

A Primary Xenograft Model of Pancreatic Neuroendocrine Carcinoma Recapitulates Hallmark Features of the Disease

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Background: For most patients with pancreatic neuroendocrine tumors (PNETs), surgery is not possible because of extensive metastatic disease. Treatment options for tumor control remain limited. Dysfunction of the mTOR pathway is a critical event in PNETs. There is a lack of suitable models to study how to optimally target mTOR in PNETs. We hypothesized that passage of human PNETs in nude mice is an effective method to maintain features typical of PNETs, which will permit investigations of PNET biology.

Methods: A patient with PNET liver metastases producing insulin underwent surgery to ameliorate refractory hypoglycemia. PNET tissue was implanted s.c. into nude mice and stained with H & E or with the antibodies indicated for immunofluorescent analysis. Real-time TaqMan RT-PCR assayed for expression of developmental transcription factors specifically expressed in NETs. The radiolabeled somatostatin analog (68)Ga-DOTATOC was used to perform PET-CT of treated PNETs *in vivo*. Mice bearing PNET xenografts were treated with everolimus or the new mTOR inhibitor INK128.

Results: PNET xenografts maintain a NET morphology, chromogranin A and insulin expression, and a NET-specific gene expression signature with serial passage. Gallium-68 DOTATOC PET-CT detected PNET xenografts, suggesting they express somatostatin receptors. PNET xenografts exhibit dysfunction of the mTOR pathway that was inhibited by everolimus or INK128, but with distinct differences. Everolimus caused up-regulation of Akt, and incompletely inhibited mTOR. INK128 prevented up-regulation of Akt activity and more effectively inhibited the mTOR pathway than everolimus.

Conclusion: We developed a patient-derived PNET xenograft model that retains the pathological and genetic aberrations typical of PNETs. This new model will be useful for studies of basic PNET biology and for preclinical investigation of therapies, such as novel mTOR inhibitors. To our knowledge, this is the only human PNET xenograft model available to study the biology of this rare and poorly understood disease.