Dissecting the significance of *ACP1* gene alterations in prostate cancer (PCa)

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Abstract

Background:

- The acid phosphatase 1 (*ACP1*) gene encodes low molecular weight protein tyrosine phosphatase (LMPTP), which is overexpressed in PCa.
- Previous studies demonstrate that LMPTP plays a critical role in PCa growth and metastasis and is evolving as a potential therapeutic target.
- Thus, we analyzed *ACP1* expression in primary and metastatic PCa samples and the association of ACP1 with molecular profiles and clinical outcomes.

Methods:

- NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed for PCa specimens (n=5028) submitted to Caris Life Sciences.
- *ACP1*-High/Low expression was defined as quartile 4 (Q4) and 1 (Q1) of RNA transcripts per million (TPM).
- DNA mutational profiles were analyzed for samples stratified by *ACP1* expression quartiles.
- Gene set enrichment analysis was used to assess the Hallmark collection of cancer pathways.
- Tumor cell PD-L1+ status (≥2+, ≥5%; SP142) was tested by immunohistochemistry.
- Immune cell fractions in the tumor microenvironment (TME) were estimated by RNA deconvolution using QuanTIseq.
- Overall survival (OS) was assessed from the time of specimen collection to death or last follow-up, with hazard ratio (HR) calculated using the Cox proportional hazards model, and P values calculated using the log-rank test.

Results

Figure 1. Transcriptional expression of *ACP1* in prostate cancer across tumor biopsy sites. (A) Differential expression of *ACP1* in tumor samples collected from prostate, lymph node, and any distant metastatic site ('Metastases'); (B) *ACP1* expression across individual metastatic sites. For panels A and B, sample sizes are noted in parentheses for each tumor site. (C) Differential expression of *ACP1* across various cancer and normal tissues from the TCGA database (FireBrowse). ***p<0.001, ****p<0.0001.

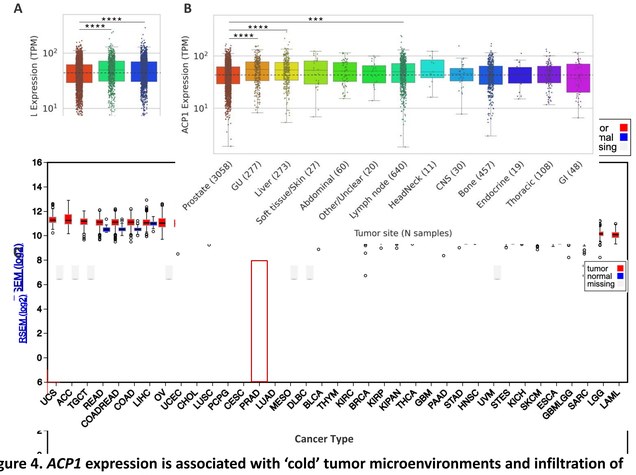


Figure 4. *ACP1* expression is associated with 'cold' tumor microenvironments and infiltration of immunosuppression cell types. (A) Median immune cell fractions for populations estimated by RNA deconvolution (quanTIseq); '+' and '-' indicate statistically significant (p<0.05) increases or decreases, respectively, among *ACP1* Q4 compared to *ACP1* Q1 subpopulations. (B) Matrix of Spearman correlations for *ACP1* expression, immune cell types, and a T cell-inflamed score predictive of response to immunotherapy. (C) Prevalence of common immunotherapy-related biomarkers across *ACP1* quartile subgroups by tumor site. *p<0.05.

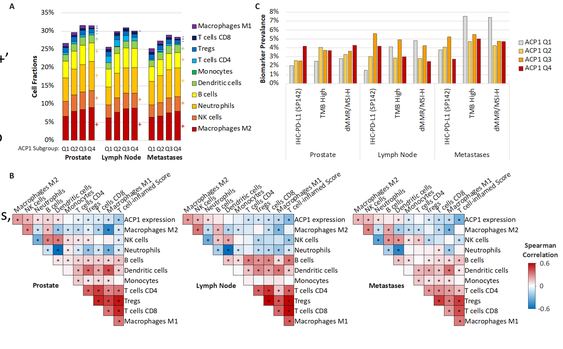


Figure 2. Genomic landscape associated with *ACP1* expression in prostate cancer by tumor site. Oncoprint of recurrent alterations occurring in >3% of the overall study among prostate (A), lymph node (B), metastases subpopulations (C) stratified by *ACP1* expression. *p<0.05, ***p<0.001.

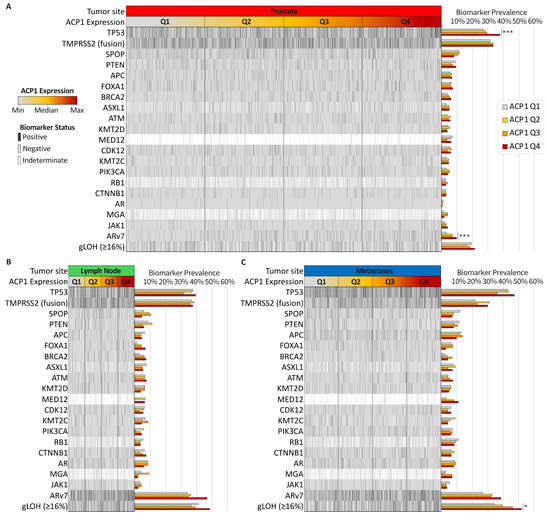


Figure 5. Real-world overall survival among patients stratified by *ACP1* expression and tumor biopsy site. (A) Overall survival from the date of biopsy for patients with *ACP1*-High (Q4) and -Low (Q1) tumors by biopsy site. (B) Forest plot of overall survival from the date of biopsy (same as panel A), the start of taxane therapy, the start of androgen receptor pathway inhibitors (ARPI), and the start of immunotherapy (IO).

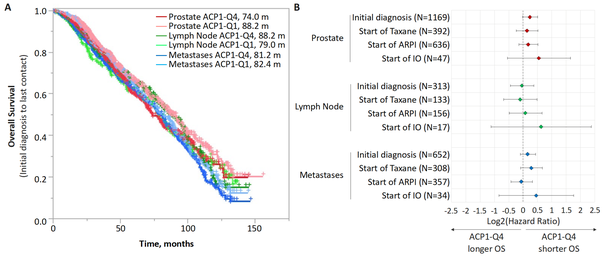
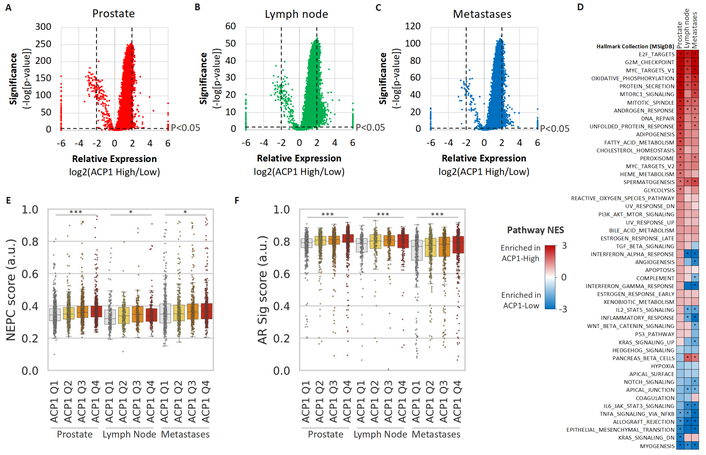


Figure 3. *ACP1* expression is associated with changes in cell cycle and metabolic pathways. (A-C) Volcano plot of differentially expressed genes in *ACP1*-High vs. *ACP1*-Low samples across tumor sites. (D) Gene set enrichment analysis of the Hallmark collection of gene sets (MSigDB). (E-F) *NEPC* and *AR* signaling transcriptional expression scores across *ACP1* quartile subgroups by tumor site.



Conclusions

- In the largest study investigating the significance of *ACP1* expression in PCa, we demonstrate that *ACP1*-high tumors exhibit a distinct molecular profile enriched for TP53 alterations and associated with a 'cold' TME.
- Our findings may provide a rationale for novel therapeutic targeting of *ACP1*-high tumors.

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