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# CaM KK Mediates MDM2 Activation in LNCaP Cells

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Abstract

Agonists and hormones that cause an influx of calcium in LNCaP prostate cancer cells activate the calcium/calmodulin-dependent protein kinase (CaM Kinase) pathway and AKT phosphorylation. CaM KK and AKT are essential for promoting LNCaP cell survival. AKT phosphorylation of MDM2 protein may negatively regulate the tumor suppressor protein, p53. CaM KK and AKT have yet to be demonstrated as upstream regulators of MDM2 and p53 in LNCaP cells. Our goals were to examine the ability of carbachol and testosterone to stimulate MDM2 phosphorylation, its association with p53, and whether CaM KK is upstream of MDM2. Stimulation of LNCaP cells with carbachol increased MDM2 phosphorylation that was blocked by the CaM KK inhibitor, STO-609 as well as the AKT inhibitor, AKT-X. Similarly, testosterone also increased MDM2 phosphorylation through CaM KK and AKT. The requirement for CaM KK upstream of MDM2 was also examined using siRNA knockdown of CaM KK. Carbachol treatment of cells triggered phosphorylation of MDM2 that was blocked in cells transfected with siRNA against CaM KK. To assess the biochemical significance of signaling through CaM KK and MDM2 in LNCaP cells we assayed MDM2 association with p53. Carbachol stimulated MDM2 association with p53 in a manner that was dependent upon CaM KK. Our results suggest that carbachol treatment of LNCaP cells promoted phosphorylation of MDM2 and its association with p53 through CaM KK.