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REGULATION AND FUNCTION OF TRANSCRIPTION FACTOR NFAT IN THE CYCLOSPORIN A-SENSITIVE EXPRESSION OF CYTOLINE GENES

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Nuclear factor of activated T cells (NFAT) is a transcription factor family that plays a pivotal role in the inducible expression of many cytokine genes including IL-2, IL-3, IL-4, IL-5, TNF-α, GM-CSF. NFAT is also of interest as it has been shown to be a major target of the immunosuppressive drugs cyclosporin A and FK-506 that have revolutionized transplant sugery. The activity of NFAT proteins is tightly regulated by the Ca^{2+}/calmodulin-dependent phosphatase calcineurin. Upon the stimulation that causes intracellular Ca^{2+} mobilization, NFAT proteins present in the cytoplasm are dephosphorylated by calcineurin and subsequently translocate to the nucleus. Cyclosporin A and FK-506 prevent dephosphorylation of NFAT proteins by inhibiting phosphatase activity of calcineurin and therefore block their translocaton to the nucleus. In addition, we found that cyclosporin A also led to phosphorylation of nuclear translocated NFAT proteins, which in turn resulted in loss of its DNA-binding activity. Dephosphorylation by *in vitro* treatment with calcineurin or alkaline phosphatase restored DNA-binding activity of NFAT. These results demonstrated that dephosphorylation of NFATp is essential for DNA binding as well as its nuclear translocation. Recently, we have isolated a cDNA clone encoding a new NFAT family protein, designated NFATc.β. NFATc.β was also capable of activating transcription driven by an NFAT site in the IL-2 promoter as other family members do, but neither bound to the k3 element (an NFAT-binding site) in the TNF-α promoter nor activated the TNF-α promoter. These data suggest that distinct members or isoforms of NFAT family may regulate inducible expression of different cytokine genes.