**ETV5 accelerates therapy-induced neuroendocrine prostate cancer development by inducing neural stem-like cell differentiation**

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**Abstract**

Neuroendocrine prostate cancer (NEPC) is a highly aggressive subtype induced by hormone therapy, posing significant therapeutic challenges due to the absence of effective treatments. In this study, we investigate the role of ETV5 in NEPC development. Analysis of multiple prostate cancer datasets reveals markedly elevated *ETV5* expression in NEPC compared to other subtypes. We demonstrate that ETV5 expression increases progressively under hormone therapy conditions through epigenetic modifications. Overexpression of ETV5 induces NEPC-like features and facilitates NEPC differentiation in LNCaP cells under hormone treatment conditions, both *in vitro* and *in vivo*. Our molecular mechanism study identifies *PBX3* and *TLL1* as critical target genes of ETV5, driving castration resistance and stemness associated with ETV5 overexpression. Remarkably, obeticholic acid, identified as a novel ETV5 inhibitor in our investigation, exhibits promising efficacy in suppressing NEPC development. This study underscores ETV5 as a key transcription factor driving NEPC progression and highlights its potential as a therapeutic target for this aggressive cancer subtype.