Duodenal Neuroendocrine Tumors Exhibit Distinct Transcriptome and Mutations Compared to Pancreatic Neuroendocrine Tumors and Ileal Carcinoids

Karen Rico¹; Sulaiman Sheriff¹; Suzann Duan¹; Sammed Mandape¹; Ritu Pandey¹; Bryson Katona²; David Metz²; Juanita Merchant¹

¹University of Arizona; ²University of Pennsylvania

BACKGROUND: Approximately seventeen neuroendocrine cell types in the GI tract may give rise to Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs). However, even when the tumors arise from the same cell type, they may behave differently. MEN1 mutations occur in 40% of pancreatic neuroendocrine tumors (PNETs) but not in small bowel NETs, suggesting additional mechanisms of pathogenesis. To determine if GEP-NETs exhibit a distinct transcriptome and whether MEN1 and somatic mutations influence tissue-specific differences

METHODS: Blood and tumor whole exome sequencing was performed in three PNETs, three duodenal neuroendocrine tumors (DNETs), and two ileal carcinoids (ICs). Somatic indels and single nucleotide variations (SNVs) were compared across tumor types. RNA-Seq was performed on two DNETs and two PNETs. We conducted a western blot and IHC of menin to determine if mutations led to loss of protein or change in subcellular localization.

RESULTS: Duodenal gastrinomas had elevated transcripts of genes related to gastrin-cell specification (NKK6-3, NKX2-2). In PNETs, increased transcripts were related to the early stages of enteroendocrine cell differentiation (ASCL1, IRX2). DNETs had MEN1 mutations in the C-terminus of menin near the nuclear localization signals. By contrast, the PNETs had MEN1 mutations closer to
the N-terminus of the protein. Menin protein was detected in GEP-NETs and was cytoplasmic. The molecular mass of menin was smaller than the protein expressed from MEN1 gene transfected in Men1-/- mouse embryonic fibroblasts, suggesting differential post-translational modification of menin. Indels were found in DNETs (MAP3K9), PNETs (RBM5) and ICs (ESRRA). The SNVs identified were PNETs (RHPN2), DNETs (MUC20) and ICs (APC).

CONCLUSION: The transcriptome and mutations in GEP-NETs are reflective of their respective tumor locations. The presence of mutations in other genes suggests that MEN1 mutations may not be sufficient to initiate tumorigenesis. Thus, the identification of altered genes and gene functions provides a promising avenue for targeted treatment of tumor specific GEP-NETs.