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Pancreatic Mixed Acinar Cell Carcinoma: Genomic Analysis and Characterization of a Patient-Derived Organoid Culture

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BACKGROUND: Mixed acinar cell carcinomas occur in <2% of all pancreatic cancers, and express markers for both neuroendocrine and acinar cell differentiation. The clinical prognosis and molecular characterization of mixed acinar cell carcinomas are not well understood.

METHODS: The goal of our study is to link genomic and transcriptomic analysis of PanNETs with pathogenesis. This case study represents a mixed acinar cell carcinoma in the pancreatic head that was surgically resected by a pancreaticoduodenectomy (pT3N1MX, Ki-67 labeling index 5%). A macrodissected tumor specimen was subdivided for genomic analysis and for explantation in organoid culture. After digestion with collagenase the tissue was washed and plated in 50% Matrigel in Human Complete Organoid media. The cultures were subsequently established and characterized by immunolabeling for neuroendocrine and acinar lineage markers and by qRT-PCR. Primary tumor DNA was extracted from FFPE sections that had >60% tumor cellularity and were analyzed by whole exome sequencing on an Illumina HiSeq 2000/2500.

RESULTS: The primary tumor showed a mixed population of cell types on H&E. Tumor cells were positive for intracytoplasmic trypsin staining indicative of acinar differentiation. The tumor cells were also positive for the neuroendocrine markers synaptophysin, and chromogranin A. The tumor was negative for gastrin, insulin, somatostatin, and glucagon. Cell growth in the initial organoid culture resulted in a mixed culture with 3D acinar structures and a second population of cells with multiple protrusions that invaded into the Matrigel. After

3 passages of the organoid cultures, the cultures were then placed in 2D culture on coated dishes. Whole exome sequencing of the dissected primary tumor from FFPE sections showed mutations in several genes including MEN1, histone modification genes, and DNA repair pathway genes.

CONCLUSION: Our approach is to combine patient-derived PanNET organoid cultures with cancer biology and molecular genetic analyses to understand their clinical significance.