IN BRIEF

PROSTATE CANCER

Different FOXA1 classes drive prostate cancer

New data, published in *Nature*, show that forkhead box protein A1 (FOXA1) alterations in prostate cancer can be categorized into three distinct structural classes. Analysis of an aggregate cohort of 1,546 prostate cancers showed that these three classes have a collective incidence of 35% but divergent clinical incidence and genetic co-alteration profiles. Class 1 activating mutations occur early in disease, acquisition of class 2 activating mutations occurs in metastatic disease and class 3 genomic rearrangements are enriched in metastatic prostate cancer. Improved understanding of the mechanisms and the roles of the classes of FOXA1 in the initiation and/or progression of prostate cancer provides a rationale for therapeutic targeting of this transcription factor.

ORIGINAL ARTICLE Parolia, A. et al. Distinct structural classes of activating FOXA1 alterations in advanced prostate cancer. *Nature* **571**, 413–418 (2019)

KIDNEY CANCER

One-carbon metabolism in RCC

The mitochondrial enzyme MTHFD2, which is involved in one-carbon metabolism, has been shown to contribute to the progression of renal cell carcinoma (RCC). MTHFD2 expression was significantly increased in human RCC tissues and MTHFD2 knockdown considerably reduced xenograft tumour growth. MTHFD2 was found to have a crucial role in controlling global N^6-methyladenosine methylation levels. It promotes the methylation of *HIF2A* mRNA, enhancing translation and promoting aerobic glycolysis. These data link one-carbon metabolism to HIF2α-dependent metabolic reprogramming in RCC. Furthermore, MTHFD2 and HIF2α promote metabolic reprogramming and tumour growth by forming a positive feedforward loop.

ORIGINAL ARTICLE Green, N. H. et al. MTHFD2 links RNA methylation to metabolic reprogramming in renal cell carcinoma. *Oncogene* https://doi.org/10.1038/s41388-019-0869-4 (2019)

BLADDER CANCER

Priming antitumour immunity in NMIBC

The CANON trial, a window of opportunity phase I study of CAVATAK in non-muscle-invasive bladder cancer (NMIBC) has shown promising results. CAVATAK is a novel bio-selected formulation of coxsackievirus A21 (or CVA21). This study included 15 patients, the first 9 of whom received intravesical CAVATAK as monotherapy. The subsequent 6 participants received CAVATAK in combination with a subtherapeutic dose of mitomycin C. Primary end points were patient safety and maximum tolerated dose. Secondary end points were evidence of viral replication, inflammatory cytokine induction, antitumour activity and changes induced by the virus in resected tumour tissue. The induction of tumour inflammation and haemorrhage showed the clinical activity of CAVATAK after a single dose or multiple administrations; complete resolution was seen in one patient. CAVATAK had an acceptable safety profile, with no substantial toxic effects reported. Alone or in combination, CAVATAK caused notable inflammatory changes in NMIBC tissue, upregulating interferon-inducible genes including PD-L1 and LAG3. These data suggest that CAVATAK could be a novel therapeutic for NMIBC and can also increase immunological heat in NMIBC.

ORIGINAL ARTICLE Annels, N. E. et al. Viral targeting of non-muscle invasive bladder cancer and priming of anti-tumour immunity following intravesical coxsackievirus A21. *Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-18-4022 (2019)

PROSTATE CANCER

AVPR1A: a target in CRPC?

Drugs targeting the arginine vasopressin receptor 1A (AVPR1A) could be repurposed for use in patients with castration-resistant prostate cancer (CRPC), according to a study in *Science Translational Medicine*.

Gene expression profiling of CRPC cells has identified *AVPR1A* as a dual target gene of androgen receptor variant 7 (AR-V7), which is constitutively active and acts as a potential driver of resistance, and its coactivator VAV3. *AVPR1A* copy number amplification is often observed in CRPC, and *AVPR1A* mRNA is increased in advanced prostate cancer compared with primary disease. AVPR1A targeting could, therefore, be a therapeutic option; an AVPR1A antagonist, relcovaptan, has been shown to be safe and efficacious in clinical trials for various disorders.

Based on these data, a team from Florida investigated the role and targeting of AVPR1A in CRPC. First, they used gene expression profiling in the CRPC cell line 22Rv1 to show that *AVPR1A* was the most downregulated gene after either VAV3 or AR-V7 depletion; a finding validated using VCaP xenografts in castrated severe combined immunodeficiency (SCID) mice. These data were in accordance with examination of publicly available data sets, which showed that *AVPR1A* mRNA is increased in advanced tumours and CRPC compared with primary tumours. Furthermore, AR^+ CRPC cell lines expressed detectable *AVPR1A* mRNA, which was not detected in AR^- cell lines or nonmaligant prostate epithelial cells.

Depletion of *AVPR1A* mRNA in *AVPR1A*-expressing CRPC cells decreased cellular proliferation; investigation of cyclin A and cleaved poly(ADP-ribose) polymerase (PARP) expression suggested that both apoptosis and cell cycle regulation might be implicated in this effect.

Stable expression of AVPR1A in androgen-dependent LNCaP cells caused them to grow rapidly in castration conditions. To demonstrate this effect in vivo, the team injected these cells into castrated nude mice and observed that $AVPR1A^+$ tumours grew faster than controls.

They then used a preclinical xenograft model that recapitulates prostate cancer progression to study AVPR1A antagonism as a therapeutic approach. Relcovaptan administered to xenografted mice whose tumours had acquired castration resistance halted tumour growth and stabilized circulating PSA, as well as reducing Ki67 and downregulating cyclin A. Relcovaptan also reduced growth of established CRPC xenograft tumours in mouse prostates. Finally, a model of bone metastasis showed that relcovaptan decreased CRPC growth in bone and improved the bone-to-total volume ratio of tumour-bearing mouse tibias to be comparable to tumour-naive tibias.

"The impressive effects we observed using an AVPR1A antagonist in the intratibial prostate cancer xenograft model support future analysis combining taxane-based chemotherapeutics with AVPR1A antagonists," comments corresponding author Kerry Burnstein.

The authors conclude: "Our preclinical data indicate that pharmacological targeting of AVPR1A is efficient and effective … AVPR1A inhibition had benefit for end-stage bone-metastatic CRPC, for which therapeutic options are limited." Recent reports have described efficacy and tolerability of AVPR1A antagonism in autism spectrum disorder and support the repurposing of AVPR1A antagonists for advanced prostate cancer. Burnstein's team also plans to evaluate effectiveness of AVPR1A antagonists in inhibiting metastatic prostate cancer growth at distal sites other than bone.

Annette Fenner

ORIGINAL ARTICLE Zhao, N. et al. Arginine vasopressin receptor 1a is a therapeutic target for castration-resistant prostate cancer. *Sci. Transl Med.* **11**, eaaw4636 (2019)