Correlation of T follicular helper cells and plasmablast with the development of organ involvement in patients with IgG4-related disease

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IgG4 related disease (IgG4-RD) is a systemic disease that is characterized by the infiltration of IgG4secreting plasma cells and effector T cells into various organs. However, the characteristic and pathological role of immune cell subsets remains unclear. The aim of this study was to investigate how the abnormality of immune network contributes to the pathogenesis of IgG4-RD.

Peripheral blood mononuclear cells were obtained from 16 patients with IgG4-RD and 26 healthy donors (HD). The phenotype of circulating T cells, B cells, monocytes, NK cells, and dendritic cells were defined based on comprehensive flow cytometric analysis for human immune system termed "the Human Immunology Project Consortium program" by NIH/FOCIS. In the biopsy site, CD4+Bcl-6+ T follicular helper cells (Tfh) were detected by immunohistochemistry. The proportion of immune cell subsets was assessed for correlations with serum IgG, IgG4, CRP, the existence of extra glandular manifestations and Tfh density in the biopsy site.

There was no difference in the proportion of Th1 cells Th17 cells between IgG4-RD and HD. On the other hand, the proportions of Treg cells and Tfh cells (CD4+CXCR5+ICOS+) were higher in IgG4-RD compare to HD. Moreover, the proportion of Tfh in peripheral blood was reflected that of Tfh in the biopsy site. In B cells, the proportion of class –switched memory B cells and double negative (effector) B cells were higher in IgG4-RD. The largest difference relative to HD was observed in the proportion of plasmablast. Among immune cell subsets, Tfh cells and plasmablast were positively correlated. Of note, the percentage of plasmablast and Tfh cells was correlated with serum IgG levels, while other T cell subsets did not. Furthermore, the proportions of plasmablast, Tfh cells and Memory Treg cells were higher in patients with extra glandular manifestations compared to patients without extra glandular manifestations. After treatment with glucocorticoids, the proportions of plasmablasts and Tfh cells decreased with improvement of clinical manifestations, but Memory Treg cells did not change.

This comprehensive immunophenotypic analysis revealed that Tfh cells induce the differentiation of B cells into IgG producing plasmablast and contribute to organ manifestation of IgG4-RD. Our findings would clarify the pathogenesis of IgG4-RD through the Tfh/plasmablast axis and suggest a potential as the therapeutic target of this disease.