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## JOURNAL ARTICLE

# Androgen receptor regulation of G1 cyclin and cyclin-dependent kinase function in the CWR22 human prostate cancer xenograft

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Human prostate cancer is initially dependent on androgens for growth, and androgen-dependent cells undergo apoptosis after castration.

However, a subset of androgen-responsive cells survives and eventually proliferates in the absence of testicular androgen. The high levels of androgen receptor in both androgen-dependent and recurrent tumors led

us to investigate androgen regulation of cell cycle proteins in human prostate cancer using the CWR22 xenograft. Cellular proliferation decreased dramatically in CWR22 tumors after castration. Testosterone propionate (TP) treatment of castrated mice restored cellular proliferation after 24-48 hours. Growth of CWR22 tumors in the absence of testicular androgen recurred several months after castration. CDK1 and CDK2, and cyclin A and cyclin B1 messenger RNAs were decreased 6 days after castration, increased 6-12 hours after TP treatment, and were expressed at high levels in recurrent CWR22 tumors. Coimmunoprecipitated cyclin B1/CDK1 and cyclin D1/CDK4 protein complexes decreased after castration and increased after TP treatment of castrated mice. In addition, CDK1 and CDK2 kinase activities were upregulated by androgen in parallel with hyperphosphorylation of retinoblastoma (Rb) protein. Despite the absence of testicular androgen in recurrent CWR22, the levels of these androgen-regulated cyclin/CDK protein complexes and hyperphosphorylation of Rb were equal to or greater than in tumors from intact mice. The results indicate that androgen receptor regulates cellular proliferation by control of CDK and cyclins at the transcriptional level and by post-translational modifications that influence cell cycle protein activity.

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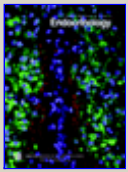
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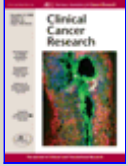
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