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PROSTATE CANCER

SRRM4 drives NEPC progression

The RNA splicing factor SRRM4 drives progression of neuroendocrine prostate cancer (NEPC) and is a potential therapeutic target, say researchers.

Next-generation androgen receptor pathway inhibition (ARPI) is associated with improved survival in castration-resistant prostate cancer (CRPC), but might result in progression to aggressive NEPC, which is not responsive to ARPI, probably through a transdifferentiation mechanism. Expression of several genes is correlated with NEPC, but none have been established to drive NEPC transdifferentiation. The authors of the new study say that although transcriptomic studies can identify genes associated with NEPC progression, analysis of NEPC-specific alternative splicing (AS) signatures to identify RNA splice factors might identify new mechanisms of NEPC progression.

Li *et al.* developed the comparative alternative splicing detection (COMPAS) tool in order to analyse alternative splicing on RNA sequencing data extracted from prostate tumours from two different cohorts: the Beltran cohort (27 adenocarcinoma prostate cancer and five NEPC patient samples) and the Vancouver Prostate Centre (VPC) cohort (three patient samples from patients undergoing radical prostatectomy and nine patient-derived xenografts).

In both cohorts, the researchers showed differential expression of many genes and differences in AS events between NEPC and prostate adenocarcinoma samples. They found that the Beltran and VPC cohorts shared 24 NEPC-specific AS events. 16 of the 24 AS events were predicted to be regulated by SRRM4. *SRRM4* was one of the most significantly upregulated genes in NEPC in both cohorts, and was negatively associated with expression of *REST*, a negative master regulator of neurogenesis. "These findings suggest a possible role for SRRM4 in driving NEPC transdifferentiation through regulating *REST* expression," say the authors. *In vitro* studies showed that SRRM4 stimulated adenocarcinoma cells to express NEPC biomarkers, an effect exacerbated by ARPI. The researchers also demonstrated that SRRM4 alters the morphology of epithelial prostate cancer cells. Loss of function of *TP53* enhanced the actions of SRRM4.

"It is anticipated that NEPC will become more prevalent with widespread adoption of potent ARPI for CRPC," the authors comment. "Consequently, better understanding of the molecular mechanisms by which NEPC develops is necessary to design therapeutic strategies for NEPC."

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ORIGINAL ARTICLE Li, Y. *et al.* SRRM4 drives neuroendocrine transdifferentiation of prostate adenocarcinoma under androgen receptor pathway inhibition. *Eur. Urol.* http://dx.doi.org/10.1016/j.eururo.2016.04.028 (2016)