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PROSTATE CANCER

Staying grounded — flightless-1 is a tumour suppressor

> "...(FLII) has a tumour-suppressive role in prostate cancer and acts via AR signalling..."

Protein flightless-1 homologue (FLII) has a tumour-suppressive role in prostate cancer and acts by mediating androgen receptor (AR) signalling, according to new research published in *Clinical Cancer Research*.

In silico analysis of sample and follow-up data from 150 men with prostate cancer showed that patients with high levels of *FLII* tumour expression had significantly better overall survival than those with low expression ($P = 0.049$) and that tumour tissue expressed decreased levels of FLII compared with adjacent normal prostate tissue. FLII expression was also observed to be inversely correlated with PSA expression in prostate cancer tissue, indicating that FLII might act through the androgen–AR signalling pathway.

In vitro examination of the interaction between FLII and the AR revealed that the ligand-binding domain of the AR is needed for FLII to bind and that dihydrotestosterone (DHT) competes with FLII for the AR binding site. Overexpression of FLII decreased DHT-induced AR translocation to the nucleus and FLII depletion increased nuclear AR localization. Treatment of cells with bicalutamide, which prevents androgen binding to the AR by blocking AR binding sites, promoted FLII binding and mitigated DHT-mediated effects. Increased expression of FLII also enhanced the sensitivity of castration-sensitive LAPC-4 cells to enzalutamide and bicalutamide, and in castration-resistant C4-2 cells it reversed resistance to these agents. Knockdown of endogenous *FLII* increased basal levels of DHT-induced PSA and TMPRSS2 and increased levels of AR, and also increased cell growth, migration and invasiveness, whereas *FLII* overexpression inhibited growth — an effect that was negated by knock down of AR.

In vivo, cell-line-derived xenografts with stable knockdown of *FLII* had increased levels of PSA, AR and Ki67, and xenografts that overexpressed FLII had decreased PSA levels.

These data provide evidence that FLII has to tumour-suppressive role in prostate cancer and acts via AR signalling. Enhancing FL11 expression has the potential to reverse resistance to endocrine therapies in this disease.

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ORIGINAL ARTICLE Wang, T. *et al.* Flightless I homolog represses prostate cancer progression through targeting androgen receptor signaling. *Clin. Cancer Res.* http://doi.dx.org/10.1158/1078-0432.CCR-15-1632