B-7

Transcriptional Alterations in Hereditary and Sporadic Non-Functioning Pancreatic Neuroendocrine Tumors According to Genotype

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BACKGROUND: Non-functioning pancreatic neuroendocrine tumors (NFPanNETs) may be sporadic or inherited due to germline mutations associated with von Hippel-Lindau disease (VHL) or multiple endocrine neoplasia type 1 (MEN1). The clinical behavior of NFPanNETs is difficult to predict, even in same stage and grade tumors. Herein we analyzed genotype-specific patterns of transcriptional messenger RNA (mRNA) levels of NFPanNETs in order to understand the molecular features that determine PanNET phenotype.

METHODS: 32 samples were included for genome-wide mRNA gene expression analysis [9 VHL-, 10 MEN1-, 9 sporadic NFPanNETs and 4 purified normal islet cells (NIC) samples]. Validation of genes was performed by Real-Time PCR and immunohistochemistry. Gene expression profiles were analyzed by tumor genotype and pathway analysis was curated.

RESULTS: Consensus clustering of mRNA expression showed separate clustering of NIC, VHL- and MEN1-associated NFPanNETs, while some sporadic tumors clustered with MEN1. Four of 5 “MEN1-like” sporadic PanNET subtypes had loss of heterozygosity at the MEN1 gene locus. Pathway analysis showed subtype-specific pathway activation comprising angiogenesis and immune response in VHL; neuronal development in MEN1, protein ubiquitination in the new MEN1/Sporadic subtype; and cytokinesis, cilium/microtubule development in

sporadic NFPanNETs. Among many genes, PDGFRB, Lef-1 and NOTCH3 as well as CDK4 and CDK6 were found to be upregulated in VHL and MEN1 NFPanNETs, respectively, providing potential subtype-specific treatment targets.

CONCLUSION: Distinct mRNA expression patterns were identified in sporadic-, VHL- and MEN1- associated NFPanNETs. Our results uncover new pathways involved in NFPanNETs that are subtype-specific and provide potential new diagnostic or therapeutic targets based on tumor subtype.