IgG4-Related Disease: A Growing Appreciation of Follicular Helper T Cell Expansion

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We read with great interest the article by Cargill et al. (1) in *Clinical and Translational Gastroenterology*. They showed the increase in programmed cell death 1-positive follicular helper T (Tfh) cells, particularly Tfh2 cell subset, in the peripheral blood as well as the presence of these cells in the affected tissues. They also demonstrated the potential of blood Tfh cells as a disease activity marker of immunoglobulin G (IgG4)-related disease. The existing evidence of Tfh cells were biased to IgG4-related orbital disease and salivary gland involvements, but the present study has revealed that the role of Tfh cells can also be applied to the other organ involvements (sclerosing cholangitis and pancreatitis).

Since our first reports in 2015 (2) and 2016 (3), the significance of Tfh cells, particularly Tfh2 cells, has become one of the most replicated evidence in IgG4-related disease worldwide. Different studies from Japan, France, China, the Netherlands, and the United Kingdom all reported the increase in blood Tfh2 cells in IgG4-related disease. Tfh2 cells from patients with IgG4-related disease had the highest ability to induce IgG4-producing plasmablast differentiation from naive B cells among Tfh cell subsets (3). Consequently, the increased number of blood Tfh2 cells correlated well with serum IgG4 levels and blood plasmablast numbers as well as disease activity index (3).

The analysis of CD4-positive T cells in the submandibular glands of IgG4-related disease using flow cytometry demonstrated that more than 70% of CD4-positive T cells in the affected tissues were CXCR5-positive Tfh cells (4). Among the Tfh cells in the affected tissues, the most predominant subset was Tfh2 cells in IgG4-related disease (5). The degree of Tfh cell infiltration at the lesion site of the disease correlated with the proportion of Tfh cells in the peripheral blood, suggesting that blood Tfh cells may be the mirror of those from the lesion sites. Indeed, we previously reported that the number of affected organs positively correlated with the number of blood-activated Tfh2 cells (3). The distribution of Tfh cells was different according to the affected organs; Tfh cells were located inside and outside of the tertiary lymphoid organs in orbital, salivary gland, and lymph node tissues of IgG4-related disease, whereas Tfh cells were randomly distributed in the affected pancreas. Taken together with the evidence shown by Cargill et al. (1), there is no doubt that Tfh cells play a major role in this disease.

The unresolved issues in this field are "what is the causal etiology leading to Tfh2 cell expansion in IgG4-related disease?" and "what is the molecular mechanism inducing Tfh2 cell expansion?" Further accumulation of evidence on the molecular mechanism of Tfh2 cell expansion is essential to elucidate more precise etiology and pathogenesis of this disease and affords new therapeutic targets.

CONFLICTS OF INTEREST

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