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Abstract

ERK is activated by increased intracellular calcium downstream of the hormone estrogen (E2). E2 activates ERK via the CaM Kinases, specifically CaM KK and CaM KI in MCF-7 cells. ERK may control cell growth and proliferation through Elk-1, Rsk, SRF, CREB, and numerous other molecules and nuclear targets. Vitamin D, a hormone, has proven to be an effective antagonist of ERK and MCF-7 breast cancer cell growth. Our goal was to evaluate if the E2 pathway working through CaM KK and ERK regulated the transcription factors Elk-1, CREB, and SRF. We also examined the ability of vitamin D to antagonize ERK activation of its downstream targets. Interestingly, E2 stimulation of MCF-7 cells activated both ERK and Elk-1 an effect that was blocked by inhibiting both CaM KK and ERK. E2 treatment of MCF-7 cells also triggered a significant increase in SRF and CREB phosphorlation in a CaM KK- and ERK-dependent manner. Dimerization of transcription factors may enhance DNA binding and gene expression. E2 stimulation of MCF-7 cells promoted the formation of a molecular complex between endogenous Elk-1 and SRF. Finally, E2 triggered a prolonged increased in ERK and Elk-1 phosphorylation, both of which were blocked by vitamin D treatment. Taken together our data demonstrates several transcriptional targets for E2 working through CaM KK and their inhibition by vitamin D signaling.