# Testosterone induces DNA damage signaling in response to oxidative stress in prostate cancer cells

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Introduction: In prostatic tissues, DNA damage response is specially activated in prostatic intraepithelial neoplasias (PINs) that are generally regarded as precursors of prostate cancer. The process of oncogenic transformation leads to enhanced DNA damage and activates the checkpoint network as an inducible barrier against cancer progression. In this study we analyzed the effects of testosterone under oxidative stress in DNA damage response to understand the biological function and the network of this signaling.

Methods: We tested the expression level of PSA and the activation of DNA damage response proteins including ATM (ataxia-telangiectasia-mutated kinase), H2AX (histone H2AX variant) and Chk2 (checkpoint kinase2) in prostate cancer cell lines (LNCaP and PC-3) with various concentration of H2O2. Apoptosis is quantified by flow cytometry and caspase-3 cleavage.

Results: H2O2 induces apoptosis and the phosphorylation of ATM, H2AX and Chk2 in LNCaP cells. ATM inhibitor Ku55933 can block the phospholyration of H2AX and Chk2, but induced the activation of alternative pathways, p38 and ERK. Activation of DNA damage response and caspase-2 cleavage was increased by testosterone. H2O2 did not induce phosphorylation of ATM, CHK2 and H2AX in PC-3 cells because of losing their expression. ATM inhibitor Ku55933 can reduce the apoptotic cells in LNCaP cells but PC-3 cells by the treatment of H2O2.

Conclusion: Oxidative stress has been associated with tumor formation. On the other hand, DNA damage pathway plays important roles in the maintenance of the cell homeostasis in response to oxidative stress. Our results indicate that androgen signaling have important roles in prostate carcinogenesis through DNA damage response pathways.