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B cell Rab7 mediates induction of AID expression and class-switching in T-dependent and T-independent antibody responses (IRM10P.605)

Zheng Lou; Egest Pone; Tonika Lam; Rui Wang; Yuhui Chen; Dongfang Liu; Aimee Edinger; Zhenming Xu; Paolo Casali

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Abstract

IgH class switch DNA recombination (CSR) is central to the maturation of the antibody response, as it diversifies antibody biologic effector functions. By constructing conditional KO Igh+/Cγ1-creRab7fl/flmice, we have previously identified a B cell-intrinsic role for Rab7, a small GTPase that regulates endosome maturation, in CSR and antibody responses. In Igh+/Cγ1-creRab7fl/flB cells, Rab7 gene is ablated within 48 h of stimulation by IL-4 plus CD154 or LPS, resulting in reduced CSR to IgG1 and IgE. Here, we have addressed the mechanisms underlying the role of Rab7 in CSR. Once Rab7 was ablated, B cells were also defective in CSR to IgA, indicating that Rab7 regulates the central CSR machinery in an Ig isotype-independent manner. Indeed, expression of AID, as essential to CSR, was reduced in Rab7 KO B cells and enforced AID expression rescued CSR. Finally, super-resolution imaging of CD154-stimulated B cells revealed that Rab7 formed foci, within which CD40 was enriched. These findings, together with our demonstration that Rab7 mediated canonical NF-κB activation, as critical to AID induction, outline a novel role of Rab7 in specific signaling pathways that lead to AID expression and CSR, likely by promoting assembly of signaling complexes along intracellular membranes.