Multiplatform molecular analysis of biomarkers in renal cell carcinoma

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Abstract

Background: Predictive biomarkers of response to targeted therapy are lacking in renal cell carcinoma (RCC). We evaluated a cohort of RCC patients referred for multiplatform molecular profiling to identify potentially actionable recurrent molecular aberrations.

Methods: 166 consecutive renal cases referred to Caris Life Sciences over 2 years were evaluated with central pathology review. Cases were subtyped into clear cell (ccRCC), n=91; papillary (PRCC), n=20; sarcomatoid, n=21; medullary, n=4, or translocation or unclassified, n=30 (removed for this analysis). Metastatic status was documented for 63% of cases; the median age was 61 overall with an age range of 19-86. 75% of subjects were male. Testing included a combination of sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]), and/or gene amplification (CISH or FISH).

Results: ccRCC had a 52% loss of PTEN, while PRCC had a 21% loss (p value=0.02). 100% of ccRCC with sarcomatoid features (n=4) showed aberrant expression of PD-L1 and were infiltrated with PD-1+ tumor infiltrating lymphocytes (TILs); of non-ccRCC with sarcomatoid features (n=10), 100% of those tested (n=2) also had aberrant expression of PD-L1. The single PRCC with sarcomatoid features also had aberrant expression of PD-L1. Loss of PBRM1 expression was observed in 60% of ccRCC. Loss of histone 3 lysine 36 trimethylation (H3K36me3), which is associated with *SETD2* mutations, was observed in 30% of ccRCC. TOP2A was overexpressed in ccRCC at 30% and in non-ccRCC at 50%. 100% of ccRCC and PRCC overexpressed EGFR. 50% of ccRCC and 68% of PRCC had cMET overexpression. VHL mutations were identified in 51% of ccRCC tumors. We observed lower rates of *TP53* (11%), *ATM* (6%), and *PIK3CA* (3% ccRCC, 6% PRCC, 11% sarcomatoid) mutations compared to other cancers.

Conclusions: Multiplatform molecular profiling of renal cell carcinoma identifies potential predictive biomarkers in RCC. Everolimus or other PI3 kinase pathway inhibitors may have utility, for those patients with PI3 kinase pathway involvement in RCC. RCC with sarcomatoid features may respond to PD1/PD-L1 targeted immunotherapies. The impact of molecular profiling in ccRCC to predict responses to currently available targeted therapy has important implications for trial design and patient selection.

Patient Demographics

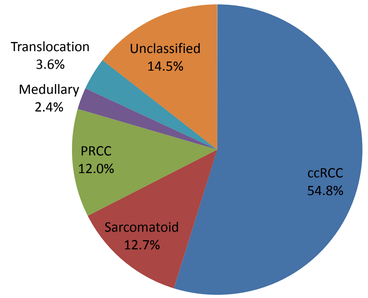
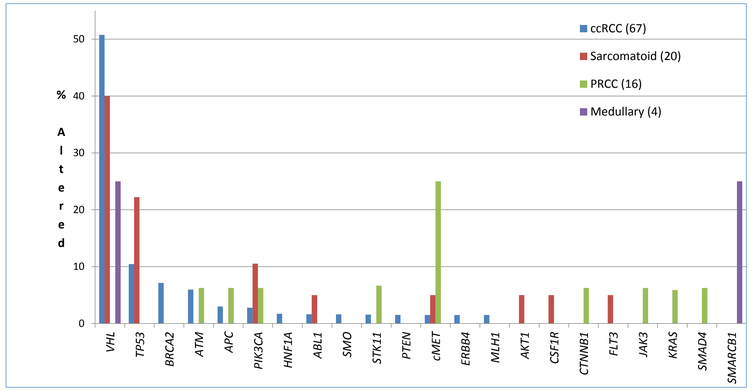


Figure 1 – Histologic subtypes. Sarcomatoids included either ccRCC (9) or papillary (1) with sarcomatoid features.

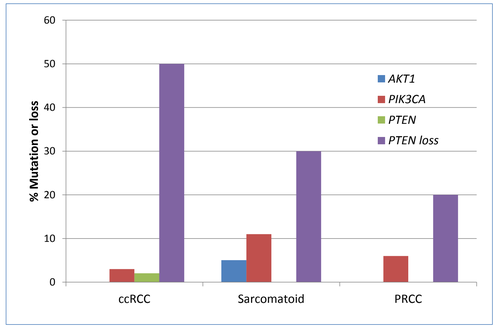
Results, Gene Mutations

Figure 2. Gene alterations. Mutations were found in 30% of 47 genes tested, across subtypes, and each subtype had unique alterations. Genes with no alterations identified included *BRAF, BRCA1, CDH1, cKIT, EGFR, FBXW7, FGFR1, FGFR2, GNA11, GNAQ, GNAS, HRAS, IDH1, JAK2, KDR, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PTPN11, RB1, RET, and SMO*.



Results, PI3 Kinase Pathway Alterations in ccRCC

Figure 5. Alterations in PI3 kinase pathway biomarkers. Loss of expression of PTEN or mutations (MT) in *AKT1*, *PIK3CA* or *PTEN* were identified more frequently in ccRCC than other subtypes.



Results, Immunohistochemistry (IHC)

Figure 3. Levels of protein expression, either overexpression, reported as percent positive of total cases tested, or loss, reported as percent negative (PD-1=presence of tumor infiltrating lymphocytes). Other markers tested but not shown include AR, ER, PR, ERCC1, HER2, PDGFRA, TS, TLE3, TS, TUBB3, TOPO1, RRM1, PGP, MGMT, cKIT, and SPARC.

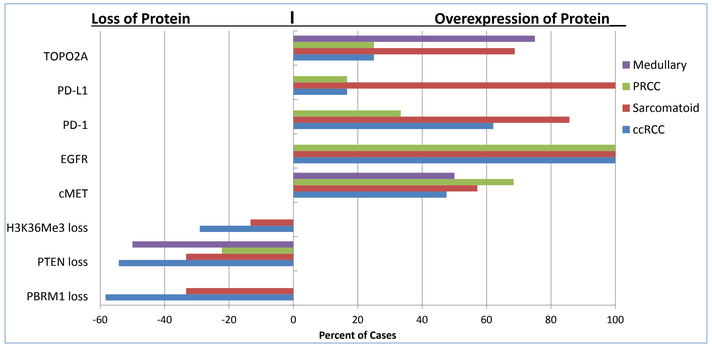
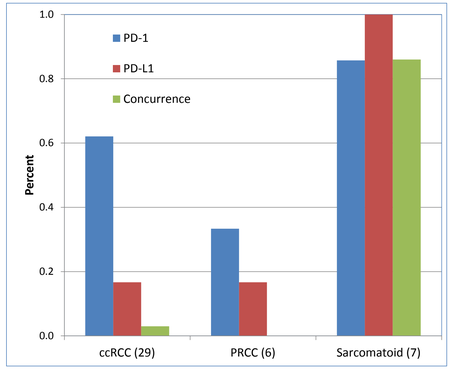


Figure 4. Comparison of PD-L1 expression, presence of PD-1 TILs, or concurrence in papillary, sarcomatoid, and ccRCC. Sarcomatoids, including ccRCC and PRCC with sarcomatoid features had higher occurrence of PD-1/PD-L1.



Conclusions

- Molecular profiling that incorporates both DNA sequencing and protein expression in renal cell carcinoma identifies potential predictive biomarkers in ccRCC.
- Alterations at multiple points in the PI3 kinase pathway may inform responses to rapalogs.
- PD-L1 overexpression and PD-1+ TILS were observed in RCC with sarcomatoid features; future studies are warranted to determine response to PD-1/PD-L1 targeted immunotherapies.
- Functional convergence on cMET activation in PRCC was observed with cMET overexpression by IHC or cMET mutations.
- The impact of molecular profiling in ccRCC to predict responses to currently available targeted therapy has important implications for trial design and patient selection.

References

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4. Simon, JM, Hacker KE et al. (2014), "Variation in chromatin accessibility in human kidney cancer links H3K36 methyltransferase loss with widespread RNA processing defects" Genome Biology 24: 241-250.