How does T-FR limit autoreactivity despite being outnumbered in the GC?

Marta Schips[1], Tanmay Mitra[1], Michael Meyer-Hermann[1,2]
[1]Helmholtz Centre for Infection Research, Department of Systems Immunology, Braunschweig, Germany
[2]Institute for Biochemistry, Biotechnology, and Bioinformatics, Technische Universität Braunschweig, Braunschweig, Germany.
marta.schips@helmholtz-hzi.de, mmh@theoretical-biology.de

Abstract

The presence of T-follicular regulatory cells (TFRs) is critical in germinal centre (GC) to limit self-reactivity in the GC and differentiation of GC B cells into the self-reactive plasma cells. Although recent evidence is suggestive of a direct physical interaction between the GC B cells and TFRs, the exact mechanism by which TFRs mediate GC reactions and control autoimmunity is controversial and largely unknown. One critical question in this context is also the functional capability of the TFRs to limit autoreactivity despite being outnumbered as compared to T-follicular helper cells (TFHs). By invoking several phenomenological models based on different physiological mechanisms and possibilities that may govern the interactions of GC B cells with TFRs and TFHs and the resultant dynamics of the constituent cells of the GC, we investigate how the control of autoimmunity can be achieved in a physiologically realistic situation. We also analyze perturbations of the mechanisms which can lead to the loss of immunological homeostasis and contribute to the emergence of autoimmunity. Our analysis speaks in favour of a mechanism wherein the TFRs are predominantly self-specific and scan through the self-reactive centrocytes in the GC in a chemokine-dependent manner. In addition, an interaction with a TFR cell requires to invoke alteration in the intracellular signalling of the self-reactive GC B cells either by promoting the DZ phenotype, thus preventing their differentiation into self-reactive plasma cells, and/or by stopping them to acquire TFH help. The thus derived theory of control of autoreactivity in GC responses is compared to experimental readouts and we propose concluding experiments to support or contradict the theory.