Gene expression profiles in renal cell carcinoma

October 23, 2014

W. Kimryn Rathmell, MD, PhD

VHL and clear cell Renal Cell Carcinoma

- VHL syndrome hallmark cancer:
  - Clear cell renal cell carcinoma (ccRCC)
- VHL mutations also a hallmark of sporadic ccRCC
- VHL mutation → HIF stabilization and gene expression changes associated with the hypoxia response.

Renal Cell Carcinoma (RCC)

- Originates in the renal cortex
- Most common solid lesion occurring in the kidney (80-85% of all primary renal neoplasms)

Expression profiling reveals cell of origin

Outline

- Gene expression profiles in clear cell renal cell carcinomas.
- Validating a prognostic signature in RCC.
- Exploring gene expression profiles in VHL syndrome RCC tumors.

Gene expression patterns show HIF-specific variability

- HIF1 drives glycolytic genes, mTOR pathway
- HIF2 drives genes involved in cell cycle and DNA damage.
- Overlap in angiogenesis and motility targets.
Using gene expression to identify tumor subgroups. ccA and ccB

K=3, K=4 still fall into two groups

ccA (classical angiogenic), ccB (bad)

Validation in a historical dataset
**Extent of Disease at Diagnosis**

- Most cancers of the kidney and renal pelvis are diagnosed when the disease is still localized to the primary site

```
Extent of Disease at Diagnosis

- Metastatic Spread 20%
- Loco-regional Spread 19%
- Localized Disease 56%
- Unknown 5%
```


**Determining Prognosis: Anatomic Extent of Disease**

- Most consistent factor used to determine RCC prognosis

```
Determining Prognosis: Anatomic Extent of Disease

5-year Cancer-specific Survival Based on TNM Stage

<table>
<thead>
<tr>
<th>TNM Stage</th>
<th>5-year Cancer-specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (N=185)</td>
<td>91 ± 2.5%</td>
</tr>
<tr>
<td>Stage II (N=67)</td>
<td>74 ± 6.9%</td>
</tr>
<tr>
<td>Stage III (N=63)</td>
<td>67 ± 6.1%</td>
</tr>
<tr>
<td>Stage IV (N=318)</td>
<td>32 ± 3.2%</td>
</tr>
</tbody>
</table>
```


**ccA/ccB predicts for cancer specific and overall survival outcomes**

```
ccA/ccB predicts for cancer specific and overall survival outcomes

Brannon, et al, Genes and Cancer, 2010
```

**Validation dataset reveals a small distinct tumor set**

```
Validation dataset reveals a small distinct tumor set

```
Cluster 3 are highly divergent from ccA and ccB in metabolic genes.


VHL mutants in both ccA and ccB


Developing a clinic tool: ClearCode34

95 clear cell tumors

LAD and ConsensusCluster analysis
Set aside arrays with non-concordant assignments

72 arrays (microarray standard set)
(69 tumors, 3 replicates)

43 ccA arrays
(42 tumors, 1 replicate)

29 ccB arrays
(27 tumors, 2 replicates)

Prediction Analysis for Microarrays (PAM)

Predictive biomarkers: ClearCode34


Prognostic value of ClearCode34 evaluated in TCGA

Prognostic value of ClearCode34 validated in UNC cohort

Integrated prognostic models can evaluate risk outcomes

RCC Algorithms for cancer-specific survival

Abbreviation: HR, hazard ratio

Subtype ccA was used as reference in univariate and multivariate analysis. Stage I was used as reference in univariate and multivariate analysis. Grade was encoded as an ordinal variable with three levels. Grade 1 and 2 were combined and used as reference in univariate and multivariate analysis. Grade was encoded as an ordinal variable with three levels.
ClearCode34 Model outperforms established algorithms

ClearCode34 Summary

- ClearCode34 can accurately classify ccRCC tumors
- Prognostic value of ccA/ccB classification validated in a TCGA and UNC cohort
- Integrated model for recurrence-free and cancer-specific survival constructed using ccRCC subtypes and traditional clinical variables stage and grade.
- This classifier adds value to predicting cancer-specific survival above and beyond established algorithms.

How do we know this is meaningful for VHL patients?

TCGA includes 14 tumors from VHL patients:
2-class comparison reveals NO significantly different upregulated genes, 209 significantly downregulated.

*VHL disease tumors and sporadic ccRCCs (the majority VHL mutated) are not distinguishable by gene expression.

VHL cases in the TCGA-A mixture of ccA and ccB
Summary

• The hypoxia gene expression signature dominates VHL mutated RCC, but many other pathways emerge.
• The expression profile matches ccRCC to the early proximal tubule.
• Tumor expression profiles can reveal relevant biology and aid in disease prognosis.

Acknowledgments

Rathmell Lab
Kate Hacker, PhD
Alex Arreola, PhD
Samira Brooks
Zufan Debebe, PhD
Sneha Sundaram, PhD
Catherine Fahey
Adam Sendor

Rathmell Lab Past Members
Rose Brannon, PhD
Oishee Sen
Shufen Chen, MD, PhD
Lance Cowey, MD
Caroline Martz Lee, MD, PhD
Tricia Wright, PhD
Neal Rasmussen, PhD

Translational Pathology Laboratory
Genomics Core, Tissue Procurement Facility

Rutgers
Gyan Bhanot, PhD
Anupama Reddy, PhD

Joel Parker, PhD

UNC Biomedical Research Imaging Center
Welli Lin, PhD
Amir Khandani, MD
Julia Fielding, MD

The Cancer Genome Atlas
Particularly: Chad Creighton, Marston Linehan, Richard Gibbs, Kenna Shaw

Clinical TCGA
Particularly: James Hsieh, Ari Hakimi, Toni Choueri

Funding: AACR INNOVATOR Award, NIH (TCGA), NIH (K24), V Foundation for Cancer Research