NFAT FAMILY OF TRANSCRIPTION FACTORS AS ONCOGENE AND TUMOR SUPPRESSOR

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Nuclear factor of activated T cells (NFAT) was first described as a major activation and differentiation factor in T cells. NFAT family comprises five different proteins, NFAT1-5. Several studies *in vitro* suggest NFAT family members as redundant transcription factors. However, NFAT1-/- mice present an opposite phenotype when compared to NFAT2-/- mice, suggesting opposite roles for different NFAT members. Also, it has been shown that NFAT downregulates expression of CDK4 and cyclin A2 genes, and induce expression of cyclooxygenase-2, c-myc and cyclin D1 allowing tumor growth and survival. These data suggests that NFAT might have an important role in cell cycle regulation and tumorigenesis. Thus, our aim is to analyze the specific roles of NFAT1 and NFAT2 proteins in cell cycle control and cell transformation. We constructed retroviral vectors containing constitutively active (CA) forms of NFAT1 or NFAT2 proteins. NIH3T3 fibroblasts expressing CA-NFAT1 showed a remarkable reduction in proliferation, increased apoptotic cell death and cell cycle arrest when compared to control. Furthermore, CA-NFAT1 showed a capacity to suppress proliferation, form colonies in soft agar and reduce focus forming in focus-forming assay in H-RasV12 transformed NIH3T3. Conversely, NIH3T3 expressing CA-NFAT2 showed increased proliferation capacity when comparing to control, and also lost of contact-mediated growth inhibition and anchorage-independent cell growth. CA-NFAT2 is also able to induce cell proliferation and inhibit cell death in privation of growth factors and induce tumor growth in nude mice. Taken together, our data demonstrated a dichotomy role of NFAT family members and corroborate the oncogenic potential of NFAT2 already proposed and suggest a tumor suppressor role for NFAT1.

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