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Estrogen Receptor Activation of CaM Kinase I and ERK

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Abstract

Cell growth and development is regulated by the cell signaling second messenger, calcium, that regulates key enzymes and genes in cells including the Calcium/Calmodulin-dependent protein kinases (CaM Ks) and their downstream target ERK. In particular, CaM KK and its substrate CaM KI promote ERK and Elk-1 activation in MCF-7 breast cancer cells. Estrogen (E2) may utilize CaM KK and ERK to promote breast cancer cell proliferation, however it is unclear which E2 receptor promotes cell proliferation through CaM Ks. Estrogen is a ligand for estrogen receptors (ER) of the alpha(α) and beta(β) forms, as well as G protein-coupled receptor 30 (GPR30). E2 has recently been shown to activate ERα and GPR30 leading to ERK activation however transgenic mice and cells that express only a membrane localized form of ERα are capable of activating ERK. The precise ER that is responsible for activating CaM KI and ERK in MCF-7 breast cancer cells remains unknown. Our goal was to evaluate which estrogen receptor controls the calcium-mediated activation of CaM KI and ERK in MCF-7 cells. E2 stimulation of MCF-7 cells potently stimulated both CaM KI and ERK phosphorylation, an effect that was blocked by the selective ERα inhibitor, MPP. MPP did not block epidermal growth factor activation of ERK. In contrast, the GPR30 antagonist, G15, did not block E2 stimulation of CaM KI or ERK. These results suggest that E2 is capable of activating CaM KI and ERK through ERα but not GPR30 in MCF-7 cells.