The analysis of NF-κB pathway in B cell development, maintenance and transformation

Summary
Transcription factors of the NF-κB family play an important role in B cell maintenance. Two major pathways leading to NF-κB activation have been described, termed the canonical and alternative pathways. For canonical NF-κB activation the IKK complex, consisting of the two kinases IKK1 (IKKα) and IKK2 (IKKβ) and a regulatory subunit, termed NF-κB essential modulator (NEMO or IKKγ), phosphorylates IκB proteins at two conserved N-terminal serine residues, leading to their polyubiquitylation and destruction by the proteasome. This pathway activates predominantly heterodimers consisting of p50, RelA and c-Rel. The alternative pathway involves the proteolytic processing of p100 to p52, initiated by NF-κB inducing kinase (NIK) and IKK1, independently of NEMO, and induces mostly RelB-containing complexes. I investigate the role of NF-κB pathways in B cells through genetic loss and gain of function experiments. Inhibition of canonical NF-κB transcription factor activity through ablation of the essential adaptor NEMO arrests B cell development at the same stage as BAFF-R-deficiency. Correspondingly, activation of this pathway by the expression of constitutively active IκB kinase2 (IKK2ca) renders B cell survival independent of BAFF-R:BAFF interactions and prevents pro-apoptotic PKCδ nuclear translocation. Continuous IKK2-activity mediates expansion of individual B cell subsets, depending on signal strength. Enhanced IKK2 signaling dramatically increases B cell numbers in spleen and peritoneal cavity and sometime induces B cell lymphoma. Recently I also found that activation of alternative pathway by the expression of constitutively active NIK rescues the development of BAFF-R deficient B cells and increase B cell numbers in spleen and lymph nodes but not in peritoneal cavity.