

# Combinatorial strategy of epigenetic and hormonal therapies: A novel promising approach for treating advanced prostate cancer

Heba Darwish, Tarek K. Motawi, Iman Diab, Maged W. Helmy, Mohamed H. Noureldin

## Abstract

### Aims

Estrogens act as key factors in prostate biology, cellular proliferation and differentiation as well as cancer development and progression. The expression of estrogen receptor (ER)- $\alpha$  appears to be lost during prostate cancer progression through hypermethylation mechanism. Epigenetic drugs such as 5-aza-4-deoxycytidine (5-AZAC) and Trichostatin A (TSA) showed efficacy in restoring ER $\alpha$  expression in prostate cancer cells. This study was designed to explore the potential anti-carcinogenic effects resulting from re-expressing ER $\alpha$  using 5-AZAC and/or TSA, followed by its stimulation with Diarylpropionitrile (DPN), a selective ER $\alpha$  agonist, in prostate cancer cell line PC-3.

### Main methods

Cells were treated with 5-AZAC, TSA, DPN and their combination. Subsequently, they were subjected to proliferation assays, determinations of ER $\alpha$  expression, protein levels of active caspase-3, cyclin D1,  $\beta$ -catenin and VEGF.

### Key findings

Treatment with these drugs exhibited an increase in ER $\alpha$  expression to different extents as well as active caspase-3 levels. Meanwhile, a significant reduction in cyclin D1, VEGF and  $\beta$ -catenin levels was achieved as compared to the vehicle (p < 0.05). Interestingly, the triple combination regimen led to the most prominent anti-tumor responses in terms of increased apoptosis, reduced proliferation as well as angiogenesis.

### Significance

The results support the notion that ER $\alpha$  acts as a tumor suppressor protein and suggest that sequential ER $\alpha$  expression and activation can offer significant anti-tumor responses. The study highlights that the strategy of merging epigenetic and hormonal therapies may be beneficial in treating advanced prostate cancer.

*Life Sciences* 2018, April