test is inadequate to diagnose early active TB disease and unable to diagnose extrapulmonary TB, sputum smear-negative TB (active pulmonary TB with less than 10,000 bacilli per ml of sputum) and childhood TB.

Studies have indicated that IGRAs show stronger responses in people with active TB than in those with latent TB [21] and high or increasing concentrations of TB specific IFN- $\gamma$  production might predict overt TB [22,23]. Others reported that IL-2, IFN- $\gamma$  [24] and TNF- $\alpha$  expression profiles of CD4<sup>+</sup> T cells [25] hold promise in detecting active TB disease. Pro inflammatory cytokines such as TNF, IL-12(p40) and IL-17 are increased in TB cases and can discriminate active TB disease from latent infection [26]. TB cases show high serum level of IL-8, IP-10, MCP-1, and MIP-1  $\beta$  in comparison with non TB cases [27-29]. Another study also reported detection of single or combinations of three host markers (selected from EGF, sCD40L, MIP-1 $\beta$ , VEGF, TGF- $\alpha$  or IL-1 $\alpha$ ) by utilizing an adaptation of the commercial QFT assay may be accurately identified active TB within 24 hours [30].

In addition, the RNA expression level of CXCL-8, FoxP3 and IL 12 $\beta$  differentiates latent TB infection from disease [31]. The relative

mRNA level of IFN- $\gamma$ , IL-4, and IL-4 $\delta$ 2 has been reported as a better marker than IFN- $\gamma$  alone, since ratios of IFN- $\gamma$  to IL-4 and IL-4 $\delta$ 2 to IL-4 decreased when contacts developed TB and increased in cured TB cases. Nemeth et al. [32] have reported specific cytokine patterns of pulmonary tuberculosis in central Africa where they detected a pronounced pro-inflammatory cytokine response in patients, with highly significantly increased levels of IL-6 and TNF- $\alpha$  accompanied by increased TGF- $\beta$ . Chegou et al. [30] also reported that the levels of IFN- $\alpha$ 2, IL-1Ra, sCD40L, IP-10 and VEGF in QFT-IT supernatants have potential to support the diagnosis of TB disease or the discrimination between TB disease and LTBI in children. On the other hand, Goletti et al. [33] reported that IFN-gamma (but not IP-10, MCP-2 and IL-2) response to RD1 selected peptides is associated with active TB with a higher specificity than QFT-IT and TST. In a recent study Chegou et al. reported Rv0081-specific levels of IL-12(p40), IP-10, IL-10 and TNF-alpha were the most promising diagnostic candidates, each ascertaining TB disease with an accuracy of 100% [34].

The levels of IL-6 and IL-9 were significantly high in plasma and after *Mtb* antigen stimulation in active TB patients and the levels of CCL1, CCL21 and IL-6 were specifically increased in pleural effusions of tuberculous pleurisy patients [35]. We have also reported that TB patients had significantly higher plasma concentrations of EGF, fractalkine, IL-4 and IP-10 and lower plasma concentration of IFN-g and MCP-3[36].

### Cytokines and chemokines as biomarkers of tuberculosis protection/cure

Sputum culture or smear microscopy status after 2 months of therapy has been used as a surrogate marker for predicting non-relapsing cure. Several studies have reported the level of cytokines and chemokines in unstimulated plasma or after stimulation with mycobacterium antigens could be used as an additional or alternative to the existing tests for the development of a rapid, sensitive and user friendly test for monitoring effective antituberculosis therapy. Currently polyfunctional CD4 and CD8 T cells expressing multiple cytokines (IL-2, TNF- $\alpha$  and IFN- $\gamma$ ) are being increasingly studied as these cells may be involved in mediating protection and curative host responses in TB [37,38]; however recent studies do not support this idea. Specific CD4 T cell response 10 weeks after BCG vaccination in new borns do not correlate with ultimate risk of TB disease. Moreover, risk of disease during the first 2 years of life in new borns was not associated with mono or polyfunctional CD 4 or CD8 T cells [39]. Another study reported polyfunctional CD4 T cells were detectable in the lungs of persons exposed to TB in HIV-1-uninfected persons but essentially absent from the lungs of highly MTB-susceptible HIV-1-infected persons [40]. A recent study also reported that Bifunctional IFN gamma(+) TNF alpha(+) CD4(+) T-cells and effector memory phenotype significantly associated with active TB compared to the LTBI group whereas "RD1"-T-cell response in cured TB and LTBI was characterized by a central memory phenotype [41]. In vitro levels of IL-10 and the ratio of IFN-  $\gamma$ /IL-10 in response to a recombinant 32-kilodalton antigen of *M. bovis* BCG has been reported as a good marker in monitoring treatment of TB [42] where the level of IL-10 decreases and the ratio of IFN- $\gamma$ /IL-10 increases after treatment. Another study reported utility of serial quantitative T-cell responses as treatment monitoring tools as they showed a significant decline in IFN- $\gamma$  in the quantitative result of both QFT-IT and T-SPOT.TB<sup>®</sup> after treatment [43]. We have also reported that the median plasma level of IL-4 and IP-10 was significantly decreased whereas the level of IFN- $\gamma$ , MCP-3 and MIP-1 $\beta$  significantly increased after treatment as compared to the base line values [44]. Other study has also showed that the IP-10

response to RD1 selected peptides (similar to IFN-gamma) might be a useful biomarker for monitoring therapy efficacy in patients with active TB [45].

## Conclusion

The development of more accurate, inexpensive point-of-care tuberculosis tests that is applicable in indicating infection, reactivation, disease or cure is very crucial for diagnosis, prognosis and developing new drugs and vaccines that help in achieving global tuberculosis control. A number of single or sets of cytokine and chemokine markers have been reported to be associated with TB infection, reactivation, disease or cure, but the reports are controversial and there are no consensus biomarkers to indicate the different disease conditions. The interest and investment on TB biomarkers study has grown with several technologies showing great promise; however the reported biomarkers so far have been inconsistent across laboratories, underscoring the need for more research at different population at different geographical locations.

Therefore, the search for surrogate markers that can provide primary measurements of the different clinical status has to be intensified using state-of-the art techniques which will help for “fishing” potential novel biomarkers that could not be affected by bacterial strains, host genetic and environmental factors rather than a targeted biomarker search.

## Conflict of Interests

The authors declared no conflict of interests.

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