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PROSTATE CANCER

A novel mechanism of neuroendocrine transdifferentiation

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New data suggest that HP1α upregulation is an early event in the transdifferentiation of castration-resistant prostate cancer (CRPC) into the neuroendocrine prostate cancer (NEPC) subtype. Furthermore, a heterochromatin molecular signature that is commonly upregulated in NEPC can distinguish NEPC from adenocarcinoma. These observations could aid diagnosis of NEPC and also provide novel targets for therapeutics aimed at treating this prostate cancer subtype.

Gene set enrichment analysis (GSEA) of patient-derived xenograft (PDX) models of NEPC and clinical cohorts revealed significant enrichment of heterochromatin-associated genes in NEPC compared with adenocarcinoma. In genetically engineered models mimicking NEPC development, heterochromatin-associated genes were enriched only if neuroendocrine differentiation occurred. Investigation of the leading-edge genes from the GSEA identified 36 genes that were included in a heterochromatin gene panel, which was able to distinguish NEPC from adenocarcinoma using hierarchical clustering.

Using their first-in-field, unique PDX model of adenocarcinoma-to-NEPC transdifferentiation (in which host castration initially causes the primary adenocarcinoma to relapse but then transdifferentiation into NEPC occurs, faithfully recapitulating disease progression in the donor patient), researchers analysed RNA sequence expression during the time frame between host castration and full NEPC transdifferentiation. HP1α expression was considerably upregulated early after host castration, and expression continued to increase during the progression of the cancer towards the NEPC phenotype. Increased levels of *HP1A* mRNA were observed as early as 1 week after castration, and increased protein expression was seen at 3 weeks.

In vitro, HP1α expression was highest in an NEPC cell line out of eight tested cell lines. Knockdown of HP1α in this cell line inhibited proliferation, stopped colony formation, and induced early apoptosis. AR and REST protein and mRNA expression were increased in these cells. In a CRPC cell line stably expressing ectopic HP1α, androgen deprivation therapy (ADT) promoted the expression of neuroendocrine markers and neuronal-associated signalling pathways, but HP1α overexpression alone was not sufficient to induce neuroendocrine differentiation. AR and REST were downregulated at both the mRNA and protein level in HP1α overexpressing cells and HP1α overexpression enriched pericentric heterochromatin machineries. Chromatin immunoprecipitation revealed that HP1α overexpression increased the occupancy of H3K9me3 on both the *AR* and *REST* promoters, whereas knockdown decreased H3K9me3 enrichment on the *AR* promoter. *In vivo*, HP1α knockdown in cell-line-derived xenografts inhibited tumour growth.

In patient samples, HP1α mRNA and protein expression were substantially upregulated compared with primary adenocarcinoma. HP1α expression positively correlated with expression of terminal neuroendocrine markers in advanced prostate cancer. Patients with cancer showing high HP1α expression had reduced disease-free and overall survival compared with those with disease with low HP1α expression.

Overall, these data suggest a novel mechanism of transdifferentiation to NEPC, in which HP1α upregulation causes abnormal pericentric heterochromatin formation, repressing AR and REST expression and promoting ADT-induced neuroendocrine transdifferentiation. Thus, HP1α could be a novel target for treatment of NEPC.

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