Renal Cell Carcinoma: Genetics & Imaging

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No financial disclosures
Acknowledgements

• Dr. Peter Choyke, NIH
• My ‘Gurus’ @ MIR, MGH
2004 WHO Taxonomy of RCC

- Histologically & biologically diverse disease
- Characteristic histology & immunochemistry
- Pathognomic molecular signatures & genetics
- Characteristic imaging findings
- Prognostication & therapeutic implications

* Eble JN et al. WHO Handbook 2004
<table>
<thead>
<tr>
<th>Histology</th>
<th>(%)</th>
<th>Cell of Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear Cell RCC</td>
<td>70</td>
<td>PCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epithelium</td>
</tr>
<tr>
<td>Papillary RCC</td>
<td>15</td>
<td>PCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epithelium</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>5</td>
<td>CCD; Type B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IC cell</td>
</tr>
<tr>
<td>Hereditary Cancer Synd</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* Eble JN et al. WHO Handbook 2004*
Hereditary RCC Syndromes

- Constitute 5% of RCC; Autosomal dominant
- Each syndrome associated by specific genetics
- A specific RCC subtype develops in each synd
- Provide valuable info about sporadic RCC
- Difficult to treat: B/L, multiple tumors
- Impetus for development of molecular therapeutics

# Hereditary RCC Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Kidney tumor</th>
<th>Systemic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>von-Hippel-Lindau</td>
<td>3p25</td>
<td>Clear cell RCC</td>
<td>Retinal angiomas, Pheochromocytomas, CNS hemangioblastomas</td>
</tr>
<tr>
<td>Hereditary Papillary RCC</td>
<td>7q34</td>
<td>Type 1 Papillary RCC</td>
<td>None</td>
</tr>
<tr>
<td>Hereditary leiomyomatosi-RCC</td>
<td>1q42</td>
<td>Type 2 Papillary RCC</td>
<td>Symptomatic Skin &amp; Uterine Leiomyomatosis</td>
</tr>
<tr>
<td>Birt-Hogg-Dube</td>
<td>17p11</td>
<td>‘Hybridomas’, Chromophobe RCC, Oncocytoma</td>
<td>Skin lesions, Lung Cysts, Pneumothorax</td>
</tr>
</tbody>
</table>

*Choyke P et al. Radiology 2003;226:33-46*
Renal Cell Carcinoma: Carcinogenesis

- Silencing of the tumor suppressor genes by Mutations or Deletions
  - VHL gene (Clear cell RCC and VHL syndrome)
    - 3p25
  - Hereditary Leiomyoma-RCC gene (Hereditary leiomyoma-RCC syndrome)
    - Fumarate hydratase gene (Mitochondrial, Kreb’s cycle enzyme gene)

* Cohen HT et al. NEJM 2005;353:2477-90
von-Hippel-Lindau Syndrome

- Autosomal dominant phakomatoses syndrome
- Kidney cysts, cystic & solid clear cell RCCs
- VHL gene absence lead to hypervascular RCCs
von-Hippel-Lindau Syndrome: Oncogenesis

- VHL gene present
  - Decrease in HIF
  - Decrease in VEGF, GFs, GluT
  - Normal Nephron

- VHL gene absent
  - Increase in HIF
  - Increase in VEGF, GFs, GluT
  - Clear cell RCC

* Cohen HT et al. NEJM 2005;353:2477-90
Sporadic Clear Cell RCC

- Most common histological subtype (70%)
- Glycogen & lipid-rich cells: ‘Clear’ cells
- Predominantly (60-80%) VHL pathway; also mTOR pathway
- Expansile, hypervascular solid tumor
- Heterogeneous tumor (necrosis & hemorrhage)
- Aggressive clinical course, worse prognosis than non-clear cell subtypes
Molecular Targets: Smart Drugs

- Temsirolimus
- mTOR
- VHL
- HIF
- VEGFR2 & PDGFRβ
- Sorafenib
- Sunitinib

* Brugarolas J. NEJM 2007;356:185-7
## Papillary RCC: A tale of 2 pathways

<table>
<thead>
<tr>
<th></th>
<th>HPRC: Type 1 Papillary</th>
<th>HLRCC: Type 2 Papillary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genetics</strong></td>
<td>Autosomal dominant</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Chromosome 7</td>
<td>Chromosome 1</td>
</tr>
<tr>
<td><strong>Oncologic Pathway</strong></td>
<td>c-MET (HGF/SF) Promoter oncogene</td>
<td>Fumarate Hydratase Silencing suppressor</td>
</tr>
<tr>
<td><strong>Clinical Syndrome</strong></td>
<td>B/L, Multiple, Micro-macroscopic RCCs</td>
<td>Single, large RCC Extensive LNpathy</td>
</tr>
<tr>
<td><strong>Natural History</strong></td>
<td>Slow growth, Low-grade, Symptoms late</td>
<td>Metastatic @ presentation Biologically aggressive</td>
</tr>
</tbody>
</table>

*Linehan WM et al. J Urol 2003;170:2163-72*
Renal Cell Carcinoma: Carcinogenesis

• Promotion of Oncogenes
  – Hereditary Papillary RCC Syndrome (type-1 Papillary)
    • Gain-of-function mutations in MET proto-oncogenes (Tyrosine Kinase Receptor) that interacts with HGF to cause tumors

* Cohen HT et al. NEJM 2005;353:2477-90
Sporadic Papillary RCC

- Constitute 10-15% of all RCC
- Papillary/tubular patterns with fibrovascular core
- 2 histologic subtypes with different biology
- Typically hypovascular tumor
- Hypointense (T2-W MR) due to necrosis & hmg
- Typically low-stage, low-grade
Birt-Hogg-Dubé Syndrome

- Autosomal dominant genodermatosis syndrome
  - Fibrofolliculomas, Lung cysts, Recurrent spontaneous pneumothorax, Kidney tumors
- Kidney: Heterogeneous tumors; B/L, multiple
  - Oncocytic ‘hybridomas’ (50%), Chromophobe RCC (34%), Clear cell RCC (9%), Oncocytoma (5%)
- BHD gene mapped to 17p11.2, encodes folliculin
- Folliculin interacts with FNIP1-2 & AMPK
- Influences mTOR pathway (Tuberous sclerosis)

Chromophobe RCC

- 5% of RCC; Mean age: 6\textsuperscript{th} decade
- Origin: Type B intercalated cells of CCD
- No sex predilection / specific symptomatology
- Low-stage tumors; excellent prognosis after Sx
Chromophobe RCC

- Soft tissue tumor with homogenous contrast enhancement on CT/MRI despite large size
- Hypovascular tumor on angiography
Medicine Advancement Model*

2008

Diagnosis → Treatment

Future

Predisposition → Focused screening
Early detection

Personalized treatment → Tailored monitoring

P4 Medicine is the future*

• “Public health demands & research advances transforming medicine”
• “Imaging: Core interdisciplinary science for generating, understanding & using biological information”
• “P4 Medicine : Future paradigm”
  – Predictive, Personalized, Preemptive, Participatory

*Zerhouni EA, Pendergrass New Horizons Lecture, RSNA 2007
Conclusion

• Recent advances in genetics & oncology: Better understanding of RCC biology
• Select RCC subtypes show signature pathways
• Drugs aimed @ molecular targets promising
• Imaging plays a greater role in diagnosis, staging & surveillance after treatment
• Quantitative methods to ascertain treatment response increasingly used