Abstract # 528

NantWorks

Genomic and immune infiltration differences between MSI and MSS GI tumors.

CONTRIBUTING RESEARCHERS

Yulia Newton[1], Justin Golovato[1], Tan Bee Huat Iain[2], Justina Lam Yick Ching[2], GUO Yu, Koo Si-Lin[2], Clarinda Chua Wei Ling[2], Joe Yeong Poh Sheng[2], Christine ENG Loan Ping[2], Anders Martin Jacobsen[2], Jonathan GÖKE[2], Mark Johnson[1], Shahrooz Rabizadeh[1], J Zachary Sanborn[1], Stephen Charles Benz[1], Charles Vaske[1], Christopher Szeto[1]

[1]NantOmics LLC., Santa Cruz, CA; [2]SingHealth, Singapore;

BACKGROUND

Dysregulation of DNA mismatch repair pathway can lead to microsatellite instability in many GI tumors, and microsatellite instability is an important diagnostic and prognostic marker. Microsatellite instable (MSI) tumors comprise about 15% of colorectal malignancies and can be found in other gastrointestinal (GI) tumor types. We present results of analysis of genomic and immune infiltration differences between MSI and microsatellite stable (MSS) GI tumors spanning multiple cancer types.

Abbreviations: Microsatellite instable (MSI), Microsatellite stable (MSS)

METHODS

A total of 521 GI patients with deep whole exome sequencing (WES) of tumor and blood samples, and whole transcriptomic sequencing (RNA-Seq) (~200M reads per tumor) were available for this analysis from a commercial database. Variant calling was performed through joint probabilistic analysis of tumor and normal DNA reads, with germline status of variants being determined by heterozygous or homozygous alternate allele fraction in the germline sample. MSI was determined via a CLIA LDT based on NGS data at microsatellite sites.

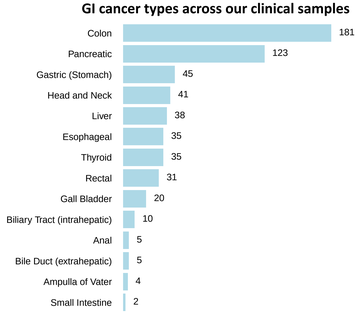

Figure 1. Distribution of GI cancer types in our clinical samples cohort.

MSI subtypes across our clinical samples

Cancer type	MSI High	MSI Low
Colorectal	15	115
Gastric (Stomach)	3	29
Liver	1	19
Pancreatic	-	79
Head and Neck	-	26
Thyroid	-	25
Esophageal	-	22
Gall Bladder	-	14
Biliary Tract (intrahepatic)	-	7
Bile Duct (extrahepatic)	-	3
Ampulla of Vater	-	2
Small Intestine	-	1

Table 1. Distribution of MSI groups across GI cancer types in our clinical cohort.

RESULTS

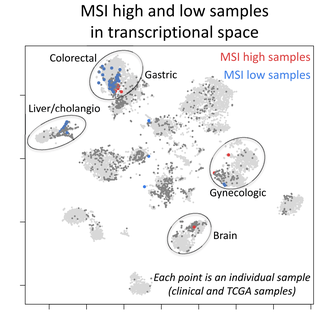

Figure 3. t-SNE projection of our clinical and TCGA samples in transcriptional space. Each point in this plot is an individual sample. TCGA samples are colored in light gray. Our clinical samples in this study are colored by red (MSI high) or blue (MSI low). Our clinical samples not utilized by the study are colored in dark gray.

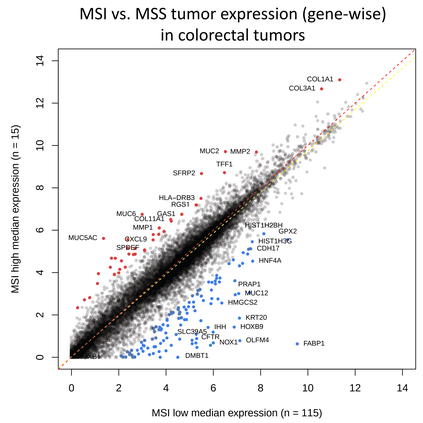

Figure 4. MSI vs. MSS differential median gene expression levels in log2(TPM+1) space. Top differential genes for each group are labeled.

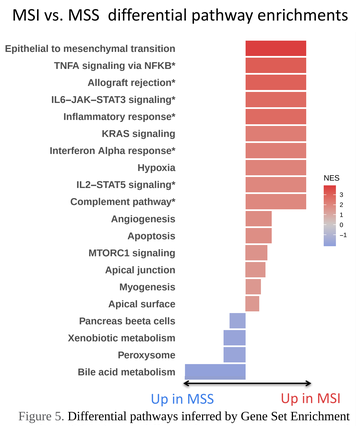

Figure 5. Differential pathways inferred by Gene Set Enrichment Analysis (GSEA) using differential expression between MSI and MSS samples (Figure 4). Red and blue bars correspond to pathways upregulated in MSI and MSS samples respectively. Color intensity corresponds to the magnitude of the enrichment score. Immune pathways are marked with *.

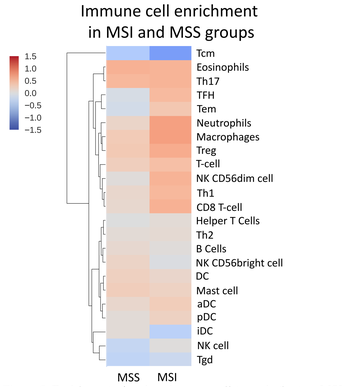

Figure 6. Enrichment of various immune cell types in the two MSI groups. The brighter the red color is the larger the enrichment is.

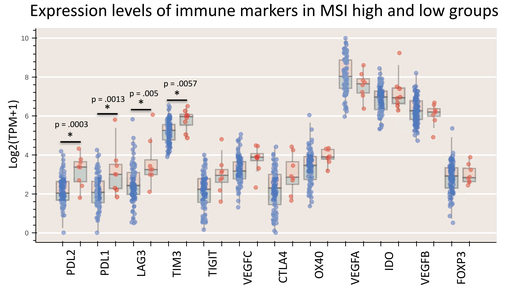

Figure 6. Expression levels of various immune markers in the two MSI groups. PDL2, PDL1, LAG3, and TIM3 are statistically significantly differentially expressed. TIM3 presents an interesting potential therapeutic target.

KEY FINDINGS

- Higher immune signaling in MSI high tumors
- Metabolic signaling is up in MSS group
- Upregulation of structural cellular integrity pathways in MSI high samples
- Some MSI samples show high CD8 T-cells enrichment
- TIM3 and LAG3are expressed at higher levels in MSI high samples
- In subset of tumors additional checkpoints are significantly differentially overexpressed in MSI malignancies

CONCLUSIONS:

MSI tumors demonstrably exhibit higher immune signaling, with many immune and checkpoint markers expressed at higher levels in MSI tumors. Some cellular integrity pathways also appear to be up in MSI cohort. A number of potentially important somatic variants are associated with MSI samples.

FOR FURTHER INFORMATION AND QUESTIONS:

Yulia.Newton@nantomics.com (Yulia Newton)

1. Kizuki Yuza, Masayuki Nagahashi, Satoshi Watanabe, Kazuaki Takabe and Toshifumi Wakai. "Hypermutation and microsatellite instability in gastrointestinal cancers". Oncotarget. 2017; 8:112103-112115. https://doi.org/10.18632/oncotarget.22783

2. Oda S, Zhao Y, Maehara Y. "Microsatellite instability in gastrointestinal tract cancers: a brief update". Surg Today. 2005;35(12):1005-15. https://doi.org/10.1007/s00595-005-3125-1

3. Margherita Ratti, Andrea Lampis, Jens C. Hahne, Rodolfo Passalacqua, and Nicola Valeri. "Microsatellite instability in gastric cancer: molecular bases, clinical perspectives, and new treatment approaches". Cell Mol Life Sci. 2018; 75(22): 4151–4162. https://doi.org/10.1007/s00018-018-2906-9