

L-Myc is a lineage-specific driver of neuroendocrine transformation in prostate cancer

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Abstract

Treatment-emergent neuroendocrine prostate cancer (NEPC) is an aggressive therapy-resistant state that arises under potent androgen receptor (AR) pathway inhibition and lacks effective targeted therapies. NEPC is characterized by collapse of AR transcriptional output and activation of neuroendocrine (NE) lineage programs, but the transcription factors required to maintain this state remain incompletely defined. While *MYC* amplification is common in prostate adenocarcinoma and *MYCN* has been implicated in NE differentiation, the contribution of the *MYCL* paralog (L-Myc) to NEPC is poorly understood. *MYCL* is expressed in a subset of clinical NEPC specimens, and despite shared DNA-binding features among *MYC* family members, cancers can exhibit context-specific paralog dependence.

Across prostate cancer models, we assessed *MYC*-family expression and dependency, and functionally tested *MYCL* by ectopic overexpression in a panel of prostate adenocarcinoma cell lines that are castration-sensitive (LNCaP, VCaP) or castration-resistant (22Rv1, LN95, LNCaP-abl, and LNCaP RB1/TP53 double knockout (DKO)), assessing effects on AR/*MYC* expression, chromatin accessibility, androgen-independent growth, and enzalutamide sensitivity. To define the molecular basis of *MYCL*'s distinct activity, we performed comparative IP-mass spectrometry of L-Myc, c-Myc, and N-Myc in the LNCaP DKO model to identify L-Myc-specific interacting partners.

We observed a divergence in *MYC*-family usage and dependency: the AR-ve NEPC model NCI-H660 expressed *MYCL* and exhibited selective dependency on *MYCL* relative to *MYC/MYCN*, whereas AR+ve adenocarcinoma models showed the expected dependence on *MYC*. Ectopic overexpression of *MYCL* in castration-resistant models decreased c-Myc and AR expression and, in the LNCaP DKO model, was associated with reduced chromatin accessibility at the AR locus. Functionally, *MYCL* induction increased androgen-independent growth and conferred resistance to the AR antagonist enzalutamide selectively in the castration-resistant setting, with minimal effects in castration-sensitive lines. After prolonged *MYCL* induction, castration-resistant cells acquired a dependence on continued *MYCL* expression for androgen-independent proliferation and failed to grow upon *MYCL* withdrawal, and *MYCL* induction increased expression of multiple neuroendocrine-associated pathways. Comparative IP-mass spectrometry identified PRMT1 and SIN3B as interacting partners unique to L-Myc relative to c-Myc and N-Myc.

These findings support L-Myc as a candidate lineage-regulating dependency in NEPC-like contexts, linking *MYCL* activation to AR suppression, induction of NE transcriptional programs, therapy resistance, and acquired *MYCL* dependence.

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