Unique T-cell phenotypes and articular involvement in sarcoidosis

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Sarcoidosis is a multisystem and heterogeneous autoimmune disease in terms of presentation, duration, and severity.[1] Usually, it affects the lungs and mediastinal lymph nodes and its pathologic hallmark is the formation of non-caseating epithelioid cell granulomas.[2] Approximately 30% of the patients with sarcoidosis are at risk of developing fibrotic disease of the lungs.[3] Sarcoidosis can develop *de novo* or present in patients with pre-existing rheumatic diseases.[4] The diagnostic methods to detect sarcoidosis at an early stage are limited, time consuming and complicated. Most methods require invasive procedures such as investigation of bronchoalveolar lavage (BAL) and evidence of granuloma formation in tissue through a biopsy. Moreover, at present, the diagnosis of sarcoidosis is confirmed only by excluding other diseases with similar presentations and pathology. A suitable biomarker for sarcoidosis has not yet become available. Serological and BAL-based biomarkers lack the necessary specificity and sensitivity. Therefore, there is a need for a precise and non-invasive biomarker to diagnose sarcoidosis at an early stage. T-cells play a significant role in the formation of granuloma.[3] Antigen presented by professional antigen-presenting cells leads to activation of T-cells and greater recruitment of neutrophils and monocytes. Several T-cell related cytokines and chemokines have been noted as a potential biomarker for sarcoidosis.[5] For example, activation of T-cells upregulates the expression of IL-2R on T cells and sheds soluble form of IL-2 in the circulation. Unfortunately, high levels of soluble IL-2R are not very specific for sarcoidosis and are elevated in other forms of granulomatous diseases. The immune-phenotyping of T-cells in pulmonary sarcoidosis has demonstrated an abundance of CD4+T cells in granulomas with fewer CD8+T cells around the periphery.[6] Other studies have also demonstrated a clear role of T-cell subtypes in pulmonary sarcoidosis.[6] However, their role in other forms of sarcoidosis remains unclear.

In this issue of the *Journal* an elegant study from Jain et al. has evaluated the peripheral blood T-cell signature in patients with sarcoidosis and assessed whether it differs in those with and without articular manifestations.[7] They found that the T-helper cell pool of sarcoid patients with articular involvement differed from those with non-articular sarcoidosis. Jain et al. reported that there was a skewing of the T-helper subtypes towards Th1, Th2 and Th17, with a reduction in T-regulatory cells along with their signature circulatory cytokines, in the peripheral blood of patients with articular involvement compared to non-articular sarcoidosis.[7] In addition, they found high granzyme B-loaded cytotoxic T-cells and a high number of B-cells in the circulation of patients with articular sarcoidosis.[7] Previously a higher frequency of Treg cells has been demonstrated in peripheral blood in sarcoidosis, but with compromised function.[8] In this scenario further investigation in patients with articular sarcoidosis of T-regulatory cells for functional activity and expression of transcription factor such as T-bet, GATA2 and ROR-gt may give us more information about the disease severity in different individuals.

This study highlights interesting potential use of such T-cell subsets in diagnostics and therapeutics of sarcoidosis. But in order to be an effective tool, several areas need further exploration. Firstly, a detailed study and advanced T-cell characterisation such as single T-cell RNA sequencing may explore the precise immunological targets in various forms

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of sarcoid. Secondly, after identifying a unique T-helper population, determination of the sensitivity and its specificity in the diverse human population would be required to use it as a diagnostic tool. Thirdly, more work is required to explore whether a different form of sarcoid such as pulmonary or articular can regulate peripheral immune cell compartments.

In conclusion, for future routine clinical practice, the present study highlights the tremendous potential of such T-cell subsets-based approach in the following two ways. For the diagnosis, an enriched unique T-cell population in sarcoidosis with articular involvement with suitable specificity and sensitivity may replace conventional invasive tools. For the treatment, detailed T-cell phenotyping and its associated signaling pathways responsible for pathology in articular or pulmonary sarcoidosis will potentially enable development of precise target-based therapeutic agents.

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