

Human BATF⁺ IL-4⁺ T follicular helper cells are linked to a polarized IgG4 switching event and accumulate primarily outside germinal centers in IgG4-related disease lesions

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Objective:

Although the germinal center is considered to be a major site of isotype switching, it is unclear whether class switching occurs primarily at the T-B interface outside germinal centers or within the light zone of the germinal center. We show here that IL-4 expressing T follicular helper (T_{FH}) cells are sparse in human secondary lymphoid organs and are primarily located outside germinal centers. In IgG4-related disease (IgG4-RD), a disorder characterized by polarized Ig class switching and prominent tertiary lymphoid organs, most T_{FH} cells in disease lesions make IL-4.

Methods:

We used quantitative multicolor immuno-fluorescence to identify IL-4 secreting T_{FH} cells in secondary lymphoid organs from healthy individuals and affected tissues from IgG4-RD and Sjögren's syndrome (SS) with active disease.

Results:

The relative proportion of IL-4 expressing T_{FH} cells is 10-20 fold higher in disease lesions compared to control secondary lymphoid organs. These IL-4 expressing T_{FH} cells are found in tertiary lymphoid organs but are primarily located outside germinal centers and large numbers of IgG4 expressing B cells are also seen in their vicinity. Human IL-4⁺ T_{FH} cells do not express GATA-3 but express BATF. In contrast to the situation in IgG4-RD, IL-4⁺ T_{FH} cells are rarely found in or around germinal centers in SS, a disorder in which IgG4 is not elevated. The proportion of CD4⁺ IL-4⁺ BATF⁺ T cells as well as of CD4⁺ IL-4⁺ CXCR5⁺ T cells in IgG4-RD tissues correlates tightly with tissue IgG4 plasma cell numbers and plasma IgG4 levels in patients but not with the total plasma levels of other isotypes.

Conclusions:

These data describe a T_{FH} sub-population in human tertiary lymphoid organs with IgG4-RD that is linked to a very specific Ig isotype switching event in vivo and support the view that isotype switching occurs primarily outside germinal centers.