Polyfunctional T cells as Biomarkers in Diagnosis of Extrapulmonary Tuberculosis

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Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) and remains an important global health problem. Extrapulmonary TB (EPTB) is usually considered a more difficult diagnostic problem than pulmonary TB because it involves relatively inaccessible sites where few *bacilli* can cause great damage. People living with HIV infection are at an increased risk of developing TB especially in EPTB. The paucibacillary nature of EPTB in combination with inaccessible disease sites causes bacteriological confirmation of TB to be more difficult and invasive procedures are often required to confirm a TB diagnosis. The diagnostic challenges are most problematic in TB endemic countries. Various National Tuberculosis Control Programmes thus have adopted clinical guidelines for diagnosis of EPTB, which alone can lead to over-diagnosis and treatment. Thus, clinical diagnosis may lead to diagnostic delays, misdiagnosis, resistant strains and increased mortality.

It is therefore important that a diagnostic technique intended for TB control at a global level should be suitable for use in a setting where it is most needed, namely in resource-poor high-burden countries in Asia. The lack of reliable biomarkers to indicate or predict the different clinical outcomes of *M. tuberculosis* infection is key reason for the failure of developing new diagnostic tool against TB. T cells are major determinant component of host immunity and capable of killing infected cells. IFN-γ producing Th1 cells provide the major effector response to TB but IFN- γ only is not sufficient for protection against disease progression. CD4+ T cells which simultaneously produce IFN-γ, TNF-α and IL-2 are termed as polyfunctional Th1 cells and play a critical role in controlling chronic bacterial and viral infections. Polyfunctional T cells expressing several cytokines in parallel have been associated with superior functional capacity as compared to single cytokine producers. There is paucity of information whether polyfunctional T-cells represent a marker of protective immunity or disease activity. However, the contradictory findings in context of T cell behaviour during TB infection add to the difficulty in defining the role of these cells during TB. Limited data is available regarding detailed analysis of polyfunctional T cells in active TB. Recently it was observed that a significant portion of *M. tuberculosis*-specific CD4+ T cells are polyfunctional at the site of EPTB infection and greater proportion of these polyfunctional cells are of effector memory [1,2]. Only few reports of polyfunctional T cells in active and latent TB patients are available in India [3,4]. How HIV co-infection affects the phenotype of *M. tuberculosis*-specific memory T cells at the disease site is still not known. Polyfunctional T cells have been implicated as both a correlate of protection and pathology in TB. Few recent studies showed that indeed polyfunctional CD4+ T cells could represent correlates of protection [5,6] although contradictory finding are also existing [7]. The reappearance of mycobacteria specific polyfunctional CD4+ T cells in HIV patients after onset of antiretroviral therapy, further strengthen the importance of polyfunctional CD4+ T cells in protection against TB in HIV- co-infected individuals [8]. The role of polyfunctional T cell subsets in diagnosis of TB is still inconclusive and needs further investigation.

Peripheral blood may not be a true representative of the host immune response, particularly at acute stage of disease. Thus, it is important to study the immune responses at the local site of infection in order to improve the understanding of the immunological mechanisms involved in containment and progression of disease. These cells could be used in future for development of better immunodiagnostic tests specifically for EPTB where TB diagnosis is more challenging and presentation of diffuse clinical manifestations, low bacterial loads or difficulty in obtaining clinical specimen from the site of *M. tuberculosis* infection, complicates TB diagnosis.

In conclusion, there is currently no consensus whether polyfunctional T-cells represent a marker of protective immunity or disease activity. The role of polyfunctional T cell subsets in diagnosis of TB is still inconclusive and needs further investigation. It is generally accepted that reasonable control of TB on a global scale depends on new interventions including a better vaccine that protects adults against TB and better diagnostic tests with the ability to rapidly detect active TB. Despite a lot of recent advances in TB immunology research, the host response required for protection in human TB has not been clearly defined. In the context of intracellular microbes such as *M. tuberculosis* and also HIV, for which effective vaccines are lacking, an increased understanding of how immune cells regulate the immune response to pathogens and how cellular arm of the host response mediates protective effects will likely aid in the development of strategies to enhance antimicrobial immunity, vaccine efficacy and diagnostic approaches.

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