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14-3-3γ Binds to CaM KKα and Blocks Estrogen Signaling in MCF-7 Cells

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Abstract

Extracellular Signal-Regulated Kinase (ERK) is activated by estrogen (E2) downstream of CaM KK leading to cell growth in MCF-7 breast cancer cells. Previous studies have shown that ERK activation may be inhibited by cAMP and PKA. PKA has numerous cellular targets including CREB, Src, Raf-1, arrestins, and CaM KK. CaM KK is inhibited by direct PKA phosphorylation and the subsequent interaction with 14-3-3γ . Agonists that activate cAMP and PKA may block CaM KK activation of ERK and cell proliferation. Our goal was to evaluate the ability of cAMP and PKA to antagonize the effects of E2 on MCF-7 breast cancer cell signaling specifically, we examined CaM KK phosphorylation and inhibition. Our results suggest that activation of cAMP and PKA with Forskolin, inhibits E2 stimulation of ERK activation. E2 treatment of MCF-7 cells did not trigger PKA phosphorylation of CaM KK. Forskolin treatment of cells increased CaM KK phosphorylation and its association with endogenous 14-3-3. Interestingly, Vitamin D also enhanced 14-3-3 binding to CaM KK. Our results suggest that PKA activation, and subsequent phosphorylation of CaM KK, inhibits its activity, and associates with 14-3-3, which in turn may remove CaM KK from the ERK signaling cascade in MCF-7 cells.