# IL-21 regulates c-Myc and mTORC1 activity in Germinal Center B cells

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## Abstract

The cyclic reentry of GC B cells between the light zone (LZ) and the dark zone (DZ) is closely associated with affinity-based selection, expansion of the selected GC B cells, and apoptosis. GC B cells induce c-Myc after integrating external cues via BCR, CD40, and cytokine receptors in the LZ; these cells are authorized to migrate into the DZ and continue proliferating due to mTORC1 activity. Given that the rate of proliferation of selected GC B cells is dependent on the amount of c-Myc, progeny of c-Myc$^{hi}$ GC B cells would predominate throughout the GC reaction, resulting in the generation of affinity-matured effector B cells from them. Therefore, it is conceivable that a regulatory mechanism for determining level of c-Myc and mTORC1 activity exists, but has not yet been identified. We first indicated fewer DZ cells and a slower rate of proliferation of GC B cells in IL-21R-KO mice than those in WT upon immunization, with no impact on apoptosis. Importantly, these results were B cell intrinsic consequences of IL-21R loss, since IL-21R-KO GC B cells exhibited identical results in mixed chimera mice, implying that IL-21 plays specific functions in the cyclic reentry program. To gain more mechanistic understanding of the regulatory roles of IL-21 in GC B cells, we employed an in vitro GC B cell culture system (iGCB) and analyzed the important characteristics of a selected GC B cell, such as c-Myc expression, mTORC1 activity, and proliferation. Indeed, the level of c-Myc, mTORC1 activity, and extent of proliferation depended on the quantity of IL-21 rather than the level of CD40 or BCR. This discovery was further corroborated by the transcriptome analysis of CD40L and CD40L+ IL-21 stimulated iGC B cells, which revealed that only IL-21 stimulated iGCB cells exhibited proliferation-related gene ontology terms. In conclusion, our findings clearly support the idea that IL-21 is a key regulator of cyclic reentry via fine-tuning the amount of c-Myc, activity of mTORC1, and degree of proliferation of selected GC B cells.