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Pten Loss Cooperates with Men1 Loss to Accelerate Tumorigenesis of Neuroendocrine Tumors

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BACKGROUND: Understanding new therapeutic paradigms in pancreatic neuroendocrine tumors (PanNETs) is essential to improve clinical outcomes. Multiple endocrine neoplasia type 1 (MEN1) patients develop PanNETs along with other NETs. The prolonged latency for tumor development in MEN1 patients indicates that other mutations likely cooperate with Men1 to induce PanNETs. We hypothesized that Pten loss can cooperate with Men1 loss to accelerate tumorigenesis.

METHODS: We generated a genetically engineered mouse model using Cre-Lox system, with insulin-specific biallelic inactivation of Men1 along with Pten. These mice were monitored for tumor development by behavior as well as by macroscopic and microscopic analysis. Histologic and molecular characterization of the tumors was performed. Rapamycin treatment was administered to these mice.

RESULTS: These mice developed well-differentiated G1/G2 PanNETs (Ki67 index range: 0.99% - 10%) and mimicked human MEN1 disease. Pten deficiency accelerated Men1-deficient PanNETs. Interestingly, these mice also developed pituitary neuroendocrine tumors (PitNETs), which were similarly accelerated by Pten loss. Treatments with mTOR inhibitor - rapamycin delayed development and prolonged survival of both types of NETs. In addition, our mouse genetics

data indicated that with deficiency of Pten or Men1, dosage of the other gene is critical. Based on our discovery, we generated a separate mouse model with a different promoter to drive Cre expression. This model only develops well-differentiated G1/G2 PanNETs, which is practical for in vivo preclinical therapeutic study for human PanNETs.

CONCLUSION: Collectively, these data support the importance of PI3K/AKT/mTOR pathway for NETs and demonstrate that Pten and Men1 function cooperatively to suppress tumorigenesis of NETs. These are the first mouse models that underscore the principal roles for Men1 and Pten inactivation in tumorigenesis of PanNETs and PitNETs, and provide a platform to study novel therapeutic opportunities for NETs through targeting PI3K/AKT/mTOR and MENIN pathways.