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AKAP7 Regulates CaM Kinase Activation in MCF-7 Cells

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Abstract

Estrogen (E2) activates calcium/calmodulin-dependent protein kinases (CaM Kinases) in MCF-7 breast cancer cells. In particular E2 activates a CaM KK, CaM KI, and ERK pathway to promote proliferation. CaM Kinase activation of ERK may be blocked by PKA in certain cell types through direct phosphorylation and inhibition of CaM KK. The ability of PKA to phosphorylate its cellular targets may be dictated by protein kinase A anchoring proteins (AKAPs). Hormones that elevate cAMP and activate PKA may utilize AKAPs to regulate signal transduction. Our goal was to evaluate the role of AKAPs in regulating E2 activation of the CaM KK and CaM KI pathway in MCF-7 cells. We also examined the ability of vitamin D (VitD) working through cAMP and PKA to block CaM KK signaling in breast cancer cells. Our results suggest that E2 activates CaM KK and CaM KI within 5 minutes. VitD promoted PKA-dependent phosphorylation of CaM KK. VitD and epinephrine treatment of cells triggered a potent increase in cAMP levels. Interestingly, purified GST-RII pulled down both CaM KK and CaM KI. Similarly, purified AKAP7 but not AKAP5 bound CaM KK and CaM KI an effect that is enhanced with E2. Endogenous AKAP7 and CaM KK associated in E2-stimulated but not in VitD-treated cells and VitD also blocked CaM KK activation in MCF-7 cells. Our results suggest that VitD blocks E2 activation of CaM Kinases and their association with AKAP7 in MCF-7 cells.