



# CDB SEMINAR

## Yoshiteru Sasaki

The CBR Institute for Biomedical Research, Harvard Medical School

Thursday, October 26

16:00~17:00 C1F CDB Auditorium

### The analysis of NF- $\kappa$ B pathway in B cell development, maintenance and transformation

#### Summary

Transcription factors of the NF- $\kappa$ B family play an important role in B cell maintenance. Two major pathways leading to NF- $\kappa$ B activation have been described, termed the canonical and alternative pathways. For canonical NF- $\kappa$ B activation the IKK complex, consisting of the two kinases IKK1 (IKK $\alpha$ ) and IKK2 (IKK $\beta$ ) and a regulatory subunit, termed NF- $\kappa$ B essential modulator (NEMO or IKK $\gamma$ ), phosphorylates I $\kappa$ B 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- $\kappa$ B inducing kinase (NIK) and IKK1, independently of NEMO, and induces mostly RelB-containing complexes. I investigate the role of NF- $\kappa$ B pathways in B cells through genetic loss and gain of function experiments. Inhibition of canonical NF- $\kappa$ B 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 I $\kappa$ B Kinase2 (IKK2ca) renders B cell survival independent of BAFF-R:BAFF interactions and prevents pro-apoptotic PKC $\delta$  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.

#### Host:

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#### Note:

**Venue has been changed from A7F to C1F Auditorium. (Updated Oct.05)**

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