O-9

Leveraging Transcriptomics to Grade Pancreatic Neuroendocrine Neoplasms(NENs) and Assess Molecular Alterations Associated with Somatostatin Receptor(SSTR) Subtype Expression

Emil Lou[1], Nishant Gandhi[2], Alex Farrell[2], Joanne Xiu[2], Andreas Seeber[3], Muhammad Shaalan Beg[4], Sourat Darabi[5], Michael J. Demeure[5], Jim Abraham[2], Matthew Oberley[2], John Marshall[6], Heloisa Soares[7].

[1]Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA; [2]Caris Life Sciences, Phoenix, AZ, USA; [3]Comprehensive Cancer Center Innsbruck, Medical University of Innsbruck, Innsbruck, Austria; [4]University of Texas Southwestern, Dallas, TX, USA; [5]Hoag Memorial Hospital Presbyterian, Newport Beach, CA, USA; [6]Georgetown University, Washington, DC, USA; [7]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA.

BACKGROUND

SSTR substypes are collectively expressed in the majority of NENs. However, SSTR subtype expression is not routinely assessed for clinical decision-making, including patients eligible for targeted radionucleotide therapy. Elucidating the landscape of SSTR subtypes in context of molecular profiles for low-grade (LG-) and high-grade NENs (HG-NENs) provides an opportunity to better tailor targeted therapy. Here, we leverage the ability of transcriptomics to predict NEN grade, while identifying molecular landscapes associated with SSTR subtype expression in Pancreatic NENs (PanNENs).

METHODS

1768 cases of NENs were analyzed using Next Generation Sequencing(NextSeq), Whole Exome or Whole Transcriptome Sequencing(WTS, NovaSeq) at Caris Life Sciences(Phoenix, AZ). Significance was determined using chi-square, Fisher-Exact or Mann-Whitney U and p-adjusted for multiple comparisons ($q<0.05$).

RESULTS

Using Receiver-Operating Characteristic analysis on 318 cases with histological grade annotation (hga), we identified a threshold of *MKI67* expression which differentiated LG- from HG-NENs, with a true positive rate of 86.84% and false positive rate of 11.9%(AUC=95%). This threshold was applied to the entire cohort to infer HG/LG. The differences between the mutational landscapes of HG- and LG-NENs were faithfully recapitulated in hga- and *MKI67*-based cohorts, including *TP53* (delta=58.2%, 42.8%), *RB1* (delta=46.6%, 35.2%), *KRAS* (delta=14.8%, 10%), and *MEN1* (delta=-18.4%, -10.8%). Further, the expression of *SSTR-1*, *-2* and *-3* were lower, while *-4* was higher in HG- vs LG-PanNENs with a similar trend in *TP53*, *RB1*, *KRAS* and *MEN1* alterations (all $q<0.05$) as mentioned above. For each SSTR subtype, we established high and low cohorts based on their median mRNA expression. Among SSTR-1,-2-high vs low HG-PanNENs, the mutational prevalence of *MEN1* (delta=29.5%, 34.4%), *ATRX* (delta=16.5%, 30.4%), and *TSC2* (delta=16.5%, 30.4%) were increased, while *KRAS* (delta=-35%, -37%) and *RB1* (delta=-35%, -41%), were decreased (all at least $p<0.05$).

Similar, but less pronounced differences were observed in LG-PanNENs. Gene Set Enrichment Analysis revealed increased adipogenesis, hedgehog and IL-2/STAT5 signaling in HG-PanNENs and increased DNA damage repair and PI3K/AKT/mTOR pathways in LG-PanNENs in the SSTR-1,-2-high cohorts. Finally, only patients with SSTR-5-high LG-PanNENs had significantly better prognosis (HR=0.248, p=0.01).

CONCLUSIONS

Here, we provide evidence that WTS can be effectively leveraged to predict NEN grade and lay the foundation for defining characteristic differences in the molecular landscapes associated with specific SSTR subtypes in HG- and LG-PanNENs. Incorporating molecular profiling in this manner can assist in tailoring treatment for patients with PanNENs.

ABSTRACT ID 21474