Understanding and targeting the myeloid response in ccRCC

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Disclosures

• Merck Advisory board
**Cancer Cell**

**Progressive immune dysfunction with advancing disease stage in renal cell carcinoma**

By David A. Stieun, Kelly Strickland, Kelly P. Burke, ... Rafael A. Iribarri, Toni K. Choueiri, Catherine J. Wu

**In brief**
The immune cell changes that occur with advancing disease stage in renal cell carcinoma are incompletely characterized. Braun et al. show that terminally exhausted CD8+ T cells and M3-like tumor-associated macrophages are enriched in advanced disease and

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**Cell**

**Single-cell protein activity analysis identifies recurrence-associated renal tumor macrophages**

By Aleksandar Obradovic, Nivedita Chowdhury, Scott M. Haskle, ... James McKierski, Andrea Califano, Charles G. Drake

**In brief**
Analysis of the tumor microenvironment using tumor and tumor-associated tissue of treatment-naive clear cell renal carcinoma resections from patients by combining single-cell sequencing and single-cell protein activity uncovers a tumor-specific infiltrating macrophage subpopulation associated with disease recurrence.

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**Tumor and immune reprogramming during immunotherapy in advanced renal cell carcinoma**

By Kevin Bi, Meng Xiao He, Ziad Balooyan, ... Ariv Reger, Toni K. Choueiri, Eliezer M. Van Allen

**In brief**
Bi et al. dissect the cancer cell and immune microenvironmental transcriptional programs in immune checkpoint blockade-exposed metastatic renal cell carcinoma, revealing immune subpopulation reprogramming and interactions with distinct cancer cell populations in the context of clinical resistance.
Krishna et al Cancer Cell 2021—
Stromal/proliferative cluster 6 is treatment resistant and seems to be enriched in myeloid populations.
Macrophages associated with poor response to TKI

Hakimi et al Canc Discovery 2019
Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma


PROTECT Trial

Study Cohort
N = 236 tumors from Placebo arm (769) of PROTECT trial

- Bulk RNAseq from primary tumor samples
- Clinicopathologic data
- IHC data (CD8, TIM3, LAG3, PDL1)

Objectives:
- Identify gene signatures predictive of recurrence in high-risk localized RCC
- Compare gene signatures to conventional clinicopathologic risk criteria and previously validated genomic models

N = 1538 patients

Inclusion Criteria:
Clear cell or predominantly clear cell histology
High risk localized disease
Multiple oncogenic and inflammatory pathways upregulated in recurrent tumors converge on IL6.

Unbiased Ingenuity pathway analysis:

Rappold, Vuong et al Cancer Discovery
Myeloid inflammatory gene signatures predict recurrence in ccRCC

Rappold, Vuong et al Cancer Discovery
Generation of non-redundant MSKI gene signature

MSK Inflammatory (7/9 genes)  Adenosine  Myeloid

- IL-1β
- CXCL5
- CXCL1 CXCL2 CXCL3 CXCL8
- PTGS2
- CXCL6
- 1

- 2
- 4
- 1

TCGA OS:
- DLBC
- KIRC
- ACC
- UVM
- GBM
- CESC
- HNSC
- STAD
- THCA
- LUSC
- LIHC
- LGG
- ESCA
- COAD
- KIRP
- LUAD
- PAAD
- UCEC

Gene Count: 0 2 4 6 8

TCGA KIRC:
- CXCL1
- CXCL2
- CXCL3
- CXCL5
- CXCL6
- CXCL8
- PTGS2
- IL1B
- IL6

HR: 0.8 1.0 1.2 1.4 1.6

-Log(p) 8 6 4 2

17/32 cancer types
7/9 genes

Rappold Vuong et al Cancer Discovery
MSKI gene signature predicts worse disease outcomes in ccRCC
TP53 mutant tumors have higher MSKI scores

Motzer et al Cancer Cell 2021
Generation of a novel electroporation-derived ccRCC syngeneic model

Rappold, Vuong et al Cancer Discovery
EP-derived tumor and cell line is ccRCC

Rappold, Vuong et al, Cancer Discovery
EP-derived syngeneic model is metastatic and transcriptomically resembles human stromal/proliferative ccRCC molecular subtype.

4/5 (80%) mice had liver or lung mets.

Motzer et al. 2020 Cancer Cell
Adenosine^{hi} tumors respond better to A2AR inhibitor CPI-444

Phase 1a Trial
Ciforadenant n = 33
Ciforadenant + Atezo = 35
Median 3 prior systemic therapies

OS 90% at 25 mo with combo therapy
Adenosine A2A receptor, but not PD-1 inhibition attenuates spontaneous ccRCC metastasis.
Takeaways:

• ccRCC heavily immune infiltrated
• Prevalent myeloid populations – associated with Tp53 alterations
• Myeloid TME relevant both for adjuvant and metastatic setting
• Targeting/rewiring specific myeloid populations will likely drive next wave of systemic therapies
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