Characterization of *NY-ESO-1* gene expression in gastric cancer (GC)

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Introduction

- Tumor specific antigens, such as *NY-ESO-1,* are emerging as key tumor immune modulating factors with great potential to be used as therapeutic targets to enhance immunotherapy efficacy and expand treatment options for GC.
- *NY-ESO-1* (New York esophageal squamous cell carcinoma 1) is a well-known cancer-testis antigen (CTAs), which is also expressed in numerous cancer types.
- *NY-ESO-1*'s ability to elicit spontaneous humoral and cellular immune responses and have a restricted expression pattern, make it a good candidate target for cancer immunotherapy.[1]
- We tested whether GC tumors expressing high levels of *NY-ESO-1* are associated with immune cell abundance in the tumor microenvironment (TME), as well as distinct molecular features and immune biomarkers in comparison to low expressing tumors.

Methods

- A total of 1967 CRC tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (Illumina Next Seq, 592 genes, or Illumina NovaSeq, WES) and RNA (Illumina NovaSeq, WTS) were analyzed.
- Top quartile transcripts per million (TPMs) for *CLDN18.1/18.2* expression were considered high (Q4) while bottom quartile low (Q1) expression.
- Tumor mutational burden (TMB) was calculated based on somatic nonsynonymous mutations. Mismatch repair deficiency/Microsatellite instability (dMMR/MSI) status was evaluated by a combination of IHC, Fragment Analysis and NGS of known MSI loci. Gene fusions were detected based on WTS.
- Cell infiltration in the TME was estimated by quanTIseq.
- Gene expression profiles were analyzed for a transcriptional signature predictive of response to immunotherapy (T cell-inflamed signature: TIS).
- X^2, Fisher-exact, and Mann Whitney tests were used for comparison and significance adjusted for multiple testing by Benjamini-Hochberg correction ($q < 0.05$).

Results

Figure 1. *NY-ESO-1* Gene Expression according to Primary Tumors vs Metastatic Sites

		TPM Values	p value
NY-ISO-1	Primary	0.09	0.03
	Metastasis	0.13	

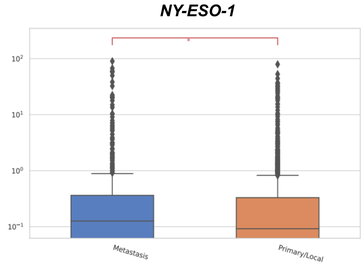


Figure 2. Primary Tumor *NY-ESO-1* Expression in relation to TME Cell Infiltration

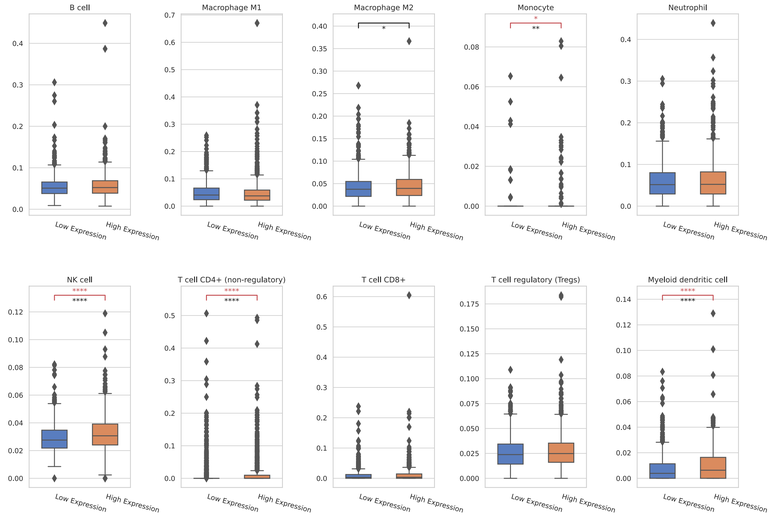


Figure 3. Primary Tumor *NY-ESO-1* Expression in relation to Immuno-Oncology Markers and TIS score

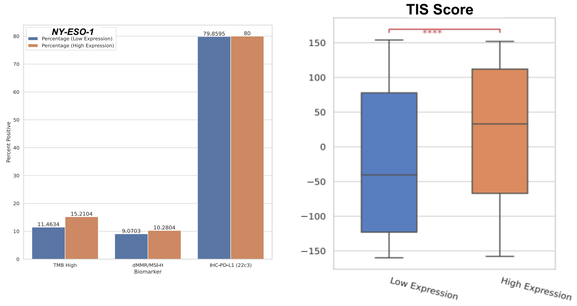
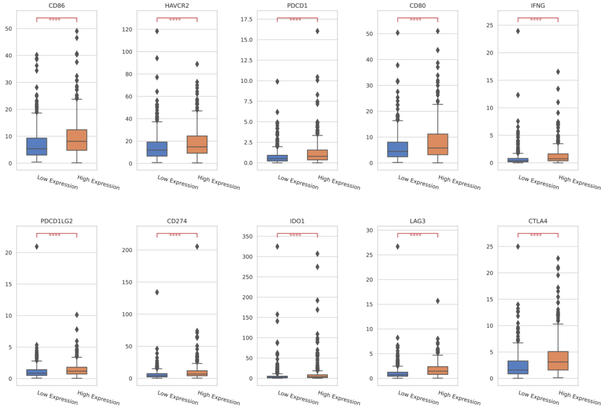


Figure 4. Association between Primary Tumor *NY-ESO-1* Expression and expression of Immune-related Genes



Summary

- Expression of *NY-ESO-1* was lower in primary/local than metastases (Fold Change FC met vs primary: 1.60, q < 0.05).
- *NY-ESO-1* expression did not appear to be strongly associated with distinct gene mutation profiles in GC (data not shown).
- There were no significant differences between low and high expression of *NY-ESO-1* with regards to well established immuno-oncology markers (dMMR/MSI, TMB, PD-L1).
- High *NY-ESO-1* expression was positively associated with immune related gene expression including *CD274*, *CD80*, *CD86*, *CTLA4*, *HAVCR2*, *IDO1*, *IFNG*, *LAG3*, *PDCD1*, and *PDCD1LG2* (FC low vs high: 0.56 to 0.79, $q < 0.0001$).
- High *NY-ESO-1* expression was also positively associated with cell abundance in the TME including NK cells (FC = 0.87, $q < 0.0001$), monocytes (FC = 0.29, $q < 0.05$), myeloid dendritic cells (FC = 0.66, $q < 0.0001$), CD4+ non-reg T cells (FC = 0.54, $q < 0.0001$), and CD8+ T cells (FC = 0.73, $q < 0.05$).
- Similarly, tumors with high *NY-ESO-1* expression were associated with higher TIS scores ($q < 0.0001$).

CONCLUSIONS

- In our large cohort of GC, tumors expressing high *NY-ESO-1* displayed a distinct landscape of immune cells in the TME.
- There was an association with high expression of immune related genes, as well as a high TIS score, which has been reported to predict benefit from anti-PD-1 treatment.
- The results of our analysis support an association between a more immunologically active tumor microenvironment and *NY-ESO-1* expression which may have relevant implications on immunotherapy treatment for GC.

References

1) Thomas R, Al-Khadairi et al. NY-ESO-1 Based Immunotherapy of Cancer: Current Perspectives. Front Immunol. 2018.