Targeting NUAK2 disrupts pre-mRNA splicing and inhibits neuroendocrine prostate cancer

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Background: Neuroendocrine prostate cancer (NEPC) is a highly aggressive subtype of prostate cancer that frequently emerges in patients receiving androgen deprivation therapy. NEPC has a poor prognosis due to a lack of effective treatments and therapeutic molecular targets. Here, we identify the serine/threonine kinase NUAK2 as a critical molecular target in NEPC.

Methods: We combined genetic and pharmacological approaches to define the functional role of NUAK2 using in vitro and in vivo NEPC models. Mechanistic studies, including phospho-proteome, interactome and transcriptomic profiling, were performed to elucidate NUAK2-driven pathways in NEPC.

Results: Gain- and loss-of-function studies revealed that NUAK2 is essential for NEPC proliferation, clonogenic growth, and tumor growth. Pharmacological inhibition of NUAK2 using the preclinical compound HTH-02-006 or the FDA-approved CDK4/6 inhibitor G1T-28 (trilaciclib) which has off target NUAK2 activity suppresses NEPC growth in vitro and in vivo. NUAK2 inhibition had additive effects when combined with carboplatin in vivo. Mechanistically, NUAK2 directly engages the spliceosome proteins, and its inhibition induces widespread pre-mRNA splicing defects—such as intron retention and exon skipping—that converge on genes regulating cell cycle progression, chromatin remodeling, and neuronal differentiation.

Conclusions: Collectively, these findings establish NUAK2 as a central regulator of RNA splicing and tumor growth in NEPC and provide strong rationale for therapeutic targeting of NUAK2 to improve outcomes in this lethal disease.

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