

P034 TIMP-3 expression in prostate stromal and tumour cells is regulated by androgen and TNF

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Tissue inhibitor of metalloproteinases-3 regulates the activity of metalloproteinases such as MMP's, ADAMs and ADAMTSs. It is sequestered in the ECM via its C-terminal domain. Prostate cancer cells are initially dependent on androgens for growth, but become androgen-independent as the disease progresses. Elevated serum levels of TNF have been reported in patients with advanced prostate cancer.

We have analysed the expression levels of TIMP-3 in prostate stromal and cancer cells, and investigated the effects of dihydrotestosterone (DHT) and TNF on its expression using (q) RT-PCR and western blotting. Prostate cancer and stromal cells were treated with TNF, DHT, and the androgen receptor antagonists Flutamide and Bicalutamide.

Stromal cells produced 90- and 45,000-fold higher levels of TIMP-3 mRNA than androgen-dependent (LNCaP) and -independent (PC3) prostate cancer cells, respectively. This expression was down-regulated by DHT in LNCaP cells and was negligible in PC3 cells. This effect was not reversed by Flutamide or Bicalutamide. TNF treatment resulted in a 70% down-regulation of TIMP-3 mRNA in stromal cells.

DHT and TNF decrease the expression of TIMP-3 in prostate cancer and stromal cells. This will favour increased metalloproteinase activity and subsequent tumour progression.