An Analysis of Proviral Insertion Site of Moloney Murine Leukemia Virus 1 Kinase (PIM1) Expression and Clinical Outcomes in Renal Cell Carcinoma (RCC)

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Introduction

Pim1 Kinase

- serine/threonine kinase
- Inhibits apoptosis, promotes cell cycle progression, promotes protein synthesis
- wild-type enzyme is constitutively active
- regulated at transcription and degradation
- protein levels are increased in renal cell carcinoma (RCC)

In clear cell RCC

- PIM1 inhibitors increase apoptosis in RCC cell lines
- PIM1 inhibitors decrease viability in RCC cell lines
- PIM1 inhibitors cause tumor regression in mouse models

Current approved RCC therapies do not have activity against PIM1 kinase

Hypothesis

In RCC, increased PIM1 expression will correlate with poor clinical outcomes

Methods

- Next-gen sequencing of patient tumor tissue submitted to Caris Life Sciences (Phoenix, AZ)
  - DNA: 592-gene panel or whole exome
  - RNA: whole transcriptome
- Pathway analysis of differentially expressed genes (DEGs) was assessed using GSEA Hallmarks collection and Reactome databases
- Overall survival (OS) was calculated from insurance claims data from either the date of tissue collect or start of therapy to last contact

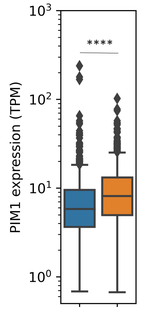

Figure 1. PIM1 kinase expression is increased in metastatic RCC. Samples from primary clear cell RCC had 5.1 TPM vs. 7.6 TPM in samples from metastatic sites (P<0.0001).

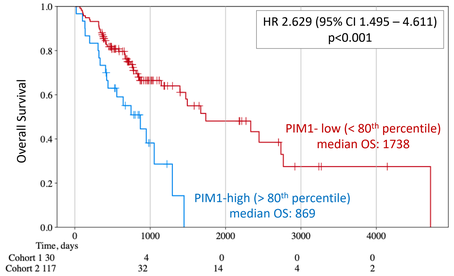

Figure 2. PIM1 kinase expression is associated with poor prognosis in RCC. Patients in the top quintile of PIM1 expression show dramatically worse survival, 869 vs 1738 median days

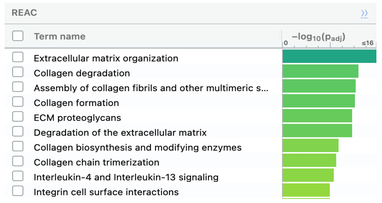

Figure 3. Many of the top 500 differentially expressed genes associated with high PIM1 are involved in regulation of the extracellular matrix

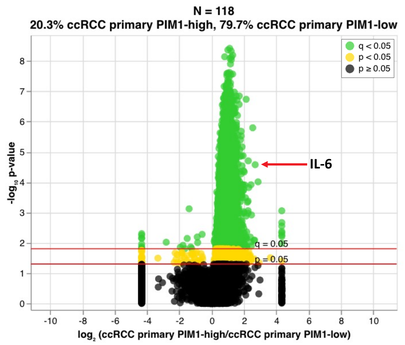

Figure 4. PIM1 kinase expression correlates with IL-6 expression in RCC. IL-6 expression, known to correlate with worse outcomes, was 6.5-fold higher in PIM1 high vs PIM1 low (13.2 vs 2.1 TPM, p<0.0001) RCC. See companion poster

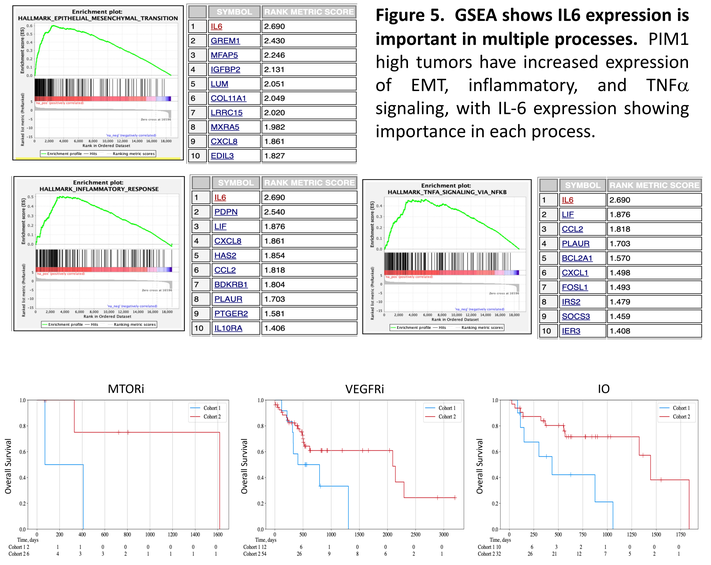

Figure 5. GSEA shows IL6 expression is important in multiple processes. PIM1 high tumors have increased expression of EMT, inflammatory, and TNFα signaling, with IL-6 expression showing importance in each process.

Figure 6. High PIM1 is associated with poor survival in all treatment cohorts. High PIM1 was associated with poor survival following checkpoint inhibition (HR 3.714, 95% CI 1.339 – 10.303, p=0.007), and a trend towards poorer survival following mTOR inhibition and VEGF inhibition. .

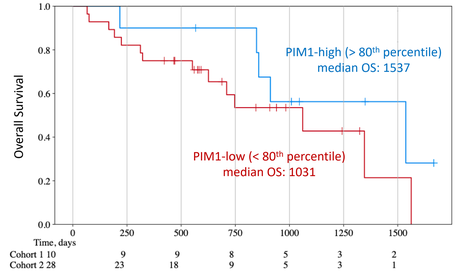

Figure 7. PIM1 kinase expression does not influence survival in papillary RCC. HR 0.543, 95% CI 0.19 – 1.55, p=0.247

Conclusions

- Real-word data show that high PIM1 expression correlates with poorer survival in clear cell RCC but not in papillary RCC.
- Poor survival in PIM1 high expressors appears independent of treatment received.
- PIM1 enrichment in metastatic clear cell RCC, and the identified DEGs, suggest that PIM1 influences the extracellular matrix to promote metastases in RCC.
- The correlation between PIM1 expression and IL-6 expression supports our data that an IL-6/JAK/STAT/PIM1 pathway is involved in clear cell RCC. Please see the companion poster at this conference: IL-6 signaling via JAK/STAT axis influences PIM1 expression in renal cell carcinoma (K. Meza)

Future directions

- Determine the effects of IL-6, JAK, STAT, and PIM1 inhibition in RCC cell lines and *in vivo*
- Determine the downstream effects of PIM1 on the cancer phosphoproteome
- Interrogate the differences in the transcriptome between PIM1 low and PIM1 high RCC