XPO1 Inhibition Suppresses the Growth of Pancreatic Neuroendocrine Tumors

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ABSTRACT

Pancreatic neuroendocrine tumors (PNETs) are rare islet cell tumors. Although slow growing in early stages, the overall survival rates of metastatic PNETs are dismally low at 25%. The main treatment option includes surgery followed by chemotherapy or targeted therapy. Unfortunately, advanced PNETs show minimal response to FDA approved therapies suggesting the urgent need for the identification of novel and effective treatments. In the present study, we have tested 1st and 2nd generation XPO1 inhibitors also known as selective inhibitors of nuclear export (SINE) on BON1 and QGP1 PNET tumor cells.

Growth inhibition was determined by MTT and colony formation assays. Apoptosis was determined by flow cytometry (annexin V-propidium iodide), real time RT-qPCR (SYBR green I), western blotting etc. For the determination of western blot band density, NIH ImageJ 1.5Oi software was utilized. Expression of PNET marker Chromogranin A was determined using immunofluorescence (IF) technique.

The IC_{50}s for SINE compounds namely KPT-185, KPT-330 (selinexor/XPOVIO), KPT-8602 (eltanexor) were 26 nM, 283 nM, 1027 nM respectively for BON1 cells. Similar trends in the IC_{50}s were observed in QGP1 cells. The 1st and 2nd generation SINE, KPT-330 and KPT-8602 respectively reduced the number and area of the colonies significantly. SINE compounds were able to induce apoptosis at pharmacologically relevant concentrations. Western blot analysis also revealed significant induction of PARP cleavage by SINE. The PNET marker Chromogranin A was found to be reduced in the SINE treated cells in IF assay.

XPO1 inhibitors also suppress pmTOR and pP70S6K along with mTORC2 pathway molecule RICTOR in QGP1 cells.

Taken together, this is the first study to reveal the therapeutic potential of novel XPO1 targeted agents for the treatment of PNETs. The *in vivo* evaluations of SINE compounds in xenograft models are underway.

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