

RET Kinase in Neuroendocrine Prostate Cancer

Background: Increased treatment of metastatic castration resistant prostate cancer (mCRPC) with second-generation anti-androgen therapies (ADT) has coincided with a greater incidence of lethal, aggressive variant of prostate cancer (AVPC) tumors that have lost androgen receptor (AR) signaling. AVPC tumors may also express neuroendocrine markers, termed neuroendocrine prostate cancer (NEPC). Recent evidence suggests kinase signaling may be an important driver of NEPC. While kinases such as AURKA have been identified as important for NEPC growth, targeting these kinases for treatment has not dramatically improved patient survival and there remains a need to improve NEPC treatment options.

Methods: To identify targetable kinases in NEPC, we performed global phosphoproteomics comparing AR-negative to AR-positive prostate cancer cell lines and identified multiple altered signaling pathways, including enrichment of RET kinase activity in the AR-negative cell lines. We also analyzed multiple clinical and patient derived xenografts transcript datasets to look for RET kinase expression and enrichment in subsets of patient populations. Finally, we utilized genetic and pharmacological approaches to reduce RET kinase activity in multiple models of NEPC to determine if RET kinase is necessary for NEPC cell growth and proliferation.

Results: We found that RET kinase was highly upregulated and enriched in the NEPC patient samples relative to AdCa or double negative tumor samples. Additionally, we found that knockdown of RET kinase reduced cell proliferation by 80% in NCI-H660 cells and 50% in PC3 cells. Pharmacological inhibition of RET with multiple inhibitors, including AD80, Blu-6667, and LOXO-292, dramatically reduced downstream signaling of ERK1/2 and reduced growth and viability in multiple mouse and human NEPC models.

Conclusions: There are limited treatment options for patients with metastatic aggressive variant prostate cancer and none are curative. Identification of aberrantly expressed RET kinase as a driver of tumor growth in multiple models of NEPC provides a significant rationale for testing the clinical application of RET inhibitors in patients with AVPC.