N-Myc induces an EZH2-mediated transcriptional program driving Neuroendocrine Prostate Cancer

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The transition from castration resistant prostate adenocarcinoma (CRPC) to neuroendocrine prostate cancer (NEPC) has emerged as an important mechanism of treatment resistance. This cell plasticity is characterized by loss of androgen receptor (AR) and prostate specific antigen (PSA), and significant over-expression and gene amplification of *MYCN* (encoding N-Myc) and *AURK*A (Encoding Aurora-A). N-Myc is an established oncogene in several rare pediatric tumors, but its role in prostate cancer progression is not well established.

Integrating a genetically engineered mouse model and human prostate cancer transcriptome data, we show that N-Myc over-expression leads to the development of poorly differentiated, invasive prostate cancer that is molecularly similar to human NEPC. This includes an abrogation of AR signaling and induction of Polycomb Repressive Complex 2 signaling. We demonstrate that N-Myc over-expression sensitizes cells to the allosteric Aurora-A inhibitor MLN8237 and EZH2 SET domain inhibitors. In addition we identify new lead small molecules that target the N-Myc/Aurora-A protein complex to diminish the aggressive nature of this cancer type. Altogether, our data establishes N-Myc as an oncogenic driver of NEPC.

Since transformation of NEPC is thought to develop in the face of hormonal therapy there is concern that with the clinical development of more potent and earlier AR targeted therapeutic strategies, the incidence of AR-negative NEPC will escalate. Therefore, small molecules identified in this study will potentially impact significantly more prostate cancer patients than previously appreciated in addition to fulfill an unmet clinical need for patient with NEPC.

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