Abstract # 601

Comprehensive –omic analysis of 152 CRC patients allows greater subclassification than CMS or sidedness alone

CONTRIBUTING RESEARCHERS

Christopher W. Szeto1, Kevin Kazmierczak1, Andrew Chambers2, Yeoun Jin Kim1, Andrew Nguyen1, Iain B. Tan3, Stephen C. Benz1, Charles J. Vaske1

1 NanOmis LLC, Santa Cruz, CA; 2 NanOmis LLC, Rockville, MD; 3 Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore

BACKGROUND

Despite relatively high TMB in CRC, immune checkpoint inhibition (ICI) response is lower than in similarly mutated tissues such as melanoma (ORR 10-20% vs. 20-50%). MSI-status can be used to pre-select likely-responders, however MSI is rare. There is a need to further guide ICI candidacy in CRC. Four transcriptomic-based CRC consensus molecular subtypes (CMS) have been described with ad hoc clinical associations. We sought to confirm these subtypes in proteomic assays and their clinical associations.

METHODS

- 152 CRC tumors from the National Cancer Centre Singapore were available for analysis
- Tumor/normal-paired DNAseq (WGS or WES) and deep RNAseq was performed
- MSI-status was determined by both PCR and WGS/WES profiles
- CMS types, checkpoint expression, and immune-infiltration deconvolution were calculated upon RNAseq data
- Significant enrichment for MSI, immune status, CMS types, and clinical covariates was analyzed
- Mass-spec based global proteomics was successfully performed on 143/152 samples. Consensus between RNAseq and global proteomics was confirmed by correlation significance analysis
- A CMS-like clustering of proteomic data was identified by analyzing homogeneity of candidate clusterings with CMS types

RESULTS

- Clustering of immune-expression deconvolution bifurcated into hot and cold tumors
- DNAseq-based MSI and PCR-based MSI were statistically equivalent
- 3075/5135 genes were significantly correlated between RNAseq and global proteomic assays (1299 after multiple test correction). The most correlated genes within COSMIC cancer-related genes were enriched for MHC binding processes
- Significant association was found between CMS1, MSI, transverse sides, and being immune hot. Conversely, CMS2 was found to be significantly MSS, left-sided, and immune cold.
- A semi-supervised clustering of global proteomic data significantly recapitulated some CMS subtypes, but grouped CMS1 (MSI enriched) & CMS3 (Ras mt enriched) subtypes. Genes driving this association were significantly enriched for ECM organization.

CONCLUSIONS:

CMS1 tumors are the best candidates for ICI therapy. CMS3 co-clusters with CMS1 in ECM genes within proteomic data, warranting further research of CMS3 ICI outcomes


150-200-2019

Scan me

ARTIFICIAL INTELLIGENCE"