B-2

Proteotranscriptomic Classification and Characterization of Pancreatic Neuroendocrine Neoplasms

K. Yang[1,2], S. Kalloger[3,4], J. Aird[3], M. Lee[5], C. Rushton[1], S. Spencer Miko[2], K. Mungall[2], A. Mungall[2], S. Colborne[2], R. Morin[1,2], J. Loree[5], M. Marra[2,6], D. Renouf[4,5], G. Morin[2,6], D. Schaeffer[3,4], S. Gorski[1,2]; [1]Molecular Biology & Biochemistry, Simon Fraser University, BC/Canada, [2]Canada's Michael Smith Genome Sciences Centre, BC Cancer, Vancouver, BC/Canada, [3]Division of Anatomical Pathology, Vancouver General Hospital, BC/Canada, [4]Pancreas Centre BC, BC/Canada, [5]Division of Medical Oncology, BC Cancer, BC/Canada, [6]Department of Medical Genetics, University of British Columbia, BC/Canada

BACKGROUND: Pancreatic neuroendocrine neoplasms (PNENs) are biologically and clinically heterogeneous neoplasms with variable patient outcomes. Our study aims to uncover the molecular factors that underlie the clinical and biological heterogeneity among PNENs for a better understanding and potential classification of this disease.

METHODS: Formalin-fixed paraffin-embedded primary tumour specimens from 92 patients with PNEN were procured for the study and split into two cohorts for discovery and validation purposes. Next-generation sequencing profiled the exome and transcriptome, and quantitative mass-spectrometry profiled the global proteome of specimens. Non-negative matrix factorization was used to identify subgroups, followed by differential analysis to identify subgroup-specific features. To corroborate subgroup-specific RNA- and protein- level distinctions, activities of key cellular regulators were inferred from target gene expression or co-expression signatures.

RESULTS: Unsupervised clustering analysis of transcriptome data identified four robust molecular subgroups that were substantiated by proteome analysis ($p=0.0005$) within the discovery cohort and validated with the validation cohort and an external cohort of PNENs from a previous microarray-based gene expression study. A proliferative subgroup was enriched with neuroendocrine carcinomas and specimens with >20% Ki67, concomitant with reduced survival probability ($p=0.0024$; logrank test) and higher mRNA expression and protein abundance of cell cycle-related genes. Increased mRNA expression of ARX or PDX1 (adjusted $p<0.05$) was found in two of the subgroups similar to a previous report. The ARX-high subgroup was characterized by enrichment of oxidative phosphorylation genes and increased relative abundance of mitochondrial proteins, while oncogenic Ras mutations were found in the PDX1-high subgroup. A fourth subgroup exhibited enrichment of stromal/mesenchymal molecular features and Hippo signaling pathway. Inferred activities of key cellular regulators further supported observed alterations within subgroups.

CONCLUSION: We identified four robust molecular subgroups among PNENs with clinicopathological associations and biological distinctions that may provide potential new directions for patient stratification and treatment strategies to facilitate treatment decisions.

ABSTRACT ID: 105