Comprehensive characterization of *PTPRT* expression in colorectal cancer (CRC)

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Introduction

- Protein Tyrosine Phosphatase Receptor Type T (*PTPRT*) is a protein coding gene involved in signal transduction and cellular adhesion. It acts as a tumor suppressor gene and mutated *PTPRT* has been implicated in the early metastasis of CRC.
- *PTPRT* mutations have been reported as independent potential biomarkers for bevacizumab resistance in metastatic CRC and linked to improved response and survival of patients treated with checkpoint inhibitors in several tumor types.
- Here we characterized the molecular features and clinical outcomes associated with *PTPRT* gene expression in CRC.

Methods

- A total of 15,025 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 for *PTPRT* expression were considered high (H) and bottom quartile low (L).
- Consensus molecular subtypes (CMS) were assessed using RNAseq. Cell infiltration in the tumor microenvironment (TME) was estimated by QuantiSEQ.
- X^2, Fisher-Exact, and Mann-Whitney tests were used and significance determined as *P*-value adjusted for multiple comparisons ($Q < 0.05$).
- Real world survival was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patients.

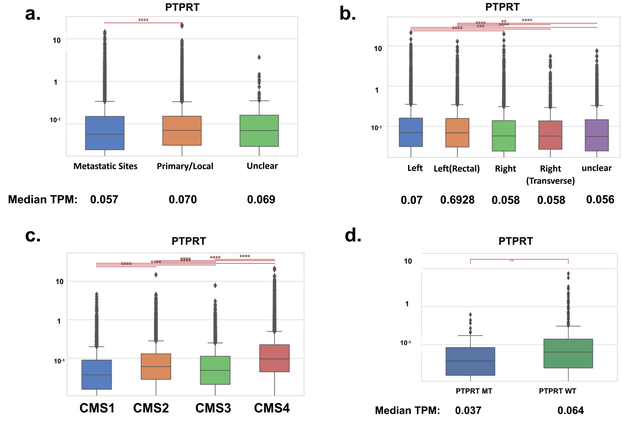
Patient Demographic

PTPRT Expression	Q1	Q2	Q3	Q4
Count (N)	3697	3696	3696	3697
Median Age (range)	64.0 (19 - >89)	63.0 (14 - >89)	62.0 (21 - >89)	61.0 (15 - >89)
Male	51.7%	54.8%	56.6%	55.9%
Female	48.3%	45.2%	43.4%	44.1%

PTPRT expression was inversely correlated with patient age (Spear coefficient -0.064, $P = 6.1e\text{-}15$).

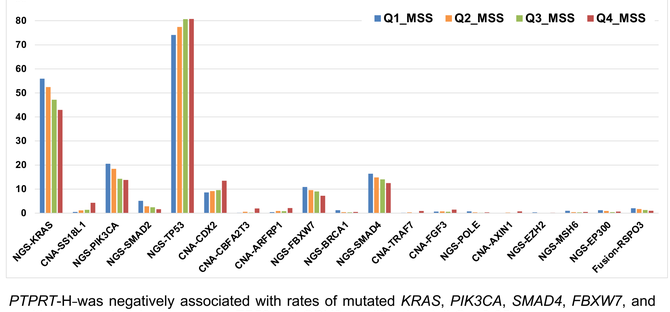
Results

Figure 1. *PTPRT* Expression According to Primary Tumor vs Metastases (a), Primary Tumor Side (b), CMS (c), and *PTPRT* mut (d).



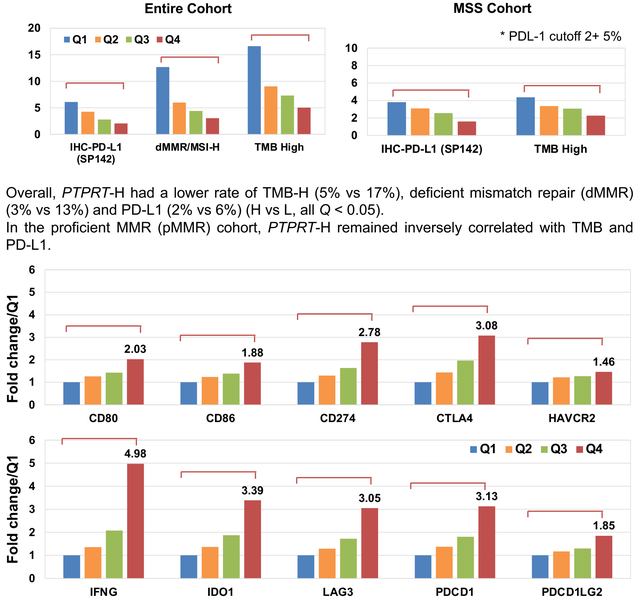
PTPRT expression was higher in left- than right-sided CRC and in primary/local tumors than in metastases; it was highest in CMS4 and lowest in CMS1 (all $Q < 0.05$).
PTPRT mutants had lower expression than wild type (0.037 vs 0.064, $Q < 0.05$).

Figure 2. Association of *PTPRT* Expression with Tumor Molecular Characteristics (MSS Cohort, significant results).



PTPRT-H-was negatively associated with rates of mutated *KRAS*, *PIK3CA*, *SMAD4*, *FBXW7*, and positively associated with mutated *TP53* and *CDX2* amplification (all $Q < 0.05$).

Figure 3. Association with Immune Markers and Immune-related Gene Expression.



Overall, *PTPRT*-H had a lower rate of TMB-H (5% vs 17%), deficient mismatch repair (dMMR) (3% vs 13%) and PD-L1 (2% vs 6%) (H vs L, all $Q < 0.05$).
In the proficient MMR (pMMR) cohort, *PTPRT*-H remained inversely correlated with TMB and PD-L1.

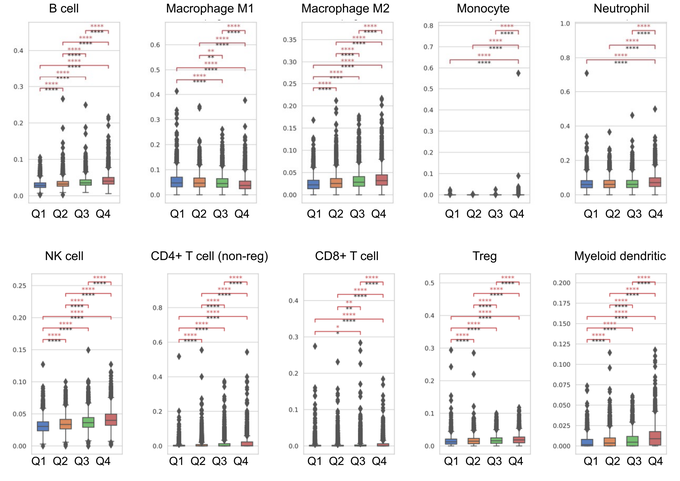
Expression of immune related genes was higher in *PTPRT*-H CRC, including *CD274*, *CD80*, *CD86*, *CTLA4*, *HAVCR2*, *IDO1*, *IFNG*, *LAG3*, *PDCD1*, and *PDCD1LG2*, regardless of MMR status (Fold Change/FC: 1.46-4.98, all $Q < 0.05$).

CONCLUSIONS

Our data show a strong association between *PTPRT* expression and distinct molecular features (including CMS and immune biomarkers), TME cell infiltration and targeted treatment outcomes in CRC.

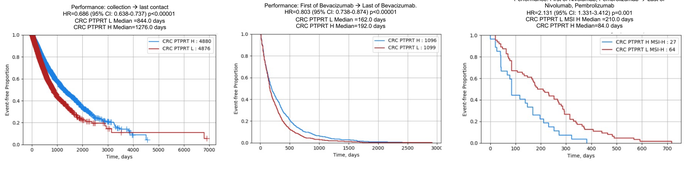
These findings support *PTPRT* as a candidate prognostic and predictive biomarker for bevacizumab and immunotherapy treatment, and as a potential target in CRC.

Figure 4. TME Cell Infiltration According to *PTPRT* Expression in MSS Tumors.



PTPRT-H was associated with higher immune cell infiltration in the TME including B cells, M2 macrophages, neutrophils, NK, Tregs, CD4+ and CD8+ T cells, and myeloid dendritic cells (fold change/FC: 1.21-7.1), but lower M1 macrophages (FC: 0.76), regardless of MMR status (all $Q < 0.05$) with the only exception of CD8+ T cells in dMMR.

Figure 5. Association between *PTPRT* Expression and Patient Outcomes.



PTPRT expression above median was associated with better OS (overall: HR 0.69, 95% CI [0.64-0.74]; pMMR: HR 0.67 [0.63-0.73]), longer time on treatment of bevacizumab (overall: HR 0.80 [0.74-0.87], pMMR: HR 0.80 [0.74-0.87]), and shorter time on immunotherapy treatment in the dMMR cohort (HR 2.13 [1.33-3.45]).