

May 10-11, 2018
Frankfurt, GermanyThomas Grundstrom, J Transm Dis Immun 2018, Volume 2
DOI: 10.21767/2573-0320-C2-004

REGULATION OF DIVERSIFICATION AND AFFINITY MATURATION OF ANTIBODIES

Thomas Grundstrom

Umeå University, Sweden

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.

Biography

Thomas Grundström has completed his Doctorate at Umeå University in 1981 and his Medical degree in 1982. He was a Postdoc during 1982-1984 in the laboratory of Professor Pierre Chambon, Institut de Chimie Biologique, Strasbourg, France, where he characterized the first discovered enhancer of transcription. He is a Professor at the Department of Molecular Biology at Umeå University since 1994. He has been studying Ca²⁺ sensor proteins and eukaryotic transcription and discovered the first direct Ca²⁺/calmodulin inhibition of a transcription factor. He has characterized the Ca²⁺ regulation of many transcription factors and other regulatory proteins with a main focus on the immune system. He is presently studying regulation of production of antibodies. He studies how somatic hypermutation (SH) and class switch recombination (CSR) are targeted and the regulation of the protein complex that performs SH and CSR.

Thomas.Grundstrom@umu.se