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Regulation of diversification and affinity maturation of antibodies

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 is key to understanding how we achieve good antibodies. The *trans*-acting factors mediating specific targeting of AID and thereby SH and CSR have remained elusive. No direct coupling between a transcription factor and the specific targeting of AID has been demonstrated, and how AID is recruited is still a big mystery. We show that mutant E2A with defect inhibition by the Ca^{2+}-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 regulation of a "mutasome", the protein complex that enables repair at high error rate of the uracils made by AID on Ig genes but not on most other genes.

Biography

Thomas Grundström completed his doctorate at Umeå University in 1981 and his Medical degree in 1982. Dr. Grundström was post-doc 1982-1984 in the laboratory of prof. Pierre Chambon, Strasbourg, France, where he characterised the first discovered enhancer of transcription. He is professor at the department of Molecular Biology at Umeå University since 1994. Dr. Grundström discovered the first direct Ca2+/calmodulin inhibition of a transcription factor (Corneliusen et al., Nature, 1994) and has characterized the Ca2+ regulation of many regulatory proteins with a focus on the immune system. Dr. Grundström is presently studying regulation of production of high affinity antibodies.

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