5. Tolerisation and specificity of immunity

1 EVOLUTION OF ANTI-DNA AUTOANTIBODIES BY SOMATIC HYPERMUTATION: EVIDENCE FOR POSTMUTATIONAL B CELL TOLERANCE

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The production of autoantibodies against nuclear antigens is a hallmark of systemic lupus erythematosus (SLE). The 33.C9 anti-dsDNA antibody is of immunoglobulin G (IgG) isotype and derived from a SLE patient. Three somatic mutations of the 33.C9gl antibody are necessary and sufficient for the binding to DNA, nucleosomes and histones as the reversion of the somatic mutations to germline sequence abolished binding to all of these antigens. The same somatic mutations that generate dsDNA binding also led to binding of apoptotic cells. The authors propose that the nuclear material from apoptotic cells accumulates in the germinal centre due to a phagocytosis defect of macrophages and selects anti-DNA B cells. These data led us to the hypothesis that autoreactive B cells are generated from non-autoreactive B cells during germinal centre reactions. Then the newly generated autoreactive B cells are positively selected on nucleosomes on follicular dentritic cells. The authors want to test this hypothesis in mice, which express the 33.C9 germline variant antibody as B cell receptor (BCR) (33.C9 gl mice). To obtain mice, which express the 33.C9 germline variant antibody as BCR the authors targeted the BCR heavy- and light chain loci to obtain 33.C9gl heavy chain and 33.C9gl light chain double knockin mice. As expected, B cells expressing the revertant BCR are developing normally and show no evidence for tolerisation. Upon immunisation with a surrogate phage antigen the transgenic B cells form germinal centres and undergo somatic hyper mutation. The three critical somatic hyper mutations, which are necessary and sufficient for the acquisition of high affinity anti-dsDNA binding, were not observed in a large collection of sequences analysed. In accordance with this, anti-DNA autoantibodies do not develop, even after repetitive immunisations and when Follicular dendritic cells were MFG-E8 deficient. These results strongly suggest a self-tolerance checkpoint by deletion of autoreactive clones during or after the germinal centre reaction.