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CaM Kinase Kinase Control of Prostate Cancer Cell Survival

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Abstract

AKT has been implicated in promoting cell survival within certain cells. Current research has shown that hormones that increase the concentration of intracellular calcium can activate AKT that in turn leads to cancer cell survival. Interestingly, LNCaP cells express the M3-subtype of GPCR's that may couple to increases in intracellular calcium and activation of the Ca2+/Calmodulin-dependent Protein Kinases (CaM Ks). Specifically CaM Kinase Kinase (CaM KK) phosphorylates its direct substrates CaM Kinase I, CaM Kinase IV, and AKT. AKT promotes cell survival through phosphorylation of its target BAD that prevents caspase activation. Our goals were to examine the mechanism of carbachol activation of AKT and BAD in LNCaP prostate cancer cells and evaluate whether CaM Ks may be mediating carbachol's activation of AKT and cell survival. The results suggest that both AKT and BAD were phosphorylated in response to a five-minute stimulation with carbachol in LNCaP cells. AKT and BAD phosphorylation were blocked by the selective CaM KK inhibitor, STO-609, suggesting the involvement of CaM KK in the pathway. In addition, BAD phosphorylation was also blocked by treating cells with the AKT inhibitor, AKT-X. Finally, our results suggest that carbachol treatment of LNCaP cells promoted cell survival through CaM KK, AKT, and the anti-apoptotic protein, BAD.