actions in prostate cancer cells. Mitchell et al. (Cancer Res. 59:5892, 1999) reported that resveratrol inhibits the growth of androgen responsive LNCaP prostate cancer cells and downregulates transcripts for androgen receptor (AR) and ARA70, a nuclear receptor co-activator with a predilection for the AR. This co-activator can potentiate the transactivational effects of the AR by up to 40-fold. Two ARA70 variants have been described based on RT-PCR using T47D breast cancer cells: ELE1α, a full-length isoform, and ELE1β, a splice variant with an internal 985bp deletion. PC-3 prostate cancer cells lack the AR but when transfected with AR cDNA secrete prostate specific antigen (PSA) and human kallikrein 2 (hK2) in response to dihydrotestosterone (DHT) treatment. To further explore the anti-androgenic effects of resveratrol, we examined its ability to modulate DHT-induced PSA and hK2 secretion and expression of ARA70 variants in PC-3 cells stably transfected with a full-length AR cDNA (PC-3(AR)2). Resveratrol alone (up to 100 μM) had no effect on PSA or hK2 secretion. However, at low concentrations (1 μM) resveratrol increased PSA and hK2 secretion following 1 nM DHT treatment, while higher concentrations (10 - 100 μM) caused a dose-dependent decrease in DHT-induced secretion. As we have previously reported, DHT treatment inhibited the proliferation of PC-3(AR)2 cells and this was not altered by concomitant resveratrol treatment. In fact, decreased cell proliferation was also observed following resveratrol treatment at concentrations ≥10 μM. As expected, resveratrol treatment did not alter steady state levels of AR mRNA in these cells. However, a decrease in the ratio of ELE1α/ELE1β protein expression was observed following treatment with either DHT or resveratrol (1-25 μM). Binding displacement assays indicated that resveratrol interferes with AR binding but only at concentrations greater than 10 μM. These findings indicate that resveratrol has dose-dependent effects upon androgen-induced PSA and hK2 secretion that do not appear to be mediated by direct interaction with the AR. Further studies to determine the impact of altering the expression of ARA70 variants are in progress.

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Differential Expression of Two Androgen Receptor Associated Protein 70 (ARA70) Isoforms Induced by Androgen and Resveratrol in Androgen Receptor Transfected Human Prostate Cancer PC-3 Cells.

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Resveratrol, a natural compound found in some red wines, has generated interest as an anticancer agent. In addition to its antioxidant properties and inhibitory effects on cyclo-oxygenase activity, resveratrol has been suggested to have anti-androgenic