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Extended Abstract
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Regulation of diversification and affinity maturation of antibodies

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B-lymphocytes can modify their immunoglobulin (Ig) genes to generate antibodies with a new isotype and enhanced affinity. Activation-induced cytidine deaminase (AID) is the key mutagenic enzyme that initiates these processes. How somatic hypermutation (SH) and class switch recombination (CSR) are targeted and regulated to understand how we achieve good antibodies. The trans-acting factors mediating specific targeting of AID and thereby SH and CSR have remained elusive. How AID is recruited was still a big mystery. We show that mutant E2A transcription factor with defect inhibition by the Ca2+ sensor protein calmodulin results in reduced B cell receptor (BCR), IL4-plus CD40 ligand-stimulated CSR to IgE. AID is shown to be together with the transcription factors E2A, PAX5 and IRF4 in a complex on key sequences of the Igh locus in activated mouse splenic B cells. Calmodulin shows proximity with them after BCR stimulation. Direct protein-protein interactions are shown to enable formation of the complex. BCR signaling reduces binding of the proteins to some of the target sites on the Igh locus, and calmodulin resistance of E2A blocks this reduction. Thus, E2A, AID, PAX5 and IRF4 are components of a CSR and SH complex that calmodulin binding redistributes on the Igh locus. We present also that initiation of antibody diversification leads to formation of a mutasome, a complex between many proteins that enable repair at high error rate of the uracils made by AID on Ig genes but not on most other genes. We show also that BCR activation, which signals end of successful SH, reduces interactions between some proteins in the complex and increases other interactions in the complex with varying kinetics. Furthermore, we show increased localization of SH and CSR coupled proteins on switch regions of the Igh locus upon SH/CSR and that BCR signaling differentially change the localization.

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