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PROSTATE CANCER

Notching up roles in advanced disease

> NOTCH1 synergizes with multiple oncogenic pathways

Neurogenic locus notch homolog protein 1 (NOTCH1) is highly expressed in localized high-risk prostate cancers and also metastatic castration-resistant prostate cancer (mCRPC). When chronically activated, NOTCH1 synergizes with multiple oncogenic pathways and promotes metastatic progression of prostate cancer. This signalling axis is a potential therapeutic target in advanced disease.

Stoyanova and colleagues first assessed differences in NOTCH1 expression between benign prostate tissue and prostate cancers at various stages of progression, including low-risk, intermediate-risk, and high-risk tumours, and also CRPC. Immunostaining for notch intracellular domain (NICD1), which is released and translocates to the nucleus after NOTCH1 cleavage where it acts as a transcriptional coactivator, was increased in high-risk disease and CRPC. Levels of NICD1 were also increased in these samples according to western blot analysis, suggesting it has a role in cancer progression.

The investigators then sought to determine whether NICD1 synergizes with known early genetic alterations that occur in prostate cancer using *in vivo* mouse models of phosphatase and tensin homolog (PTEN) loss and activation of the Ras–Raf–mitogen-activated protein kinase (MAPK) signalling pathway. Overexpression of NICD1 alone was not sufficient to initiate prostate cancer development, but it strongly synergized with myrAKT (mimicking PTEN loss), $KRas^{G12D}$ (which causes Ras–Raf–MAPK activation), and myc proto-oncogene protein (MYC) to cause prostate adenocarcinoma.

Tumours that developed in these models were highly proliferative, exhibited androgen receptor expression, loss of p63 expression, and had high self-renewal activity and metastatic potential. Cells derived from these hormone-naive tumour models were transplanted into immunocompromised mice, which were then surgically castrated. The tumours that developed from these cells continued to grow after androgen deprivation, indicating a castration-resistant phenotype. Gene-set enrichment analysis showed that genes associated with epithelial–mesenchymal transition were enriched.

In vitro, inhibiting γ-secretase, which cleaves NOTCH cell-surface receptors resulting in NICD1 moving to the nucleus, inhibited prostate cancer cell line growth and colony formation. Knocking out NOTCH1 also inhibited cell growth in 22Rv1 cells. *In vivo*, NOTCH1 inhibition reduced tumour growth.

These data provide evidence that NICD1 synergizes with many pathways implicated in prostate cancer progression and that NOTCH1 is a promising therapeutic target for patients with mCRPC.

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ORIGINAL ARTICLE Stoyanova, T. *et al.* Activation of Notch1 synergizes with multiple pathways in promoting castration-resistant prostate cancer. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1614529113 (2016)