PROSTATE CANCER

PTEN loss and PSGR overexpression promote cancer progression

The development of a new mouse model by Rodriguez *et al.* has provided insights into the synergistic action of prostate-specific G-protein-coupled receptor (PSGR) overexpression and phosphatase and tensin homologue (PTEN) loss in the progression of prostate cancer.

“...a synergistic mechanism between PTEN and PSGR in prostate cancer...”

PTEN is the most frequently deleted tumour-suppressor gene in prostate cancer and its loss predicts poor prognosis and progression to a castration-resistant phenotype. Rodriguez and colleagues observed that *PTEN* was deleted or mutated in 21% of prostate cancers according to TCGA analysis. Conversely, PSGR is overexpressed in prostate tumours and expression levels correlate with cancer progression; when the team investigated genomic data sets they found that four of 10 displayed PSGR upregulation.

They then investigated how these two lesions collaborate to enhance prostate cancer development, creating a bigenic mouse model that overexpresses human PSGR with a conditional *Pten* knockout. Analysis at 12 months showed that the prostates of these double-mutant mice had a deformed structure and occlusion of the adjacent seminal vesicles. Ki67 staining revealed increased cell proliferation in prostate tissue. Invasive prostate tumours that featured Akt activation, infiltration by inflammatory cells and loss of E-cadherin had also developed. Further study revealed that stromal androgen receptor (AR) expression was increased. This increase might indicate that nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) activity is upregulated as a consequence of PSGR overexpression, as it regulates stromal AR expression. These data suggest the possibility of a synergistic mechanism between PTEN and PSGR in prostate cancer progression.

In vitro, PSGR overexpression affected oncogenic properties of cells directly and

indirectly. PSGR-overexpressing LNCaP cells (which have an inactivating mutation in *PTEN*) showed increased proliferation, whereas LNCaP cells with PSGR knockdown showed decreased proliferation and cell migration. Coculturing LNCaP cells that overexpress PSGR with stromal WPMY-1 cells and Raw264.7 macrophages induced stromal AR expression and a further increase in PSGR, suggesting that intercellular crosstalk can occur.

These results suggest that loss of *Pten* and overexpression of PSGR, which occur together in the majority of prostate cancers, act synergistically to accelerate tumour development. A new model is also described that will enable investigation of the collaboration between these two lesions in the context of prostate cancer.

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Original article Rodriguez, M. *et al.* Prostate-specific G-protein-coupled receptor collaborates with loss of PTEN to promote prostate cancer progression. *Oncogene* doi:10.1038/onc.2015.170