Gene Expression Profiling (GEP) of non-clear cell renal cell carcinoma (nccRCC) identifies a unique spectrum of transcriptional signatures with clinical potential

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Background:

- Tumor GEP has identified RCC subgroups with distinct transcriptional profiles that are predictive of anti-angiogenics and immune checkpoint blockade (ICB) response.
- As prior work largely characterized ccRCC patients from the IMmotion151 trial, we examined transcriptional profiles of real-world RCC patient samples, including nccRCC histologies.

Methods:

- DNA/RNA next-generation sequencing was performed for samples submitted to a commercial CLIA-certified lab (Caris Life Sciences).
- Central pathology review confirmed diagnoses of nccRCC samples.
- Molecular subgroups were defined according to Motzer et al., 2020, with subgroups determined by a weighted average of gene expression levels.

Results:

- RCC patient samples [n=657; median age: 62 years (range 14-90), 70.6% men] were profiled, including papillary (9.6%), chromophobe (4.6%), medullary (1.2%), collecting duct (0.9%), and mixed (6.2%) nccRCC subtypes (**Table 1**).
  - Biopsies were collected from kidney (51.7%), lung (11.4%), bone (6.8%), lymph nodes (5.2%), liver (4.2%) and other metastatic sites (20.7%).

Table 1 – Patient and tumor characteristics by histology

	Histology						
Characteristic	Clear cell 1	Chromophobe 2	Collecting duct carcinoma 3	Medullary 4	Mixed 5	Papillary 6	P-value (Test)
Total samples	509	30	6	8	41	63	------
- % of total	77.5%	4.6%	0.9%	1.2%	6.2%	9.6%	
Age							
- Median, yr	62	63	63.5	23.5	62	66	**P<0.0001**
- Range, yr	19-90	24-77	61-75	14-41	30-81	21-87	(Kruskal-Wallis)
Gender							
- Male (%)	355 (69.7%)	21 (70.0%)	4 (66.7%)	7 (87.5%)	27 (65.8%)	50 (79.4%)	P=0.5339
- Female (%)	154 (30.3%)	9 (30.0%)	2 (33.3%)	1 (12.5%)	14 (34.1%)	13 (20.6%)	(Chi-square)
Biopsy site							
- Primary (%)	250 (49.1%)	17 (56.6%)	5 (83.3%)	4 (50.0%)	21 (51.2%)	39 (61.9%)	P=0.2508
- Metastatic (%)	259 (50.9%)	13 (43.4%)	1 (16.7%)	4 (50.0%)	20 (48.8%)	24 (38.1%)	(Chi-square)

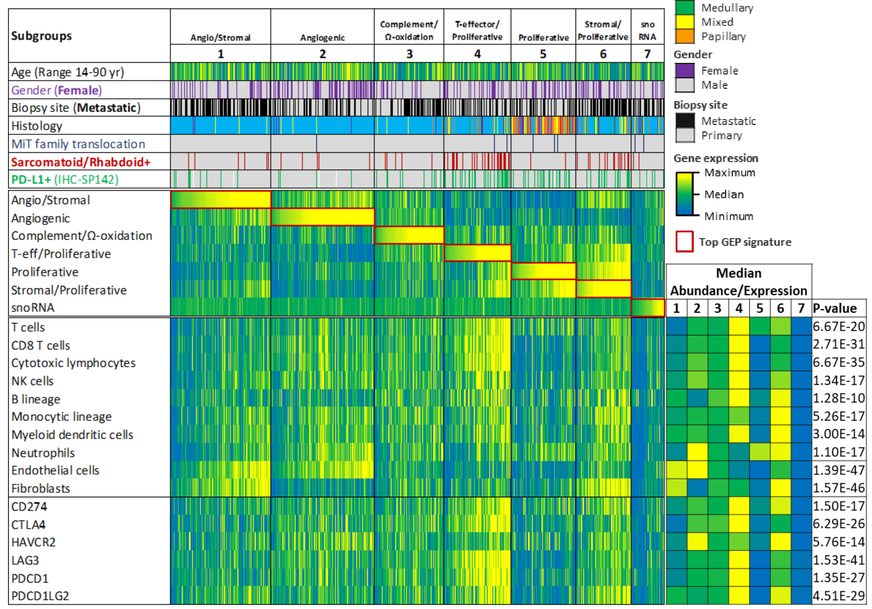
(Note: P-values reflect comparison across all histology subgroups.)

Table 2 – Patient and tumor characteristics by GEP subgroup

	GEP Subgroup							
Characteristic	Angio/ Stromal 1	Angiogenic 2	Complement/ Ω-oxidation 3	T-effector/ Proliferative 4	Proliferative 5	Stromal/ Proliferative 6	snoRNA 7	P-value (Test)
Total samples	133	138	93	89	86	74	44	---------
- % of total	20.2%	21.0%	14.2%	13.5%	13.1%	11.3%	6.7%	
Age								
- Median, yr	63	63.5	62	62	63	58	63	**P=0.0464**
- Range, yr	34-88	19-90	37-82	14-83	21-81	21-87	32-85	(Kruskal-Wallis)
Gender								
- Male (%)	102 (76.7%)	77 (55.8%)	78 (83.9%)	65 (73.0%)	58 (67.4%)	49 (66.2%)	35 (79.5%)	**P<0.0001**
- Female (%)	31 (23.3%)	61 (44.2%)	15 (16.1%)	24 (27.0%)	28 (32.6%)	25 (33.8%)	9 (20.5%)	(Chi-square)
Biopsy site								
- Primary (%)	50 (37.6%)	88 (63.8%)	48 (51.6%)	52 (58.4%)	52 (60.5%)	24 (32.4%)	22 (50.0%)	**P<0.0001**
- Metastatic (%)	83 (62.4%)	50 (36.2%)	45 (48.4%)	37 (41.6%)	34 (39.5%)	50 (67.6%)	22 (50.0%)	(Chi-square)

(Note: P-values reflect comparison across all GEP subgroups.)

Figure 1 – Overview of study cohort patient demographics, tumor histology, GEP signatures, and tumor microenvironment. Heatmap sorted by top GEP signature (red boxes) within each subgroup (ascending left to right).



Results:

- Sarcomatoid/rhabdoid features were associated with 'T-effector/Proliferative' (4) and 'Stromal/Proliferative' (6) subtypes (**Figure 1**)

- 'T-effector/proliferative' (4) samples were commonly associated with increased immune cell infiltration compared to other subgroups based on Microenvironment Cell Population (MCP)-counter analysis of the tumor microenvironment (**Figure 1**).
  - Increased abundance of pro-immune cell types was concurrent with high expression of immune checkpoint genes in 'T-effector/Proliferative' (4)
  - Immunosuppressive cell types most abundant in 'Stromal/Proliferative' (6)
  - Endothelial cells most abundant in 'Angiogenic' (1) and 'Angio/stromal' (2) subtypes

- While most ccRCC samples were classified as 'Angiogenic' or 'Angio/stromal' (50%), these molecular subgroups comprised < 10% of nccRCC samples, which were predominately classified as 'Proliferative' (49%) (**Figure 2**).

- PD-L1+ (SP142; 2+|5%) rates were higher in nccRCC (range 16.7%-37.5%) compared to ccRCC (12.0%), with the highest rate observed in medullary samples (**Figure 3**)
  - dMMR/MSI-H (a composite assessment of MMR protein expression and/or sequencing of microsatellite loci) and TMB-High (≥ 10 mutations/Mb) rates were highest (33.3%) in collecting duct carcinoma and rarely observed (< 3.5%) in all other histological subgroups (**Figure 3**).

Figure 2 – Distribution of GEP subgroups by histology
- Numbers overlaid on bars represent number of samples within molecular subtype

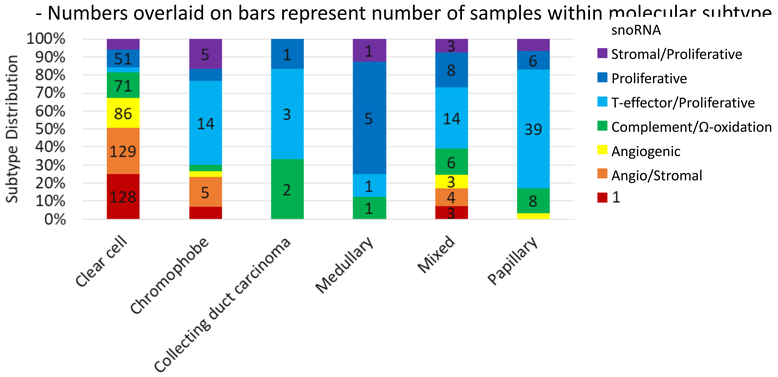
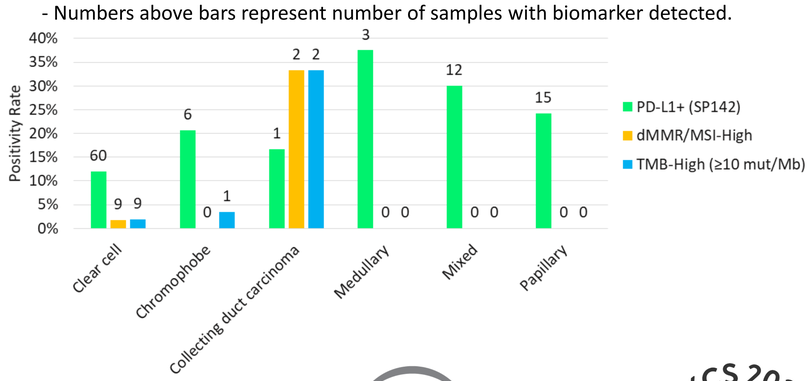


Figure 3 – Frequency of immunotherapy-related markers by histology
- Numbers above bars represent number of samples with biomarker detected.



Conclusions:

- In our analysis of real-world RCC samples, nccRCC was strongly associated with the 'Proliferative' subtype and weakly associated with 'Angiogenic' subtypes compared to ccRCC.
- Despite the small representation of some tumor subtypes, these observations provide a new understanding for personalized treatment of nccRCC and warrant further evaluation in prospective trials.