Comprehensive Molecular Characterization of Renal Cell Carcinoma: The TCGA Experience

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Outline

- **Background**
- The Cancer Genome Atlas initiative
- Clear Cell RCC
- Papillary RCC
- Chromophobe RCC
- Comparisons Across the Spectrum

Disclosures

- No relevant financial conflicts of interest or disclosures

RCC Histological Subtypes

The Cancer Genome Atlas

- Clear Cell 75%
- Papillary 15%
- Chromophobe 5%

Cortical tumors

Courtesy of Jonneman Dhillon, MD

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The Cancer Genome Atlas (TCGA)

• “...is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. TCGA is a joint effort of the NCI and NHGRI...”
• 100's of collaborators, multiple institutions, “team science”

Platforms

<table>
<thead>
<tr>
<th>DNA Seq (Exome, Genome, Mt)</th>
<th>RNA Seq</th>
<th>miRNA Seq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copy Number Analysis</td>
<td>DNA Me</td>
<td>Protein Expression</td>
</tr>
</tbody>
</table>

Von Hippel-Lindau Syndrome

- Hemangioblastomas
- Pheochromocytomas
- PNET
- Renal tumors & cysts
- Pancreatic cysts
- Endolymph. sac tumor

Phenotype includes bilateral clear cell RCC

VHL+/− (Germline mutation) → VHL−/− (Somatic Mutation (LOH))
Somatic Alterations in ccRCC
Loss of 3p, VHL Changes Remain Dominant

Chromatin Regulators and RCC

Metabolism Impacts Survival

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Genetic Syndromes & Papillary RCC

**Hereditary Papillary Renal Carcinoma (HPRC)**
- Autosomal dominant
- Highly penetrant
- Multifocal, bilateral renal tumors → type 1 papillary
- Germline MET mutations

**Hereditary Leiomyomatosis and RCC Syndrome (HLRCC)**
- Autosomal dominant
- Highly penetrant
- Cutaneous & uterine fibroids, type 2 papillary RCC (aggressive)
- Fumarate hydratase mutations

Type 1 Papillary RCC & MET

- Convergent Evolution
  - Somatic & germline mutations
  - Novel fusion
  - Promoter mutations
  - Trisomy 7

- Foretinib active in pRCC with MET mutations (germline)

Distinct Subtypes, Distinct Genomics

Emerging Drivers in Type 2 Papillary RCC

- CDKN2A-altered cases (n=30)
- NRF2/ARE Activation Correlates with Inferior Survival

NRF2/ARE Mutations
Further Resolution of Type 2 pRCC

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Chromophobe RCC & Genetic Diseases

Birt-Hogg-Dubé
- Pulmonary cysts, fibrofolliculomas
- Bilateral, multi-focal kidney cancer
  - ~30% penetrance
  - Typically chromophobe & oncocytoma
- FLCN (Chr 17): Energy & metabolism sensing through mTOR
  - Cowden & TSC also associated with chRCC

Chromophobe RCC: Unique Genomic Pattern

- Monosomy 1, 2, 6, 10, 13, 17, 21
- Less pronounced (absent) in eosinophilic subtype
- Low mutational burden
- mtDNA mutations in eosinophilic subtype
Unique Metabolic Features of chRCC

- mDNA Mutations
- Increased Mitochondria
- Compensatory Mitochondrial Proliferation (Defective ETC)?
- Metabolic Reprogramming?

Increased Oxidative Phosphorylation

Increased Krebs & ETC

Includes ETC WT Tumors

Kataegis & Increased Telomerase Activity

- Increased Kataegis & Rearrangements
- TERT Promoter Alterations
- SV → Inc TERT Expression

Kataegis → Inc TERT Expression

TERT Promoter SV: tandem duplication, inversion, deletion, deletion-insertion, interchromosomal translocation

Distinct Cell of Origin, Distinct Biology

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PLoS ONE (2012);7:e46876.
Genomic (in)Stability in RCC

- Relatively lower mutational burden in Clear Cell RCC
- Chromophobe RCC: monosomy
- pRCC-I: Trisomy 7 (MET)
- pRCC-II: 9p loss (CDKN2A)

Common Theme of Chromatin Modifiers

<table>
<thead>
<tr>
<th>Clear Cell RCC Somatic Mutations</th>
<th>Location</th>
<th>Mutation Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL</td>
<td>3p</td>
<td>52.3</td>
</tr>
<tr>
<td>PBRM1</td>
<td>3p</td>
<td>32.9</td>
</tr>
<tr>
<td>SETD2</td>
<td>3p</td>
<td>11.5</td>
</tr>
<tr>
<td>BAP1</td>
<td>3p</td>
<td>10.1</td>
</tr>
<tr>
<td>KDM5C</td>
<td>Xp</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Translocation RCC

- MIT Family of Transcription Factors
  - MITF
  - TFE3
  - TFE6
  - TFE5
- Chromosome 3p and Xp commonly mutated
- papillary RCC: 7q31.2 gain (MET)
- pRCC-I: 9p loss (CDKN2A)
- pRCC-II: 3p14.1 gain

CDKN2A/RB Alterations & Poor Outcomes

- ccA: ccB
- ccA: CCND1/P27
- ccB: CCNB1/P21
- ccA: CCNB1/P21

CDKN2A deletions enriched (53% vs. 26% for others)

Translocation RCC

- Papillary type 2 & Clear Cell RCC
- ccRCC Translocation RCC

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RCC: A Metabolic Disease

**Clear Cell & Papillary RCC**
- Increased: Oxidative phosphorylation (Krebs, ETC), Lipid synthesis
- Decreased: Gluconeogenesis

**Chromophobe RCC**
- Increased: Glycolysis, PPP
- Decreased: Krebs, ETC, Mitochondrial mass

Summary

- Proximal Convoluted Tubule
- Distal Convoluted Tubule

Acknowledgements

**The Cancer Genome Atlas Research Network**

- 100s of skilled & dedicated researchers
- Multiple institutions
- NIH/NHGRI

- ccRCC Project Leaders: W. Marston Linehan, Richard A. Gibbs
- pRCC Project Leaders: W. Marston Linehan, W. Kimryn Rathmell
- chRCC Project Leaders: Chad Creighton

- VHL Alliance & Meeting Organizers