CLEAR CELL RENAL CELL TUMORS

DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS

Satish K. Tickoo
RENAL CELL TUMORS WITH CLEAR CELL FEATURES
Clear cell renal cell carcinomas that may not look like clear cell RCC
A clear picture of renal cell carcinoma

A Ari Hakimi, Can G Pham & James J Hsieh

![Genetic diagram showing 3p loss and genes involved in renal cell carcinoma]
MOLECULAR PATHWAYS IN CLEAR CELL RENAL CELL CARCINOMA

**Hypoxia/silenced VHL**

- VHL complex
- HIFα
- HIFβ
- PI3K
- Ras
- AKT
- Raf
- mTOR
- MEK 1,2
- MAPK
- VEGF
- PDGF
- EPO
- GLUT1
- CA9
- VEGF
- PDGF

**NORMOXIA**

- VHL complex
- HIFα
- Ub
- Proteasome

**Endothelial or Stromal cell**

HIF Responsive Elements
EXAMPLES
Clear cell vs. Not clear cell
High grade tumors

- 2/3 RCCs are still clear cell RCC
- Unless the tumor shows features specific to other tumor types, do not completely give up on clear cell RCC
- Careful examination for even very focal typical clear cell RCC areas is imperative
- In some cases, CA-IX may help
BACK TO THE GROSS SPECIMEN
May look like clear cell RCC but are not
CLEAR CELL PAPILLARY RENAL CELL CARCINOMA
Abnormal oxidative metabolism in a quiet genomic background underlies clear cell papillary renal cell carcinoma

• Wild-type nuclear genome
• Severe depletion of mitochondrial DNA and RNA
• Exhibit high levels of oxidative stress
• Distinct metabolic phenotype characterized by accumulation of the sugar alcohol sorbitol.

Other tumors with clear cytoplasm, prominent fibromuscular stroma, and CK7 positivity
TCEB1-mutated RCC

- Encodes Elongin C, a 112-residue protein identified as a subunit of the heterotrimeric RNA polymerase II elongation factor complex (Elongin)
- A vital component of the VHL complex
- Located on Chromosome 8

- Exclusively involves two conserved amino acids, Tyr79 and Ala100
- TCEB1 mutations always accompanied by loss of chromosome 8
TCEB1-mutated RCC
TSC-associated RCC
- Multifocality, variable tumor types
- Cysts
- Angiomyolipomas

TSC-associated RCC
MiTF/TFE family translocation-associated RCC
Clear cell carcinoma with prominent fibromuscular/leiomyomatous stroma and CK7 positivity
Chromophobe RCC
Unsupervised clustering of DNA copy number profiles
# Clear cell RCC - TCGA Case Outliers*

## Pathology review**

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
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<tbody>
<tr>
<td>Clear cell/likely clear cell</td>
<td>18</td>
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<tr>
<td>Clear cell papillary</td>
<td>4</td>
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<tr>
<td>Chromophobe/likely chromophobe</td>
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<td>Oncocytoma/likely oncocytoma</td>
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<tr>
<td>Not clear cell or chromophobe</td>
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<tr>
<td>Not reviewed</td>
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<tr>
<td><strong>Total</strong></td>
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</tbody>
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*Outliers:
- Chomo-like genotype
- wtVHL
- No 3p loss

**Pathologists**
- Victor Reuter (MSKCC)
- Satish Tickoo (MSKCC)
- Pheroze Tamboli (MDACC)
- Maria Merino (NCI)
- Sabina Signoretti (DFCC)
Papillary RCC
Thank you