Integrative Clinical and Molecular Characterization of Translocation Renal Cell Carcinoma


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Declaration of interests

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➢ **Honoraria:** UpToDate
Introduction

Translocation renal cell carcinoma (tRCC)

- Aggressive and rare, 2-5% of adult RCC
- MiT/TFE gene fusion
  - TFE3
  - TFEB
  - MITF
- Pathology can closely mimic ccRCC and pRCC
  - Missed diagnoses
- Molecular diagnosis
  - TFE3 IHC and break-apart FISH
- Median age ~40 y.o.
- Female > male bias in cancer incidence

No therapies targeted at the biology of the disease

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Introduction

Comprehensive genomic analysis of translocation renal cell carcinoma reveals copy number variations as drivers of disease progression

Julian Marcon¹, Renzo G. DiNatale¹,*, Alejandro Sanchez¹,*, Ritesh Kotecha², Sounak Gupta³, Fengshen Kuo⁴, Vladimir Makarov⁴, Amar Sandhu⁵, Roy Mano⁶, Andrew W. Silagy⁷, Kyle A. Blum⁸, Daniel E. Nassau⁹, Nicole E. Benfante¹, Michael V. Ortiz⁵, Maria I. Carlo⁹, Timothy A. Chan⁴,*. Robert J. Motzer², Martin H. Voss², Jonathan A. Coleman¹, Paul Russo¹, Victor E. Reuter³, A. Ari Hakimi¹,*, Ed Reznik⁵,*.7

Too rare for one/a few sites to study...

N=7 WES/RNA-Seq

N=22 Panel/WES

## Methods

<table>
<thead>
<tr>
<th>Sequencing Method</th>
<th>Method to Identify tRCCs</th>
<th>Number of RCCs</th>
<th>Percentage of Total Samples</th>
<th>Number of tRCCs</th>
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<tr>
<td>Exome</td>
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<td>Wang et al.</td>
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<td>Sato et al.</td>
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</table>

The diagram on the right shows the distribution of RCCs across different methods with a focus on tRCCs.
A Silent Genome

TMB = 0.82 (0.43 - 1.28) muts/Mb
The Fusion

chr1, chr17, chrX

GO Biological Process
- RNA processing (GO:0006396)
- RNA splicing (GO:0008380)
- RNA splicing with bulged adenosine (GO:0000377)
- mRNA metabolic process (GO:0016071)
- mRNA splicing via spliceosome (GO:0000398)
- mRNA processing (GO:0006397)
- Inhibition of cellular biosynthesis (GO:0031327)
- Transcription from RNA Pol II promoter (GO:0006366)
- Wnt signaling/plantar cell polarity (GO:0060071)
- Regulation of planar polarity (GO:0090175)

-log10(p-value)
Transcriptional program

Mock
WT TFE3
APSCR1-TFE3
NONO-TFE3
PRCC-TFE3
SFPQ-TFE3

Transfection

293T

RNA-Seq

Fusion-specific Transcriptional Signature

17 tRCC
1001 non-tRCC

15 tRCC
807 non-tRCC

TCGA

PCAWG

IMmotion151

#KCRS21

2021 Kidney Cancer Research Summit
Transcriptional program
NRF2 Activation

NRF2 sig – TFE3 vs Mock

NES = 1.39
p = 0.053

Dox-inducible shNRF2

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NRF2 and ICI

Cell lines (CTRP)

- Oxidative Stress Inducer
- PX-12
- ML210
- PRIWA-1
- 1S,3R-RSL-3
- piperlonguminine
- aminobis
- temsirolimus
- sunitinib
- temsirolimus

Progression-free survival (%)

IMmotion151 Trial

- tRCC
- AtezoBev
- Sunitinib
- p=0.004

ccRCC tumors

- AtezoBev
- Sunitinib
- p=0.095

IMmotion151 Trial - ccRCC Sunitinib Arm

- NRF2 Signature
- NRF2-Low
- NRF2-High
- p=0.002

IMmotion151 Trial - ccRCC AtezoBev Arm

- NRF2 Signature
- NRF2-Low
- NRF2-High
- p=0.344

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Conclusions

Silent genome
➢ 9p21.3, TERT, DDR

Fusion
➢ Structural recurrence
➢ Functional recurrence

Transcriptional program
➢ Fusion++
➢ mTOR, NRF2

Immunotherapy
➢ Responses
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- Thomas Denize
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