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Sex-specific Transcriptional Differences and Loss of Gene Imprinting in Pancreatic Neuroendocrine Tumors

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BACKGROUND: Pancreatic neuroendocrine tumors (PNETs) occur more frequently in men and are associated with higher mortality in males; however, the molecular basis for these sexual dimorphisms is unclear. We hypothesized that transcriptional and epigenetic differences may contribute to these observed epidemiologic differences.

METHODS: We generated RNA sequencing data from 21 primary PNETs (9 (F)emale, 12 (M)ale) resected at our institution. Total RNA was extracted from tumor tissues using the RNeasy mini kit (Qiagen) and sequencing was performed on HiSeq 2500/4000 (Illumina) sequencers. Transcript quantification was performed with Salmon (v1.4.0). To validate our results, we downloaded a publicly available PNET dataset (10F, 14M). To explore the role of DNA methylation (DNAm) in sex-specific gene expression differences, we further downloaded matched DNAm - gene expression data for 23 primary PNET samples (9F, 14M) and DNAm data for 64 non-neoplastic pancreatic islet tissue samples (18F, 46M). Analyses were done in R (v4.0.3) using minfi (v1.36.0) and DESeq2 (v1.30.0) packages.

RESULTS: We found that there were significantly more genes differentially expressed by sex in PNETs as compared to control pancreatic islet tissues ($p=6.5x10-5$). Furthermore, PNETs were found to be associated with the emergence of unique sex-specific gene expression differences that are not observed in non-neoplastic pancreatic islet tissues. Some of the genes we found to be uniquely differentially expressed by sex in PNETs play known roles in tumorigenesis, including RASSF7, IGF2,and SOX15. Sex-specific PNET gene expression differences were not associated with DNA methylation. However, while widespread sex-specific differences were present in the DNAm landscapes

of control pancreatic islets at the level of single CpGs (N=38,623), they were almost completely erased in the cancer state (N=4). This included a loss of gene imprinting in 87 genes.

CONCLUSION: These results depict an emergence of sex-associated genetic and epigenetic dysregulations in PNETs.

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