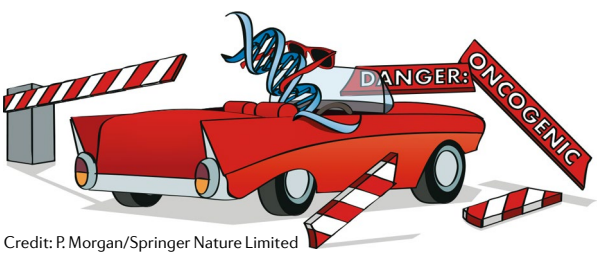
PROSTATE CANCER

New genomic drivers identified

Three studies recently published in *Cell* improve our understanding of the complex epigenomic and genomic aberrations driving metastatic castration-resistant prostate cancer (mCRPC) and, in doing so, identify novel therapeutic vulnerabilities at the genetic, transcriptomic, and immunophenotypic levels.

Wu and colleagues used an integrative genomics approach to profile 360 mCRPC tumour samples, which revealed a novel molecular subtype typified by biallelic inactivating mutations in the cyclin-dependent kinase 12 (*CDK12*) gene. Importantly, mCRPC tumours had a higher frequency of biallelic *CDK12* loss than localized primary tumours, and *CDK12*-mutant tumours were genetically, transcriptionally, and phenotypically distinct from those driven by other known genetic drivers. Biallelic *CDK12* loss was strongly associated with genomic instability resulting from focal tandem duplications, which led to increased gene fusions, distinct gene expression profiles, and highly-recurrent gains in cell cycle and DNA replication genes. Accordingly, *CDK12*-mutant tumours had elevated neoantigen burden and, consequently, an immunological phenotype defined by immune cell infiltration and altered chemokine signalling, suggesting that biallelic *CDK12* inactivating mutations can predict response to immune checkpoint inhibition.



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Using an integrated epigenomic approach to annotate active enhancers (and promoters) in localized and mCRPC tumours, Takeda et al. identify a somatically-acquired enhancer upstream of the androgen receptor (*AR*) gene that is frequently amplified and activated during the transition to mCRPC. CRISPR–Cas9-mediated perturbation of this enhancer decreased tumour cell proliferation, whereas insertion of an additional enhancer copy increased proliferation and decreased enzalutamide sensitivity. A further integrated analysis of DNA methylation and histone patterns found that the *AR* enhancer is hypomethylated in both benign prostate tissue and localized tumours, but devoid of histone marks, suggesting that this region is a developmental enhancer that becomes reactivated. The findings challenge the long-held assumption that the *AR* gene is the sole target of the *AR* locus amplicon and suggest that epigenetic targeting of this *AR* enhancer (and/or factors that bind to it) is a viable therapeutic strategy. "We are currently using novel strategies to identify the transcription factors that bind to this region, and are trying to identify other non-coding regions that have functional relevance in disease progression," explains lead author Matthew Freedman.

The study by Viswanathan et al. investigated structural alterations in the non-coding mCRPC genome. Using a linked-read whole-genome sequencing approach in 23 mCRPC biopsy samples, the investigators resolved key haplotypes and frequent rearrangements. Enhancer duplications were found near the *AR* gene — sometimes in the absence of *AR* alterations — in 70–87% of mCRPCs compared with <2% of primary tumours, suggesting that the *AR* is transcriptionally activated in mCRPC via somatic alterations in its enhancer. Furthermore, a genome-wide tandem duplicator phenotype linked with *CDK12* inactivation was uncovered in a mCRPC subset and was associated with *AR* or *MYC* enhancer duplications. In the context of therapeutic resistance, complex rearrangements driving *AR* gene and enhancer copy number gain in mCRPC were also discovered both before and after androgen pathway inhibitor treatment. "Future studies will be needed to determine if alterations in the *AR* enhancer are prognostic and/or predictive of response to particular therapies," says Srinivas Viswanathan.

"Our data is linked with the evidence presented in the Takeda paper, which showed that the amplified region near the *AR* is indeed an enhancer, and the Wu paper, which also identified the specific *CDK12* inactivated subset of prostate cancer," concludes co-author Matthew Meyerson.

In addition to revealing new oncogenic alterations in mCRPC, the collective findings reinforce the notion that additional genomic perturbations remain to be elucidated with future characterization of the non-coding genome.

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ORIGINAL ARTICLES Wu, Y.-M. et al. Inactivation of *CDK12* delineates a distinct immunogenic class of advanced prostate cancer. *Cell* **173**, 1770–1782 (2018) | Viswanathan, S. R. et al. Structural alterations driving castration-resistant prostate cancer revealed by linked-read genome sequencing. *Cell* https://doi.org/10.1016/j.cell.2018.05.036 (2018) | Takeda, D. Y. et al. A somatically acquired enhancer of the androgen receptor is a noncoding driver in advanced prostate cancer. *Cell* https://doi.org/10.1016/j.cell.2018.05.037 (2018)