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PROSTATE CANCER

Castration resistance driven by a GI transcriptional circuit

Aberrant expression of a gastrointestinal (GI)-lineage transcriptome, independent of androgen receptor (AR) signalling, can drive castration resistance in prostate cancer.

Investigators observed unexpected expression of a GI-lineage transcriptome in ~30% of castration-resistant prostate cancer (CRPC) samples. "This transcriptome is governed by aberrant activation of GI transcriptional master regulators HNF1A and HNF4G," Yu Chen, corresponding author, tells *Nature Reviews Urology*. "CRPC models that express this transcriptome require HNF1A and HNF4G for growth," he continues. *In vitro*, knockdown of HNF1A and HNF4G in 22Rv1 cells (which express the GI-lineage transcriptome) suppressed cell growth. Furthermore, knockdown of HNF1A and HNF4G in patient-derived metastatic CRPC organoids that express these factors at high levels also suppressed growth. *In vivo*, 22Rv1-derived xenografts subjected to HNF4G suppression also showed inhibited growth.

Further analysis revealed that HNF4G binds to and maintains a cistrome that regulates a GI-lineage transcriptome in prostate cancer that is distinct from AR signalling. Moreover, *in vitro*, exogenous expression of HNF4G in hormone-sensitive LNCaP cells caused endogenous HNF1A expression and vice versa, and both treatments resulted in upregulation of genes associated with the GI-lineage transciptome. Interestingly, treatment of LNCaP xenografts (either expressing or not expressing HNF4G), with enzalutamide caused increased HNF4G expression.

"Enforced expression of HNF1A and HNF4G in hormone-sensitive models activates the GI transcriptome and conveys castration resistance," Chen explains. "Going forward, we are working to define the role of HNF4G as a potential biomarker for resistance to AR-targeted therapies and to identify compounds that target HNF1A and HNF4G," he concludes.

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> HNF4G binds to and maintains a cistrome that regulates a GI-lineage transcriptome

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