Summary

Expression of IL-2 by activated T helper cells is a key event of the adaptive immune response after antigenic stimulation. The dysregulation of IL-2 is of fundamental consequence for the homeostasis of the immune system *in vivo*. While the molecular analysis of IL-2 transcriptional regulation has been extensively studied the cellular decision processes leading to IL-2 expression are not known.

In this study is shown that in human periphal $CD4^+$ Th cells the transcriptional response of IL-2 can be modulated after initial mitogenic stimulation and is followed by a binary and not a graded decision process. The titration of the Ca^{2+} ionophore ionomycin or inhibition of mitogenic stimulation by the classical calcineurin inhibitor cyclosporine A only changed the frequency of IL-2 producing cells but not the intensity of IL-2 production per cell. The molecular decision process leading to the binary IL-2 expression pattern shown here was examined for the first time and on individual cells. On this account, the IL-2 capture assay was used to separate IL-2 producing and non-producing cells after stimulation. For single cell analysis, a method for cytometrical detection of the activated transcription factors NFATc2 and NF-κB (p65) in isolated nuclei was developed.

The results proved NFATc2 as a cellular switch of Ca^{2+}/calcineurin dependent T cell activation. The IL-2 production showed great dependancy on the intracellular level of expressed NFATc2 and results in binary IL-2 expression pattern after all-or-non activation of NFATc2 in individual cells.

Graded stimulations by titration with Ionomycin or CsA lead to an all-or-non NFATc2 but graded NF-κB (p65) nuclear translocation per cell. Mathematical modeling predicts that cooperativity of at least 7 of the 13 NFATc2 dephosphorylation sites after graded stimulation by ionomycin would be sufficient to induce a binary IL-2 expression.

By translating the strength of antigenic T cell stimulation into the frequency of cytokine producing Th cells, the described NFATc2 switch is a general hub for productive adaptive immune response.