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T cell response to hnRNPA2 in patients with rheumatoid arthritis

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Keywords

Rheumatoid arthritis, T cell response, hnRNPA2

Context

Rheumatoid arthritis (RA) is systemic joint disease characterized by infiltration of many immune cells such as B and T cells and macrophages in the synovial membrane leading to a chronic inflammatory joint disease. To better understand the role of T cells in the pathogenesis of RA, the authors studied the T cell response against two Ag (hnRNPA2/RA33 and filaggrin (fil)) targeted by Abs of patients with RA. These Ag seem to be specific for RA as Abs to A2/RA33 and Fil are detected in 1/3 and 40-50% of RA patients respectively. Because Abs directed to Fil recognize the citrulinnated form of the protein, T cell responses were studied against both the unmodified and the citrulinnated form of Fil.

Significant findings

PBMC and synovial T cells from RA patients proliferate strongly in response to A2/RA33 (60% vs 20% in controls). In contrast, no difference was found in response to Fil between RA patients and controls. T cell response to A2/RA33 in RA patients is HLA-DR restricted and characterized by a Th1 cytokine profile with high IFN-γ and low IL-4 secretion in both RA and control PBMC, and higher IL-2 production by PBMC of RA patients. T cell lines specific to A2/RA33 were established from PBMC of RA patients and healthy donors. In the term of proliferative response, no significant difference was found between T cell lines from RA patients and those of controls. In contrast, the majority of RA T cell lines are CD4+CD8- with Th1 phenotype, whereas T cell lines generated from healthy donors show heterogeneous phenotype and secrete significantly less IFN-γ than clones from RA patients. Finally, the authors also found that A2/RA33 is abundantly expressed in RA synovial tissues and interestingly, was detected not only in the nucleus but also in the cytoplasm of RA synovial cells. The characterization of autoreactive T cells to A2/RA33 associated with overexpression of a relocalized protein leads the authors to conclude that A2/RA33 may be an important autoAg in RA.

Comments

The most important result of this work is the identification of autoreactive T cells specific to A2/RA33 present both in PBMC and synovial tissues. Because CD4+ T cells are known to deliver a signal to B cells leading to the production of Abs, identifying such T cells is of a major interest to develop Ag specific therapy. Another important point, is the overexpression of A2/RA33 especially in the cytoplasm. Factors that lead to the breakdown of tolerance still remain elusive. The accumulation of autoAg in an aberrant localization may be involved in this process, leading to elevated amounts of the Ag that can differ in that case of the nuclear form. The authors did not find any T cell response to Fil. As it was recently shown that the major synovial targets of anti-filaggrin Abs are deiminated form of fibrin and that Abs to Fil are only cross-reactive Ag, it should be interesting to test the response of RA T cells to citrullin-containing fibrin proteins.

Methods

T cell stimulation assays, T cell lines, immunohistochemistry

References

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