

## **Deregulation and function of the FOXO1 tumor suppressor in prostate cancer**

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Forkhead box O (FOXO) transcription factors are critical regulators of diverse cellular processes, including apoptosis, cell cycle arrest, DNA damage repair and oxidative stress resistance. Our laboratory has been focusing on how the potent functions of FOXO1, a key member of the FOXO family, is deregulated in prostate cancer. Our studies demonstrated that the tumor suppressor function of FOXO1 is inhibited by androgen signaling and Skp2-mediated proteasome ubiquitination degradation. We also showed that the activity of FOXO1 is inhibited by phosphorylation promoted by cyclin dependent kinases CDK1 and CDK2 and that this phosphorylation functions a critical molecular switch in mediating DNA damage-induced apoptosis. We demonstrated recently that in a manner independent of CDK4 and CDK6 cyclin D1 directly interacts with and inhibits FOXO1. More importantly, cyclin D1-FOXO1 interaction blocks FOXO1-mediated anoikis, a specific form of apoptosis induced by cell detachment. Additionally, we discovered that FOXO1 possesses a transcriptional independent function in inhibiting androgen-independent activation of the androgen receptor in prostate cancer cells and that this function also plays an essential role in inhibition of the androgen receptor induced by the chemotherapeutic agent taxol. Our findings and those from other groups suggest that deregulation of FOXO proteins may play an important role in development and progression of prostate cancer and that they may be targeted for effective therapy of advanced prostate cancer.