

Promotion of bladder cancer development and progression by androgen receptor signals

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摘要

Abstract

BACKGROUND: Males have a higher incidence of bladder cancer than females, but the reason remains unknown. Unlike prostate cancer, human bladder cancer is not generally considered to be dependent on hormone activity. We investigated the possible involvement of androgens and the androgen receptor (AR) in bladder cancer. **METHODS:** We used N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) to induce bladder cancer in wild-type male and female mice, with and without castration in males, and in AR knockout (ARKO) male and female mice, with and without dihydrotestosterone (DHT) supplementation in males. We also treated human bladder cancer cell lines, including TCC-SUP and UMUC3, and mouse xenograft models established from these same lines with androgen deprivation therapy (antiandrogen treatment or castration), AR-small-interfering RNA (AR-siRNA), or the anti-AR molecule ASC-J9, which causes selective degradation of the AR. **RESULTS:** More than 92% of wild-type male and 42% of wild-type female mice treated with BBN eventually developed bladder cancer, whereas none of the male or female ARKO mice did. Treatment with BBN induced bladder cancer in 25% of ARKO mice supplemented with DHT and in 50% of castrated wild-type male mice. Androgen deprivation of AR-positive human bladder cancer cells by androgen depletion in vitro or castration in mice and/or by treatment with the antiandrogen flutamide in vitro or in vivo, as well as AR knockdown by AR-siRNA or by ASC-J9, suppressed cell proliferation in vitro and xenograft tumor growth in vivo. **CONCLUSIONS:** Our findings implicate the involvement of both androgens and the AR in bladder cancer. Targeting AR and androgens may provide novel chemopreventive and therapeutic approaches for bladder cancer.