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Rab7 plays a B cell-intrinsic and critical role in T-dependent and T-independent antibody responses by mediating AID expression and class switch DNA recombination

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Abstract

Rab7 is a small GTPase that mediates endosomal functions and regulates T cell homeostasis. Here, we have addressed the B cell-inherent role of Rab7 in antibody responses and underlying mechanisms by constructing Igh+/Cγ1-cre Rab7fl/fl mice. These mice displayed normal B cell and T cell development and survival, and were knocked-out of the Rab7 gene specifically in B cells activated to undergo IgH germline Iγ1-Sγ1-Cγ1 transcription. This transcription process is induced by IL-4 plus a primary CSR-inducing stimulus, and is required for antibody switching from IgM to IgG1, but not to other Ig isotypes. Igh+/Cγ1-cre Rab7fl/fl mice had virtually abrogated levels of IgG1, but normal levels of IgM and other switched Ig isotypes, and failed to mount specific IgG1 responses to T-dependent or T-independent antigens. They showed markedly reduced IgG1+ B cells and antibody-forming cells, with unaltered B cell proliferation, survival and differentiation into germinal center B cells and plasma cells. Purified naïve B cells from these mice were defective in CSR to IgG1, despite normal proliferation and plasma cell differentiation. These together with the unaltered germline transcription but significantly decreased expression of AID (essential for CSR and SHM) demonstrate that B cell Rab7 mediates CSR and, therefore, the antibody response by upregulating AID, likely by regulating intracellular membranes that facilitate signal transduction for activation of specific transcription factors.