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Meeting abstract

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The inducible transcription factor NFATc1 controls the survival of germinal center B lymphocytes

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In almost all lymphocytes the three members of NFAT family of transcription factors, NFATc1, c2 and c3, are expressed. While the nuclear transport, the DNA binding and, therefore, the activity of all three NFATc members is commonly controlled by the Ca^{2+}-dependent phosphatase calcineurin, their transcriptional regulation differs from each other. In the majority of lymphocytes both NFATc2 and c3 are constitutively expressed, whereas immunoreceptor and co-receptor signals enhance rapidly the levels of NFATc1 in effector T and B lymphocytes. This results in the rapid synthesis of NFATc1/alphaA, a short NFATc1 isoform, which differs mainly by the lack of a C-terminal stretch of approximately 245 amino acid residues from other NFAT proteins. By inactivating the endogenous NFATc1 gene and re-introducing human NFATc1/alphaA into chicken DT40 B cells we show here that high NFATc1/alphaA levels protect B cells against B cell receptor-mediated AICD. Prominent target genes of NFATc1/alphaA in DT40 B cells are the Bcl-6, PKC-theta and Bag-2 genes whose expression is strongly enhanced in DT40 cells expressing human NFATc1/alphaA. The anti-apoptotic activity of NFATc1/alphaA appears to be due to an enhancement of NF-kappaB signals and of binding of NFATc1 to promoters of anti-apoptotic genes. Similar to the HIV-1 LTR and IL-8 promoters, the promoters of numerous anti-apoptotic genes contain composite kappaB/NFAT sites to which NFATc1 can bind (as homodimers, similar to NF-kappaB) in human NFATc1/alphaA expressing DT40 cells. Since NFATc1/alphaA suppresses the RNA synthesis of secreted IgM and Blimp-1 but enhances Bcl-6 and Bach-2 RNA levels, NFATc1/alphaA appears to control the affinity maturation of Ig genes in germinal center (GC) B cells. Immuno-histochemical stainings with an Ab raised against NFATc1/alpha protein shows that – in striking contrast to the cytosolic localisation of NFATc1 in the majority of lymphoid cells – NFATc1/alpha is constitutively expressed in nuclei of a subset of GC B cells, as well as in Burkitt's lymphomas which originate from GC B cells. Most of these GC B cells expressing nuclear NFATc1/alpha do not express IgM and apoptotic markers suggesting NFATc1/alpha contributes to the survival of a subset of matured GC B cells. This hypothesis is currently tested by more immunohistochemical stainings and the use of genetically modified mice carrying NFATc1 flx/flx alleles and AID- and CD23-Cre for the inactivation of NFATc1gene in GC B cells, or just before GC formation. All our data indicate that in T and GC B cells the inducible synthesis of short NFATc1/alphaA isoforms contributes to the survival of lymphocytes while – as we have shown earlier (see Chuvpilo et al., Immunity 2002) – the NFATc proteins NFATc2 and c3 support the Activation Induced Cell Death (AICD) of T (and B) lymphocytes upon TCR (BCR) stimulation.