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PROSTATE CANCER

Box clever — YB-1 has a role in CRPC

New data from a kinome array study, published in the *Journal of National Cancer Institute*, has revealed the kinome of castration-resistant prostate cancer (CRPC) and identified kinases that are involved in Y-box-binding protein-1 (YB-1, also known as nuclease-sensitive element-binding protein 1) phosphorylation. This modification has a role in the progression of prostate cancer to castration resistance and YB-1–ribosomal s6 kinase (RSK) signalling is known to be involved in the regulation of androgen receptor (AR) splice variants.

In vitro analysis of the kinome of androgen-sensitive LNCaP and castration-resistant derivatives of LNCaP cells, called LNCaP-CxR cells, revealed that the top 30 phosphorylation sites were increased in LNCaP-CxR cells. Assessment of the phosphorylation status of these kinases showed that extracellular signal-regulated kinase (ERK)1/2 and RSK1 were hyperphosphorylated in LNCap-CxR cells. Screening revealed that YB-1 is the direct substrate of these kinases and that its phosphorylation is increased in castration-resistant cells, indicating that the ERK–RSK–YB-1 phosphorylation cascade is activated in CRPC cells.

Investigation of other prostate cancer cell lines showed that YB-1 phosphorylation was most pronounced in castration-resistant 22Rv1 cells and this cell line was the only one to express the AR variant AR-V7. Knockdown of *YBX1* significantly decreased protein and messenger RNA (mRNA) levels of AR-V7 in these cells, but had no effect on full-length AR, whereas YB-1 overexpression increased AR-V7 levels. Treatment of 22Rv1 cells with the RSK inhibitor SL0101 decreased YB-1 phosphorylation and AR-V7 protein and mRNA levels; however, levels of YB-1 and full-length AR were unaffected. Enzalutamide treatment induced RSK1 phosphorylation followed by YB-1 phosphorylation, which resulted in transcriptional increases in full-length *AR* and *AR-V7*. Combination of enzalutamide treatment with *YBX1* knock down or SL0101 augmented the effects of enzalutamide on cell proliferation.

In vivo, tumours from LNCaP xenograft mouse models of progression to castration resistance showed increased *YBX1* and YB-1 expression and YB-1 phosphorylation. Full-length AR and AR variant protein and mRNA levels were also increased in these tumours. Analysis of tumour samples from men with metastatic prostate cancer who had received primary androgen-deprivation therapy (ADT) showed that polymorphism in *YBX1* rs12030724 is associated with YB-1 expression in prostate cancer tissues and could be a predictive biomarker for ADT.

These results suggest that YB-1 is a promising target in the quest to prevent castration resistance in prostate cancer, even when AR variants are expressed, and *YBX1* polymorphism at rs12030724 could be a predictive biomarker of ADT success.

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ORIGINAL ARTICLE Shiota, M. *et al.* Potential role for YB-1 in castration-resistant prostate cancer and resistance to enzalutamide through the androgen receptor V7. *J. Natl Cancer Inst.* http://dx.doi.org/10.1093/jnci/djw005 (2016)