Targeting RET Kinase in Neuroendocrine Prostate Cancer

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Abstract

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 samples 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 in vivo 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 ADca negative tumor samples. Additionally, we found that knockdown of RET kinase reduced cell proliferation by 80% in NCI-H660 cells and 50% in DU145 cells. Additionally, pharmacological inhibition of RET kinase in multiple human xenografts, including AD80, Blu-667, and LOXO-202, dramatically reduced tumor growth and viability in multiple human and 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.

Global phosphorylation and kinase signaling pathways are differentially regulated in AVPC cell lines compared with adenocarcinoma cell lines.

REMARKABLE CONTRIBUTIONS

1. Global transcriptional and phosphorylation profiling in 13 xenograft xenograft models (NPI-2164, NCI-H660, NCI-1251, 115-1, 115-2, 115-3, and NCI-HPC; 80-3, 64-1, 74-1, and 80-1) revealed multiple predictive alterations in RET kinase activity and its downstream targets in NEPC. 

Relevant background: With the availability of new murine xenograft models, we applied global phosphoproteomic and transcriptional analyses to compare AR-positive prostate adenocarcinoma lines (DU145, PC3, 80-3, 100-1, and NCI-HPC) with AR-negative xenografts (NPI-2164, 80-1, 74-1, 64-1, 115-1, 115-2, and 115-3). These analyses identified unique patterns of RET kinase signaling and transcriptional activity in AR-negative xenograft cell lines compared with AR-positive adenocarcinoma lines. These findings provide a foundation for the development of novel therapeutic strategies targeting RET kinase in NEPC. 

The RET pathway is perturbed by RET inhibitors in NCI-H660 cells. AD80 reduces NCI-H660 xenograft tumor growth.

- RET transcripts and signaling is upregulated in NEPC
- Downstream targets of RET and tumor growth can be inhibited with multiple RET inhibitors
- RET kinase may be an actionable target in the treatment of NEPC

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