Tristetraprolin Is a Prognostic Biomarker for Prostate Cancer

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Learning Objectives

1. Discuss the need for improved biomarkers to more accurately risk-stratify patients for appropriate therapeutic recommendations

2. Explain Tristetraprolin’s (TTP’s) biological function

3. Evaluate if TTP is a clinical biomarker for determining prostate cancer risk, especially in low-grade prostate cancer
Overtreatment of Prostate Cancer

- PSA testing has increased the diagnosis of early prostate cancer resulting in an epidemic of overtreatment for men with very-low-risk and low-risk prostate cancer.

- Growing evidence supports the use of active surveillance in very-low-risk and low-risk prostate cancer patients as a means to decrease overtreatment and improve quality of life.

- However, ~30% of patients in North American long-term active surveillance studies were ultimately reclassified as harboring aggressive disease and required therapeutic intervention.

- Thus, there is an unmet need for improved prognostic prostate cancer biomarkers.
Tristetraprolin (TTP)

- RNA binding protein containing tandem zinc finger domains that bind to adenosine-uridine (AU) rich elements located in the 3′ UTR of many mRNAs with short half-lives.
Tristetraprolin (TTP)

- AU-rich elements are present in numerous genes involved in cancer development, including genes that control proliferation, metabolism, immune responses, angiogenesis, and metastasis.

- TTP suppresses Myc-induced B cell lymphoma development and maintenance. (Rounbehler et al., Cell, 2012)
TTP Inhibits Prostate Tumor Growth and Metabolism

Berglund et al., Oncotarget, 2016
Low *TTP* Expression Connotes Poor Prognosis for Prostate Cancer
**TTP RNA Levels Are Lower in Prostate Tumors that Progress to Biochemical Recurrence**
Prostate Tumors with Low $TTP$ RNA Expression Have an Increased Biochemical Recurrence Rate
TTP RNA Is a Clinically Relevant Biomarker of Biochemical Recurrence Risk Assessment

Univariable Analysis of TTP Expression for BCR Risk Assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>MCC RNA</td>
<td>0.54 (0.37-0.78)</td>
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Prostate Tumors with Low TTP Protein Have an Increased Biochemical Recurrence Rate
**TTP RNA Is a Clinically Relevant Biomarker of Biochemical Recurrence Risk Assessment**

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### Univariable Analysis of TTP Expression for BCR Risk Assessment

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<tr>
<td>MCC TMA</td>
<td>0.56 (0.34-0.93)</td>
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TTP RNA Levels Are Lower in Prostate Tumors that Progress to Metastasis
**TTP RNA Is a Prognostic Biomarker of Metastatic Risk Assessment**

**Univariable and Multivariable Analysis of TTP RNA Expression and Metastasis**

<table>
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<th>Cohort</th>
<th>UVA</th>
<th>MVA</th>
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<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P</td>
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<tr>
<td>JHMI</td>
<td>0.54 (0.33 to 0.88)</td>
<td>.013</td>
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<tr>
<td>Mayo II</td>
<td>0.52 (0.30 to 0.89)</td>
<td>.017</td>
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Conclusions

- TTP is a clinically relevant biomarker for predicting which prostate cancer patients may have poor outcomes following radical prostatectomy.
Future Questions

Can TTP levels be utilized as a clinical biomarker to:

1) improve post-surgical risk assessment?
## Acknowledgements

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References

