IL-21 acts beyond the immunological synapse to establish and sustain germinal center dynamics.

I. Quast[1], A.R. Dvorscek[1], C. Pattaroni[1], C.I. McKenzie[1], Z. Ding[1], T. Steiner[2], C. Pitt[1], K. O'Donnell[1], D. Hill[1], M. Robinson[1], D. Zotos[1], R. Brink[3], D.M. Tarlinton[1]

[1]Monash University, Department of Immunology and Pathology, Melbourne, Australia, Isaak.quast@monash.edu; [2]Peter Doherty Institute for Infection and Immunity, Melbourne, Australia; [3]Garvan Institute of Medical Research, Sydney, Australia.

Abstract

Germinal center (GC) formation relies on the coordinated behavior of T and B cells. The pleiotropic, T cell derived cytokine IL-21 is central to GC biology, but how it functions is incompletely understood. Here, we generated T cell- and B cell-receptor transgenic mice deficient or sufficient for IL-21 and/or IL-21R to genetically restrict production and receipt of IL-21 *in vivo*. Using this system, we reveal how the independent actions of IL-21 on T and B cells combine to regulate the GC. During response initiation, IL-21 promoted CD4 T cell expansion and Tfh differentiation in a dose-dependent, paracrine manner. Simultaneously, IL-21 activated AKT and S6 in pre-GC B cells and accelerated both their cell cycle speed and cyclic re-entry. This effect occurred over a wide range of initial B-cell receptor affinities, increasing their numerical contribution to the ensuing GC. Moreover, the size of the B cell response closely correlated with plasmablast output irrespective of IL-21, arguing against a direct role for IL-21 in early plasmablast differentiation. Within GC, IL-21 specifically promoted B cell centroblast identity and, when bioavailability was high, plasma cell output. Critically, these actions occurred outside the confines of cognate T:B interactions, making IL-21 a general promoter of growth rather than mediating affinity-driven selection. Collectively, our results highlight the unique role of IL-21 in establishing GC dynamics by controlling separately the magnitude of the initial Tfh and B cell responses. This activity, together with its promiscuous activity within GC, explains the profound consequences of IL-21 deficiency on antibody-based immunity.