ONECUT2 Drives Neuroendocrine Prostate Cancer Through Hypoxia Signaling

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ABSTRACT

Background: Neuroendocrine prostate cancer (NEPC), a lethal form of the disease, is characterized by the loss of androgen receptor (AR) pathway and subsequently AR expression during neuroendocrine transdifferentiation, which results in resistance to AR-targeted therapy. Histologically and clinically, NEPC resembles other types of small cell neuroendocrine tumors such as small cell lung cancer.

Methods: Through a pan-neuroendocrine cancer analysis, we identified ONECUT2 (OC2) as a candidate master transcriptional regulator of neuroendocrine tumors including prostate cancer.

Results: ONECUT2 alone was sufficient to induce neuroendocrine transdifferentiation in prostate adenocarcinoma and synergized with hypoxia in driving NEPC. Specifically, ONECUT2 regulates hypoxia signaling through modulation of HIF1A chromatin-binding, leading to NEPC being more hypoxic than prostate adenocarcinomas. Treatment with hypoxia-activated prodrug TH-302 potently reduces tumor growth in NEPC patient-derived xenograft models.

Conclusions: Collectively, these results suggest that ONECUT2 drives NEPC through hypoxia signaling, and emphasize the potential of hypoxia-directed therapy for patients with NEPC.

CONFLICT of INTEREST: The authors declare no conflicts of interest.

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