Pinpointing the role of IL-21 in directing B cell fate within germinal centers

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Abstract

Abundant experimental evidence has linked defective B cell and T cell interactions with the development of autoimmunity, highlighting the importance of further investigations into pathways underpinning B cell and T cell collaboration in health and disease.
Elevated levels of the archetypal follicular helper T-cell cytokine interleukin 21 (IL-21) have been reported in many autoimmune conditions including type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus, and IL-21 has been widely shown to promote pathology in animal models. However, the underlying mechanisms of IL-21-dependent regulation of humoral immunity as well as their contribution to the development of autoimmunity remain incompletely understood.
This study homed in on the role of IL-21 in the regulation of germinal center (GC) responses. Crossing IL-21R-/- animals to mice rendered deficient for T-cell peripheral regulator CTLA-4 allowed us to investigate the contribution of IL-21 signaling to the development of chronic autoimmune GC, while a comparison of immunized wildtype and IL-21R-/- mice provided insights into IL-21-dependent regulation of transient GC responses. We were able to demonstrate that IL-21 signaling was essential for an efficient formation and expansion of the GC dark zone compartment in both settings. The GC light zone skewing observed in the absence of IL-21R expression is highly reminiscent of that reported in cyclin D3 deficient animals, and we show here that IL-21 can directly upregulate this cell cycle regulator and thereby tune dark zone inertial cycling. Furthermore, we are also able to demonstrate that IL-21 shapes the quality of the GC dark zone compartment by promoting light zone GC B cell positive selection.
Our study provides novel insights into IL-21 involvement in the regulation of GC processes that are central to the development of robust humoral immunity but that may also aid disease pathogenesis in the context of autoimmunity.