ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Commentary

The Quest for Potential Host Blood Biomarkers for Tuberculosis Diagnosis, Severity and Treatment Effect: Are we there Yet?

Amar Singh[1]* and Sujata Prasad[2]

[1]*Schulze Diabetes Institute, Department of Surgery, University of Minnesota, Minneapolis, MN, United States*

[2]*Department of Medicine, Neurovirology Laboratory, University of Minnesota, 3-107 Microbiology Research Facility, Minneapolis, MN, United States*

***Corresponding Author:** Amar Singh, Schulze Diabetes Institute, Department of Surgery, University of Minnesota, Minneapolis, MN, United States. **E-mail:** singh423@umn.edu

Received: April 06, 2019; **Published:** May 21, 2019

Tuberculosis (TB) continues to have a major impact on global health. As per WHO report in 2017 [1], an estimated 10 million people developed tuberculosis and 1.3 million dies from it, despite extensive vaccination and drug treatment programmes. Millions of cases of TB go undiagnosed each year since the current diagnosis of tuberculosis relies heavily on century-old techniques, hampering not just treatment but also the development of new drugs and vaccines. Emerging resistance to current TB drugs necessitates the development of newer and better drugs. Therefore, biomarkers that serve as indicators of clinical outcome or response to treatment are required to accelerate anti-tuberculosis drug development and to screen new compounds in clinical trials [2]. Identification of clinically relevant biomarkers is urgently needed to ensure better care for TB patients and to stop the spread of TB. Hence "biomarkers" indicating disease status would boost the development of better drugs, vaccines, and diagnostics [2-5]. Any biological factors that can objectively measure and whose estimated value is consistently associated with changing health or disease states or directly involved in pathogenesis or protection responses to a therapeutic intervention could be identified as biomarker [2]. Recent years have seen the initiation of several large-scale studies aiming to identify new biomarkers of TB infection, risk, and disease for control of the ongoing TB pandemic [6]. The present work provides a general overview of blood cells TB biomarkers research.

Blood cells biomarker; host immune cells, cytokines or chemokines

The cytokines, chemokines have a major role in immunological response during the pathogenesis of pulmonary TB. Biomarker research in TB has been very effectively highlighted by quite a few research articles recently. Several potential host biomarkers in blood or blood cells in tuberculosis were identified in recent years these include IP-10, IL-6, IL-10, IL-4, FoxP3, PD-1, PD-L1 and IL-12. Similarly, IFN-γ, TNF-α, IL-2, IP-10, IFN-γ/TNF-α, IFN-γ/IL-2 and IL-13 were identified as strong candidate biomarkers that were upregulated in latent TB compared to healthy uninfected controls in stimulated blood samples [2-8]. These biomarkers would again find an application in the diagnosis of a latent TB infection. IL-6, IL-10, IP-10 and TNF-α as the most promising markers for active TB while FoxP3, IL-4 and IL-12 were identified as the most promising biomarkers for immunological correlates of protection. Recently we have shown therapy induced decline of $FoxP3^+$ Treg cells paralleled with the decline of *M. tuberculosis*-specific IL-10 along with the elevation of IFN-γ production and raising the IFN-γ/IL-4 ratio. Interestingly, the persistence of Treg cells tightly correlated with MDR tuberculosis [9]. This finding further substantiates the utility of Treg cell monitoring as an important predictive biomarker for MDR tuberculosis and response to the anti-tuberculosis chemotherapy. Recently, we observed that PD-1 expressing T cells were increased during active tuberculosis, and steadily declined in the PBL of PTB patients during successful anti-tubercular therapy. In this study, we found a tight correlation between the bacillary load and frequency of $PD\text{-}1^+$ T cells, and decreases of $PD\text{-}1^+$ T cell frequency was associated with an increase in the *M. tuberculosis*-specific IFN-γ/IL-4 among PTB patients [10]. Thus, the study highlights the importance of $PD\text{-}1^+$ T cells in human tuberculosis and reinforces its use as

a useful biomarker to monitor treatment outcomes during therapy and/or vaccine trial for tuberculosis patients. These biomarkers are important due to two reasons: (i) discriminating TB disease and infection and (ii) identifying correlates of protective immunity. These protective immunological correlates would, in turn, be useful for vaccine efficacy studies. Validation of these biomarkers in a large set of individuals across populations could identify a TB biosignature as well as "immunological correlates of protective immunity".

In two subsequent study, Adekambi and Rengarajan., *et al.* reported host blood-based biomarkers on *M. tuberculosis*-specific $CD4^+$ T cells [11,12]. The authors identify $CD38^+IFN\text{-}\gamma^+$, $HLA\text{-}DR^+IFN\text{-}\gamma^+$, $Ki\text{-}67^+IFN\text{-}\gamma^+$ [11] and $caspase\text{-}3^+IFN\text{-}\gamma^+$ [12] are substantially high on *M. tuberculosis*-specific $CD4^+$ T cells and these markers accurately classified ATB and LTBI status, with high specificity and greater sensitivity. They provide direct correlates of *M. tuberculosis* load (TB bacilli) *in vivo*, suggesting utility as surrogate markers of treatment response. These blood-based biomarkers could be employed for predicting treatment efficacy, cure, and relapse in patients undergoing anti-TB treatment for both drug-susceptible as well as drug-resistant TB and in clinical trials evaluating the efficacy of new therapeutics.

Recent study on blood cytokines response to early secreted protein antigen-6 (ESAT-6) and culture filtrate protein-10 (CP-10) *M. tuberculosis* antigens was performed among drug-susceptible pulmonary TB patients before and after 2 months after 2 months anti TB therapy [13] shows significant decline in TNF-α, IL6 and IL10 following treatment whereas the IFN-γ and IL-4 increased significantly after treatment. This study also suggests that cytokines that observed during the treatment of TB patients play a very important role in monitoring pulmonary TB and can be suitable biomarkers to assess the effectiveness of anti-TB therapy in patients with TB. In contrary to study ESAT-6 response on host cells direct measurement of intracellular ESAT-6 proteins within host cells also allow discriminating latent TB infection (LTBI) vs active TB [14]. In this study, author developed flow cytometry methods identification of intracellular (i/c) ESAT-6 in host cells would be a direct marker of *M. tuberculosis* infection. Another recent study [15] conducted on 227 subjects consisting of active TB patients, LTBI individuals, and healthy controls discovered 8-marker biosignature (eotaxin, MIP-1α, MDC, IP-10, MCP-1, IL-1α, IL-10, and TNF-α) identify ATB and 5-marker biosignature (IP-10, MCP-1, IL-1α, IL-10, and TNF-α) for diagnosing LTBI. Among these plasma cytokines, the 3-signature biosignature (eotaxin, MDC, MCP-1) are able to differentiate active TB from LTBI with high sensitivity and specificity.

The key finding from recent work suggests that there is no shortage of potential host biomarkers for TB. Immune subsets, cytokines, chemokines or upregulated, downregulated receptors are readily measured in peripheral blood. However, clinical studies done so far are small, focused on limited cohorts, restricted to single regions, often lack detailed microbiological, immunological and, clinical descriptions and are usually cross-sectional. Further, most of these TB biomarker discovery studies are having a deficit of poor experimental design, cohort size, and its findings are rarely confirmed in independent studies. More intensified research with large-scale, multiple institutional, longitudinal studies in TB endemic regions with clearly defined recruitment criteria and endpoints are needed to validate the suggested biomarkers and then reduce them to clinical practice. Therefore, cumulative efforts of TB researchers and health care providers are warranted to (i) to eliminate the gap between the exploratory up-stream identification of composite biomarkers and their validation against clear clinical endpoints in different populations and (ii) to the develop simple point of care tests applicable in low resourced settings. Achieving this could offer the possibility of better clinical management of TB, identification and characterization of TB patients, and assigning them in an appropriate treatment regimen. Improved understanding of the biology of immune "Biomarkers" is the new hope in the landscape of TB control and elimination.

Disclaimer

The findings and conclusions in this publication are those of the author and do not necessarily represent the official position of the University of Minnesota, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

Disclosure

The authors declare no conflicts of interest.

Bibliography

1. Ghosh S and Saxena RK. "Early effect of Mycobacterium tuberculosis infection on Mac-1 and ICAM-1 expression on mouse peritoneal macrophages". *Experimental and Molecular Medicine* 36 (2004): 387-395.

2. Doherty M., *et al*. "Biomarkers for tuberculosis disease status and diagnosis". *Current Opinion in Pulmonary Medicine* 15.3 (2009): 181-187.

3. Parida SK and Kaufmann SH. "The quest for biomarkers in tuberculosis". *Drug Discovery Today* 15.3-4 (2010): 148-157.

4. John SH., *et al*. "Host biomarkers of clinical relevance in tuberculosis: review of gene and protein expression studies". *Biomarkers* 17.1 (2012): 1-8.

5. MacLean E., *et al*. "A systematic review of biomarkers to detect active tuberculosis". *Nature Microbiology* 4 (2019): 748-758.

6. Doherty TM., *et al*. "Biomarkers of disease activity Experimental and Molecular Medicine y, cure, and relapse in tuberculosis". *Clinics in Chest Medicine* 30.4 (2009): 783-796.

7. Wallis RS., *et al*. "Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice". *Lancet* 375.9729 (2010): 1920-1937.

8. Walzl G., *et al*. "Immunological biomarkers of tuberculosis". *Nature Reviews Immunology* 11.5 (2011): 343-354.

9. Singh A., *et al*. "Foxp3+ regulatory T cells among tuberculosis patients: impact on prognosis and restoration of antigen specific IFN-gamma producing T cells". *PLoS One* 7.9 (2012): e44728.

10. Singh A., *et al*. "Inhibiting the programmed death 1 pathway rescues Mycobacterium tuberculosis-specific interferon gamma-producing T cells from apoptosis in patients with pulmonary tuberculosis". *Journal of Infectious Diseases* 208.4 (2013): 603-615.

11. Adekambi T., *et al*. "Biomarkers on patient T cells diagnose active tuberculosis and monitor treatment response". *Journal of Clinical Investigation* 125.5 (2015): 1827-1838.

12. Adekambi T., *et al*. "High Frequencies of Caspase-3 Expressing Mycobacterium tuberculosis-Specific CD4(+) T Cells Are Associated With Active Tuberculosis". *Frontiers in Immunology* 9 (2018): 1481.

13. Mvungi HC., *et al*. "Blood cytokine responses to early secreted protein antigen-6/culture filtrate protein-10 tuberculosis antigens 2 months after antituberculosis treatment among patients with drug-susceptible pulmonary tuberculosis". *International Journal of Mycobacteriology* 8.1 (2019): 53-59.

14. Poulakis N., *et al*. "Intracellular ESAT-6: A new biomarker for Mycobacterium tuberculosis infection". *Cytometry Part B: Clinical Cytometry* 90.3 (2016): 312-314.

15. Luo J., *et al*. "Diagnostic performance of plasma cytokine biosignature combination and MCP-1 as individual biomarkers for differentiating stages Mycobacterium tuberculosis infection". *Journal of Infection* 78.4 (2019): 281-291.

Volume 8 Issue 6 June 2019