

 PROSTATE CANCER

BRN2 is a neuroendocrine driver

The neural transcription factor BRN2 is a driver of neuroendocrine differentiation and tumour growth under androgen receptor (AR) control, according to a recent study in *Cancer Discovery*.

“Neuroendocrine prostate cancer (NEPC) is a highly aggressive subtype of castration-resistant prostate cancer (CRPC), which is characterized by loss of AR signalling and expression of neuroendocrine lineage markers, with an extremely poor prognosis,” corresponding author Amina Zoubeidi told *Nature Reviews Urology*. “Androgen pathway inhibitors (APIs), such as enzalutamide, have become commonplace in the treatment of CRPC; however, resistance to such therapies can rapidly develop and can be a precursor to differentiation into NEPC. Small-cell morphology, neuroendocrine markers, and reduced AR expression and activity are all hallmarks of the NEPC subtype.

In order to determine how this change occurs, Zoubeidi’s team developed a preclinical mouse model of API resistance and used RNA sequencing to identify transcription factors and drivers associated with NEPC development. Their studies showed that the neural POU-domain transcription factor *BRN2* was strongly upregulated in enzalutamide-resistant

tumours. Validation in other models supported the hypothesis that BRN2 expression is associated with neuroendocrine differentiation.

They then tested human prostate tumour samples, and found that *BRN2* expression was higher in NEPC tumours than in CRPC or adenocarcinoma. Silencing and knockdown of *BRN2* or its deletion using CRISPR-Cas9 prevented an enzalutamide-induced increase in NEPC markers, confirming that BRN2 is required for NEPC development. Furthermore, the team identified the AR as a direct transcriptional repressor at the *BRN2* locus, linking AR inhibition to *BRN2* expression and, therefore, progression to CRPC-NE.

Zoubeidi concludes: “These seminal findings highlight BRN2 as a principal driver of CRPC-NE, and targeting BRN2 has the potential to ameliorate, and possibly even cure, the disease.”

Annette Fenner

ORIGINAL ARTICLE Bishop, J. L. et al. The master neural transcription factor BRN2 is an androgen receptor suppressed driver of neuroendocrine differentiation in prostate cancer. *Cancer Discov.* <http://dx.doi.org/10.1158/2159-8290.CD-15-1263> (2016)

FURTHER READING Nadal, R. et al. Small cell carcinoma of the prostate. *Nat. Rev. Urol.* **11**, 213–219 (2014)