RESEARCH HIGHLIGHT

T follicular regulatory cells keep B cell-directed autoreactivity in check

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The immune system well illustrates the need for balance between aggression and tolerance: mechanisms are needed to drive the production of antibodies effective against pathogens whilst preventing the emergence of antibodies targeting our own cells. T follicular regulatory cells can suppress spontaneous antibody-mediated autoimmunity by vetoing B cell-directed reactivity.

The protection against infection relies, to a large extent, on high-affinity antibodies that tightly bind and neutralize invading pathogens. The high affinity results from a process akin to Darwinian evolution that takes place within anatomical structures named germinal center (GC) that emerge in lymphoid tissue following infection or immunization. There, B cells with initial poor affinity undergo proliferation and mutation of the immunoglobulin genes encoding the B cell receptor (BCR) and, ultimately, the antibodies (Fig. 1). The B cells with mutated BCRs compete for antigen (the foreign molecule that triggers the antibody response). B cells with BCRs with increased affinity have an advantage in this competition and, consequently, excel in capturing and presenting portions of that antigen to specialized helper T cells named T follicular helper (Tfh) that, in turn, provide signals stimulating further proliferation and mutation of the B cell. BCRs with poor affinity lose the competition for antigen, and those B cells failing to interact with Tfh cells do not survive. These cycles of mutation and selection within the GC, ensure the survival of the fittest B cells in terms of their ability to differentiate into memory cells and plasma cells that produce high-affinity protective antibodies.

Additionally, the immune system requires mechanisms to prevent the production of antibodies that target the body's own tissues. B cells undergo multiple checkpoints during their development in the bone marrow to ensure the inactivation or elimination of self-reactive cells. However, the effectiveness is not absolute, with some surviving autoreactive B cells passing these checkpoints. Furthermore, the random BCR mutations within GCs can potentially generate cross-reactive receptors. Hence, in addition to tolerogenic mechanisms during B cell development, regulatory mechanisms operating within the GC are necessary. T follicular regulatory (Tfr) cells were identified as a subtype of Foxp3$^+$ regulatory T cells specialized in the regulation of GC responses.[1–4] To prevent the emergence of self-reactivity within the GC, it was postulated that the antigen specificity of Tfr cells was directed towards self-antigens. In contrast, the specificity of Tfh cells within the same GC was biased towards the foreign immunizing antigens.[5] Nevertheless, in addition to autoreactive Tfr cells, some Tfr subsets derived from Tfh cells and specific for the immunizing antigen were implicated in the termination of GC responses.[6–9]

GCs can also form spontaneously. These spontaneous GCs, resembling those induced by immunization, featuring GC B cells and follicular dendritic cells, have been observed in individuals and animal models with autoimmunity.[10] Now, Lin and colleagues demonstrate that GCs can develop spontaneously in non-autoimmune mouse strains during homeostasis in a T cell-dependent manner.[11] Remarkably, the B cells within the spontaneous GCs were biased towards B cell-derived autoantigen (BDA), including FcγRIIB, a low-affinity IgG Fc receptor. As FcγRIIB is constitutively expressed by follicular B cells, it becomes an abundant follicular autoantigen.

The development of spontaneous GCs depends on Tfh cells and is limited by Tfr cells. SLAM-associated protein (SAP) is essential for cognate T–B interactions and, therefore, for GC formation. SAP deficiency or CD40L blockade resulted in fewer spontaneous GCs and plasma cells, implying a dependence on Tfh cells for their formation. Importantly, Tfr cells suppressed this response, as mice lacking Tfr cells had more spontaneous GCs and plasma cells, which was accentuated in older mice, suggesting a potential age dependency.[11]

The T cell receptor (TCR) sequences from Tfh and Tfr cells within spontaneous GC demonstrated that these populations undergo greater clonal expansion than their non-follicular counterparts, suggestive of ongoing antigen stimulation.[11] Furthermore, two TCRs with identical amino acid sequences were identified in Tfh and Tfr cells, along with two abundant clones found only in Tfh cells. Retroviral transduction of those TCRs into polyclonal T cells revealed that these four TCRs selectively recognized BDAs.[11] As all B cells can potentially present BDA to Tfh cells, the fact that GCs contain Tfh cells specific for BDA provides an explanation for the occurrence of spontaneous GCs, and the requirement for Tfr-mediated regulation of BDA-specific responses.

GCs induced following immunization or infection still contained Tfh and Tfr cells with BDA-biased TCR repertoires. In accordance with previous studies showing that, in the same GC, Tfh cells have TCRs targeting foreign antigen while Tfr cells express potentially autoreactive TCRs to prevent autoreactivity,[5] the percentage of Tfh cells specific to BDA was found to be much lower than those specific to external antigens and the Tfr

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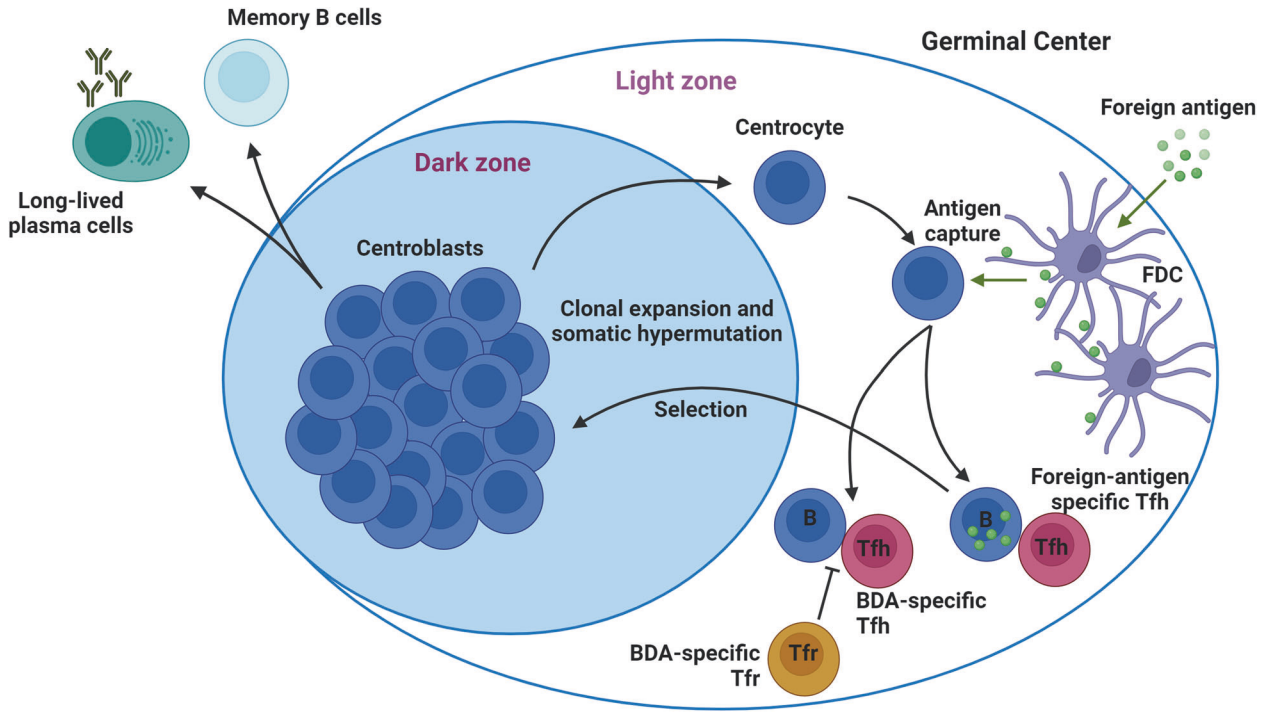

Fig. 1 Tfr cells specific for BDA suppress GC autoreactivity. Following immunization, GCs are formed where B cells undergo proliferation and mutation of their BCRs, followed by selection mediated by Tfh cells of B cells where the mutation leads to increased affinity for the foreign antigen (green). These cycles ultimately lead to production of memory B cells and long-lived plasma cells with high-affinity BCRs. However, GCs can have Tfh cells specific for BDA, antigens that any B cell can present potentially leading to spontaneous GC formation. Tfr cells specific for BDA can veto the triggering of B cell-directed autoreactivity, suppressing the emergence of spontaneous GC and GC autoreactivity.

repertoire was minimally affected by immunization.[11] Considering these findings, Tfr-mediated suppression may be primarily targeting BDA-reactivity that drives spontaneous GC, co-existing within GCs induced by immunization or infection (Fig. 1). Importantly, the Tfr-to-Tfh ratio was notably larger in spontaneous GCs compared to immunization- or infection-induced GCs, highlighting the potential significance of Tfr cells in modulating the immune response within GC when conditions favor the production of autoantibodies and the potential development of autoimmune diseases.

While the finding that Tfr cells veto Tfh-triggered B cell-directed autoreactivity is a major advance, some questions remain. Whether other GC autoantigens are equally targeted by Tfr cells, or whether BDA-specific Tfh and Tfr cells impact affinity maturation to foreign antigens remains to be addressed. What is becoming clear is the need for a combination of Tfr populations with distinct specificities and ontogeny to ensure healthy humoral responses.

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ADDITIONAL INFORMATION

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