Genomic Analysis of Clear Cell Carcinomas

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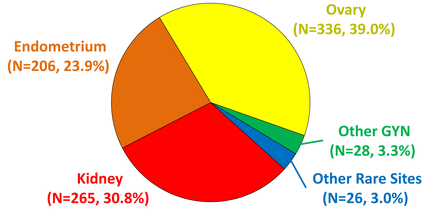
Background

- Clear cell carcinomas (CCC) are rare histologies outside of the kidney and are typically less sensitive to standard treatments.
- Genomic alterations in chromatin remodeling pathways involving ARID1A or the intracellular PI3K-mTOR signaling pathway are found in both renal and ovarian CCC.
- It is unclear whether CCCs originating from different anatomic sites share a common genomic landscape.
- This CARIS Precision Oncology Alliance project sought to determine whether CCC of different organs shared similar genomic signatures and to identify potential pathways that could be targeted in a tumor-agnostic clinical trial

Methods

- CCCs (N = 861) from multiple primary tumor sites, including kidney (30.5%), ovary (39%), endometrium (23.9%), other gynecologic sites (e.g., cervix, fallopian tube, 3.3%), and miscellaneous (non-kidney or gynecologic sites, 3.3%) were analyzed at the Caris Life Sciences Laboratory (Phoenix, AZ).



- Using hierarchical clustering (HC) and principal component analysis (PCA), the samples were compared across 648 total genes from five metabolic-related gene sets consisting of angiogenesis, glycolysis, hypoxia, oxidative phosphorylation, and fatty acid metabolism.
- Gene Set Enrichment Analysis (GSEA) was further conducted on the samples across fifty hallmark gene sets representing specific biologic processes and expression.
- Samples were also analyzed for individual genomic alterations and immune-oncology associated biomarkers.
- PD-L1 (SP142) expression was evaluated by immunohistochemistry (positive threshold: 2+ stain intensity and ≥ 5% tumor cells)

Results

Table 1 – Cohort demographics by primary tumor site

Characteristic		Kidney	Endometrium	Ovary	GYN	Other
Count (N)		265	206	336	28	26
Median Age (range)		61.0 (34 – 86)	69.0 (34 – 89)	57.0 (24 – 85)	62.0 (36 - 89)	70.0 (34 – 85)
Gender	Female	30.6% (81/265)	100.0% (206/206)	100.0% (336/336)	100.0% (28/28)	73.1% (19/26)
	Male	69.4% (184/265)	0.0% (0/206)	0.0% (0/336)	0.0% (0/28)	26.9% (7/26)
Metastatic		52.1% (138/265)	26.2% (54/206)	32.1% (108/336)	28.6% (8/28)	47.6% (10/21) [5 unclear]

Figure 1 – (A) Two-way hierarchical clustering of metabolism-related gene expression in CCC, with samples color-coded by primary tumor site along top dendrogram. Rows comprise 648 genes from 5 Hallmark gene sets[3]. **(B)** Principal Component Analysis of all genes from the 5 genes sets. CCC from Kidney forms distinct clusters from other primary tumor sites, while non-Kidney clusters are intermixed CCC from ovary, endometrium, and rare sites.

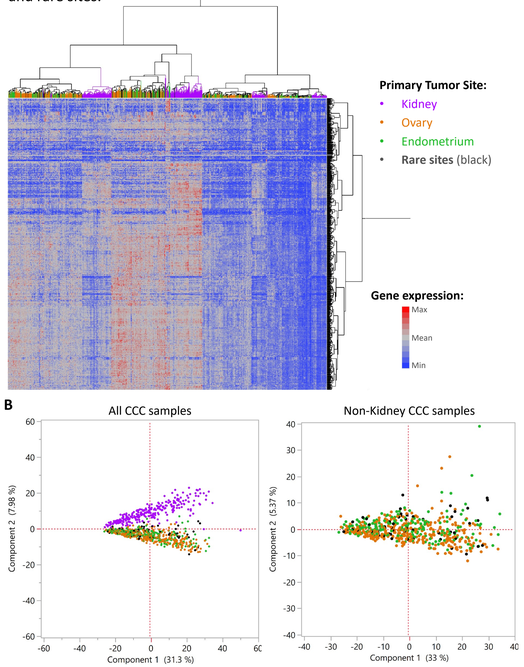


Figure 2 – Genomic alterations across different primary sites of origin. All biomarkers shown had significantly increased or decreased rates between 2 or more primary site subgroups, including mutations (mut), copy number amplifications (amp, ≥6 copies), fusions, and genome-wide loss-of-heterozygosity (gLOH, ≥16%).

- Kidney CCC enriched in VHL, PBRM1, SETD2, KDM5C, and BAP1 mutations
- TP53 mutations most common in Endometrium CCC (61.7%), followed by 'Other GYN' CCC (33.3%)
- PIK3CA and ARID1a mutations enriched in Ovary and 'Other GYN' CCC
- EWSR1 fusions exclusively found in 'Other Rare' CCC (11.5%)

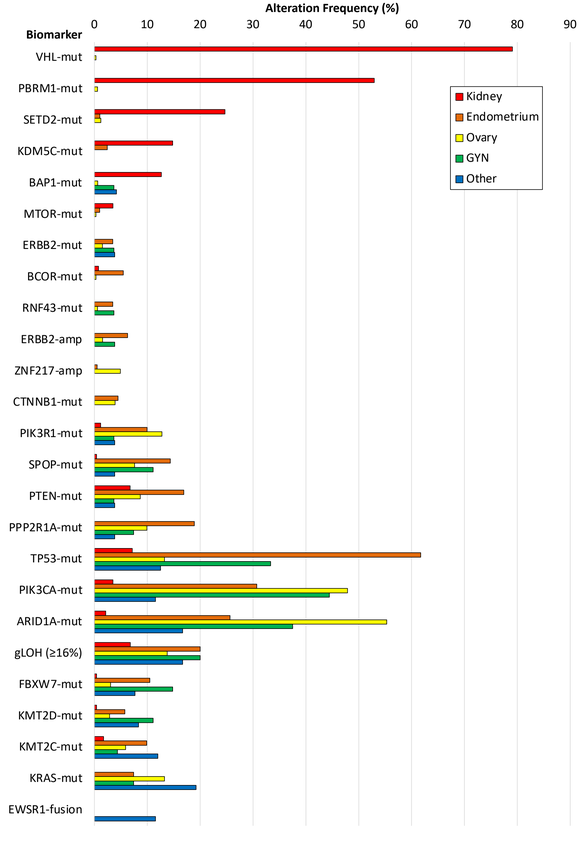
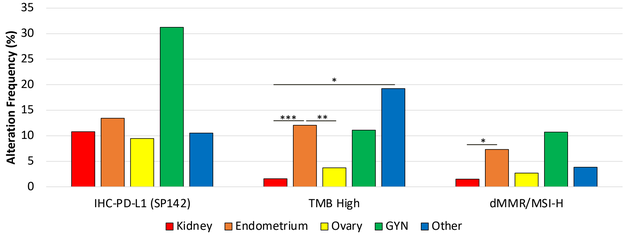


Figure 3 – Frequency of immunotherapy-related biomarkers in CCC by primary site. PD-L1 expression, high tumor mutational burden (≥10 mutations/Mb), and deficient mismatch repair/microsatellite instability rates across sites

- PD-L1 (IHC, SP142) expression frequency was highest in 'Other GYN' CCC but was not significantly different across primary site subgroups
- TMB-High (≥ 10 mut/Mb) frequency was highest in 'Other Rare' CCC samples and lowest in Kidney CCC
- dMMR/MSI-High rates were consistent with TMB-High rates, with except of 'Other Rare' CCC samples that showed relatively low dMMR/MSI-High frequency



Conclusions

- Initial metabolic gene expression clustering analysis shows that CCCs do not separate by organ of origin beyond renal versus extra-renal.
- TP53, ARID1A, and PIK3CA were the most frequently altered genes in non-renal CCC.
- Out of fifty hallmark gene sets, only two were statistically significantly different among gynecological CCCs.
- This similarity between gynecological CCC can be leveraged by targeting pathways such as PI3K-AKT-mTOR, DNA repair, and MYC targets in a site agnostic manner.

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References

1. Ji, J.X., Wang, Y.K., Cochrane, D.R. and Huntsman, D.G. (2018), Clear cell carcinomas of the ovary and kidney: clarity through genomics. J. Pathol, 244: 550-564. https://doi.org/10.1002/path.5037
2. Marks EI, Brown VS, Dizon DS. Genomic and Molecular Abnormalities in Gynecologic Clear Cell Carcinoma. Am J Clin Oncol. 2020 Feb;43(2):139-145. doi: 10.1097/COC.0000000000000641. PMID: 31764020.
3. Liberzon A, Birger C, Thorvaldsdóttir H, Ghandi M, Mesirov JP, Tamayo P. The Molecular Signatures Database (MSigDB) hallmark gene set collection. Cell Syst. 2015 Dec 23;1(6):417-425. doi: 10.1016/j.cels.2015.12.004. PMID: 26771021; PMCID: PMC4707969.

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