**Targeting HP1α in neuroendocrine prostate cancer**

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**Background**

Neuroendocrine prostate cancer (NEPC) is a lethal subtype of prostate cancer (PCa) arising mostly from adenocarcinoma via cell lineage transition following androgen deprivation therapy. However, mechanisms contributing to both NEPC development and its aggressiveness remain elusive. New therapeutic targets and more effective treatments are urgently needed to improve the management of NEPC.

**Methods**

Transcriptomic analyses were performed using RNA-seq and microarray data from our patient-derived xenograft (PDX) models and multiple clinical cohorts. Function of HP1α knockdown in NEPC cell line NCI-H660 was evaluated both in vitro and in vivo. Charcoal-stripped serum coupled with enzalutamide treatment was applied to LNCaP-V16D cell to induce NE phenotype. In silico drug screening pipeline was applied to discover HP1α targeted small molecule inhibitors (SMI). Bio-layer interferometry and cell viability assays were used to determine SMI specificity.

**Results**

We identified 36 heterochromatin-related genes that are significantly enriched in NEPC. Among them, heterochromatin protein 1α (HP1α) expression increased early and steadily during NEPC development and remained elevated in the developed NEPC tumor. HP1α knockdown in NEPC cell dramatically inhibited proliferation, completely ablated colony formation, and induced apoptotic cell death, ultimately leading to tumor growth arrest. HP1α ectopic expression significantly promoted NE transdifferentiation in adenocarcinoma cells. Mechanistically, HP1α reduced expression of androgen receptor (AR) and RE1 silencing transcription factor (REST) and enriched the repressive histone mark trimethylation of histone H3 at Lys9 (H3K9me3) on their respective gene promoters. VPC27084 was discovered as a pre-lead SMI specific binding to HP1α protein and killing NEPC cell.

**Conclusions**

HP1α is an early functional mediator for NEPC development and aggressiveness. VPC27084 is a pre-lead SMI targeting HP1α.

**Conflict of Interest:** The authors have no conflicts of interest to disclose.

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