

Correspondence

The call for considering follicular helper T cells in IgG₄-related disease

To the Editor:

I read with great interest the research article by Heeringa et al¹ recently published in the *Journal*, describing the involvement of peripheral T_H2 and regulatory T cells in the pathogenesis of IgG₄-related disease (IgG₄-RD). The authors conducted for the first time a comprehensive analysis of circulating immune cell subsets and reported the significance of the modified T_H2-type response in their article, but they overlooked the importance of T follicular helper (Tfh) cells in IgG₄-RD.

Peripheral tissue of patients with IgG₄-RD contains not only fibrosis and IgG₄⁺ plasma cells but also massive lymphoid follicles in which IgG₄-class switching takes place.² Tfh cells, but not T_H2 cells, induce B-cell maturation and differentiation as well as immunoglobulin-class switching in lymphoid follicles.³ Previous studies reported that the expression of Bcl-6 (a transcription factor for Tfh cells) in peripheral tissue of IgG₄-RD was significantly higher compared with controls,² whereas that of GATA-3 (a transcription factor for T_H2 cells) was not different.⁴ These evidence suggest that not only T_H2 cells but also Tfh cells play a role in the pathogenesis of IgG₄-RD.

The strongest concern in the study by Heeringa et al is that the authors reported no increase in circulating CXCR5⁺Tfh cells in IgG₄-RD.¹ That analysis may be insufficient because the number of circulating CXCR5⁺Tfh cells tended to be higher compared with controls even though the number of examined samples of IgG₄-RD was small.¹ Furthermore, the authors also did not show circulating Tfh subsets (Tfh1, Tfh2, and Tfh17 cells) and their activated phenotype expressing PD-1.^{5,6} The significance of those Tfh-cell phenotypes in peripheral blood of IgG₄-RD was reported in recent studies,^{5,6} indicating the need to analyze those subsets in IgG₄-RD. Particularly, circulating Tfh2 cells and their PD-1⁺-activated phenotype were significantly increased in patients with IgG₄-RD, correlating with disease activity.⁵ Of note, we previously reported that Tfh2 cells from patients with IgG₄-RD actually induced naive B cells to differentiate into IgG₄-producing plasmablasts more efficiently compared with those from healthy controls.⁵ Because naive B cells do not express IgG₄ antibody, Tfh2 cells are culprit immune cell type truly inducing IgG₄ production from B cells.⁵ In fact, B cells from

patients with IgG₄-RD exhibit enhanced somatic hypermutation, indicating that those B cells are assisted by Tfh cells.⁷ IL-4 was considered to be exclusively produced by T_H2 cells for a long time, and thus T_H2 cells were misunderstood to be the primary providers of “help” to B cells. However, it is now well known that Tfh cells are the specialized providers of help to B cells.³ It should be noted that IL-4 secreted from Tfh cells but not T_H2 cells is the primary inducer for immunoglobulin-class switching.³

In conclusion, the analysis of Tfh-cell-associated molecules in the study by Heeringa et al was relatively rough compared with that reported in previous studies. Further studies are needed not to overlook the importance of Tfh cells in the pathogenesis of IgG₄-RD.

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