Checkpoint Kinase 2 and Androgen Receptor Function in Prostate Cancer.

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It has long been known that the AR is regulated not only by its cognate steroid hormone, but also by interactions with a constellation of co-regulatory and signaling molecules. Therapeutic targeting of kinase cascades may overcome compensatory signaling mechanisms that limit the effectiveness of androgen ablation. Our research suggests a CHK2–CDC25C–CDK1–AR phosphor-S308 signaling pathway in the regulation of AR activity and prostate cancer cell growth. CHK2 depletion hypersensitized prostate cancer cells to castrate androgen levels whereas CHK2 overexpression decreased cell growth. The CHK2-mediated effects on growth required the downstream signaling proteins CDC25C and CDK1. Additionally, we have established through multiple approaches that CDK1 phosphorylates the AR on S308 during the G2/M phase of the cell cycle and that AR phosphorylated on S308 is excluded from chromatin. We also found that reduced CHK2 protein levels correlated with increasing Gleason score in patient samples. CHK2 knockdown increased AR transcriptional activity on both androgen-activated and androgen-repressed genes, providing evidence that CHK2 affected prostate cancer proliferation, at least in part, through increasing AR activity. Remarkably, we further show that CHK2 is a novel AR-repressed gene, indicating of a negative feedback loop between CHK2 and AR. Additionally, we provide evidence that CHK2 kinase activity is required for this association and a CHK2 variant associated with prostate cancer has reduced AR binding. Our data substantiates a new role for CHK2 in the regulation of androgen sensitivity and prostate cancer growth, and directly links a critical member of the DDR with AR-mediated transcription and proliferation in prostate cancer. These findings are clinically relevant since several CHK and second-generation CDK1 inhibitors are in clinical trials and the CHK2 signaling pathway is activated in response to radiation-induced DNA damage. These data may assist in the rational application of existing therapies and lead to the development of novel prostate cancer therapeutics.

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