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Meeting abstract

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With a little help from a friend – CaN cooperates with Bcl-10 to activate NF-κB

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Antigen-specific stimulation of T helper cells induces activation of the main transcription factors NFAT, NF-κB and AP1 which are important for expression of cytokines such as IL-2 and IFNγ. It is known that the immunosuppressive drug Cyclosporin A (CsA) blocks the activity of the Ser/Thr phosphatase calcineurin and thereby the activation of the transcription factor NFAT. However, we observed that this drug does not only inhibit the activation of NFAT but also blocks the activation of NF-κB. In experiments dissecting the NFAT and NF-κB pathway we identified that CsA and other calcineurin inhibitors interfere with the phosphorylation of Bcl-10 induced by T cell receptor (TcR) or PMA/ionomycin stimulation of primary Th cells. CsA causes a faster degradation of Bcl10 and therefore inhibition of NF-κB activation. In contrast, CsA did not affect phosphorylation of Bcl10 induced in TNFα stimulated primary Th cells. Using immunoprecipitation we showed that calcineurin indeed interacts with Bcl-10. We hypothesize that calcineurin interacts with the CARMA/Bcl-10/MALT1 complex and dephosphorylates Bcl-10 and, thus, promotes NF-κB activation. Therefore, Calcineurin is not only a hub for NFAT but also for NF-κB activation in TcR-triggered Th cells.

Our data are used to sculpt a mathematical model because we could not cope with the complexity of the interfering signaling pathways and their kinetics. Our model predicted a complexity even higher as assumed before and showed the need of modelling to understand complex signaling processes.