Abstract ID# 5022: Association of Adaptive Immunity/ Inflammatory Genes with Survival in Prostate Cancer

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Background

- Advances in immunotherapy have had little impact on prostate cancer (PCa) treatment outcomes.
- We have previously examined the immune microenvironment in both localized and metastatic PCa and found that primary PCa shows local inflammation/adaptive immunity whereas metastatic disease shows a shift towards immune suppression (Deichaite, 2022).
- Herein, we examine immune remodeling in PCa by evaluating changes in gene expression between localized and metastatic disease with heterogeneous treatment patterns in both primary and metastatic samples.

Methods

- Tumors from PCA (N = 5,419) were tested at Caris Life Sciences (Phoenix, AZ) with NextGen DNA Sequencing (592-gene or whole exome) and RNA (whole transcriptome).
- Samples collected from the prostate gland (N = 3,284) or metastatic sites (N = 2,135) were analyzed.
- The Mann-Whitney U test was applied as appropriate, with P-values adjusted for multiple comparisons ($q < .05$).
- Real-world overall survival (OS) data was obtained from insurance claims and Kaplan-Meier estimates were calculated for molecularly defined subpopulations. Survival for tumors with high (-H) and low (-L) expression of genes of interest, defined as top and bottom quartile of expression (transcripts per million, TPM) across all tumors, was investigated.

Results

1. Expression of immune related genes between primary and metastatic sites

We observe differences in expression of genes associated with immune regulation between primary and metastatic sites. This suggests that site-based differences influence immune signaling.

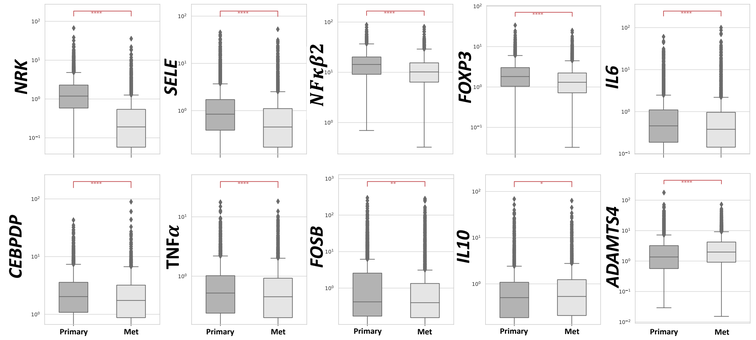


Figure 1: Gene expression (TPM) for the indicated gene for tumors biopsied at a primary or metastatic site, asterisk indicates significance * $p < 0.05$, ** $p < 0.005$, **** $p < 0.00005$)

2. Correlation between *FOSB* and upstream genes

A weak relationship between *TNFα* and *FOSB* was observed regardless of site. *SELE* and IL6 genes had a stronger association with *FOSB* in tumors biopsied from the primary as opposed to the metastatic site.

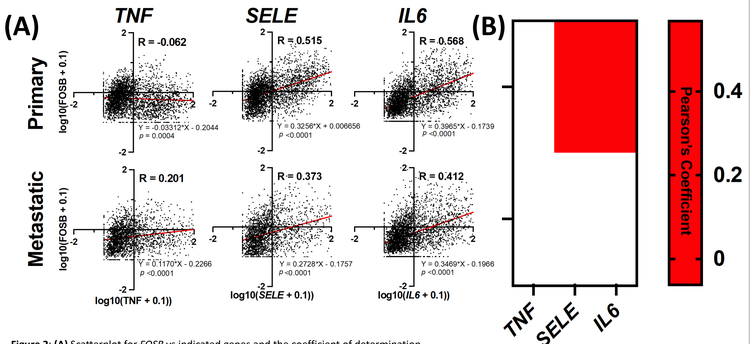


Figure 2: **(A)** Scatterplot for *FOSB* vs indicated genes and the coefficient of determination (Pearson's) for tumors biopsied at either a primary or metastatic site **(B)** Heatmap of Pearson's correlation coefficients.

3. Correlation between *TNFα* and immune checkpoint genes

A strong relationship is observed between immune check point genes and the *TNFα* ligand across tumors biopsied at either a primary or metastatic site.

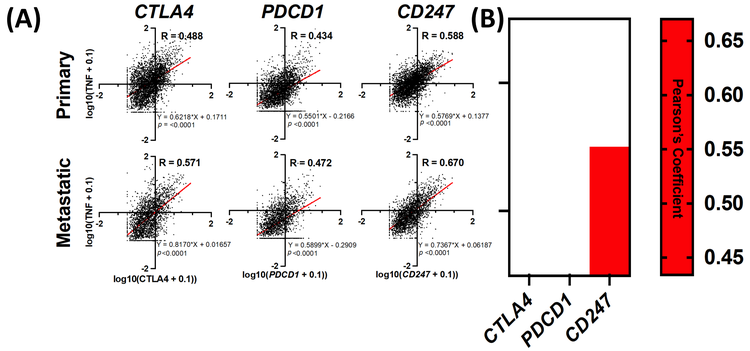


Figure 3: **(A)** Scatterplot for *TNFα* vs indicated genes and the coefficient of determination (Pearson's) for tumors biopsied at either a primary or metastatic site **(B)** Heatmap of Pearson's correlation coefficients.

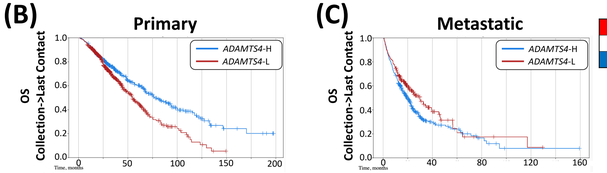
4. Outcomes data in primary vs metastatic sites

High expression of *ADAMTS4* is associated with better overall survival (OS) in the primary site but is associated with worse OS in the metastatic site. A similar trend is observed for *IL10* and *CEBPD2* gene expression.

(A)

	Primary						Met					
	HR	CI	CI	p	N Q1	N Q4	HR	CI	CI	p	N Q1	N Q4
IL6	0.55	0.45	0.68	**< 0.001**	458	534	0.88	0.72	1.09	0.237	370	289
IL10	0.78	0.64	0.95	**0.014**	522	489	1.09	0.88	1.34	0.418	305	332
NRK	0.46	0.35	0.61	**< 0.001**	113	738	0.90	0.69	1.18	0.452	683	106
SELE	0.51	0.42	0.63	**< 0.001**	361	598	0.87	0.70	1.07	0.19	457	227
CEBPD	0.93	0.78	1.11	0.422	436	1089	1.22	1.02	1.45	**0.025**	380	568
NFKB2	0.90	0.74	1.10	0.3	389	620	0.68	0.54	0.84	**<0.001**	424	216
FOSB	0.56	0.47	0.66	**< 0.001**	982	564	0.78	0.65	0.95	**0.013**	672	262
ADAMTS4	0.67	0.55	0.81	**<0.001**	616	443	1.30	1.04	1.63	**0.021**	221	372
TNFα	1.07	0.88	1.30	0.476	468	545	1.04	0.85	1.28	0.699	350	289
FOXP3	0.96	0.78	1.17	0.669	402	609	0.91	0.74	1.13	0.402	410	230
Median	HR	CI	CI	p	Below median	Above median	HR	CI	CI	p	Below median	Above median
IL2	0.62	0.54	0.75	<0.001	954	1067	0.79	0.68	0.92	0.002	714	555

(B)



(C)

Figure 4: (A) Table of HR ratios segmented on gene expression (Q1 vs Q4) for tumor biopsies taken from the primary or metastatic site. Kaplan-Meier curves for high and low expression of ADAMTS4 in the **(B)** primary or **(C)** metastatic site.

Study Highlights

- *SELE* and *IL6* genes had a stronger association with *FOSB* in tumors biopsied from the primary as opposed to metastatic site.
- A strong correlation is observed between immune check point genes and the *TNFα* across tumors biopsied at primary or metastatic sites.
- High expression of *ADAMTS4* is associated with better overall survival (OS) in the primary site but is associated with worse OS in the metastatic site.

Conclusions

- We identified significant differences in the expression of inflammatory regulators and cytokines between localized and metastatic PCa tumors, which correlate with OS.
- These changes in the immune microenvironment can be leveraged for rational immunotherapy development and better targeted approaches.

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