Multi-platform molecular analysis of sarcomatoid renal cell carcinoma (sRCC)

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Updated Abstract

Background: Patients with sRCC have a have a poor prognosis and decreased likelihood of response to targeted therapy or IL-2. Predictive biomarkers of response are lacking in sRCC. We evaluated a cohort of RCC patients to identify potentially actionable recurrent molecular aberrations.

Methods: 112 renal cases referred to Caris Life Sciences over 2 years were evaluated for sarcomatoid differentiation with central pathology review. 91 cases were clear cell (ccRCC) and 21 were sRCC. Testing included sequencing (next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]), and gene amplification (CISH or FISH). For sequencing, DNA was isolated by microdissection of the sarcomatoid component. 19 RCC cases with sarcomatoid differentiation from Mayo Clinic Arizona were analyzed for external validation.

Results: The sRCC cohort showed 54% aberrant expression of PD-L1 and all but 1 case was infiltrated with PD-1$^+$ tumor infiltrating lymphocytes (TILs). 100% of ccRCC with sarcomatoid features (n=4) showed aberrant expression of PD-L1 and were infiltrated with PD-1$^+$ TILs; of ccRCC without sarcomatoid features, only 17% had PD-L1 and 62% had PD-1 involvement. Key differences are shown:

	% Overexpression			TILs	% Loss		
	TOPO2A	AR	PD-L1	PD-1	RRM1	PBRM1	H3K36Me3
ccRCC	25	26	17	62	100	58	26
sRCC	67	5	54	96	74	30	18
p value	0.0001	0.04	0.005	0.003	0.0001	0.02	0.32

Conclusions: Multi-platform molecular profiling of sRCC identifies numerous predictive biomarkers to cytotoxic agents and immunotherapies. In other solid tumors, overexpression of TOPO2A and loss of RRM1 are associated with sensitivity to anthracyclines and gemcitabine, respectively. sRCC have increased infiltration of PD-1$^+$ TILs and may respond to PD1/PD-L1 targeted immunotherapies. Further evaluation of TOPO2A, RRM1 and PD-1/PD-L1 as predictive biomarkers in sRCC is warranted.

Results, Immunohistochemistry

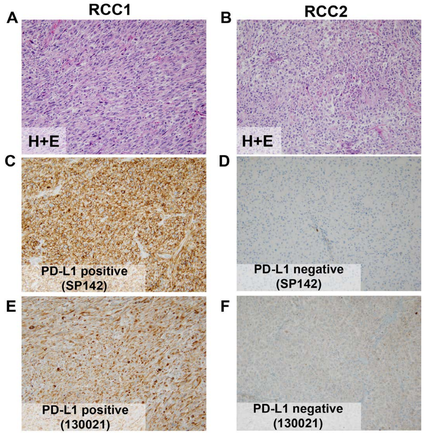


Figure 1. Representative PD-L1 staining (×20 magnification) in sRCC. (A, B) H+E, (C) PD-L1 positive (SP142), (D) PD-L1 negative (SP142), (E) PD-L1 positive (130021), and (F) PD-L1 negative (130021).

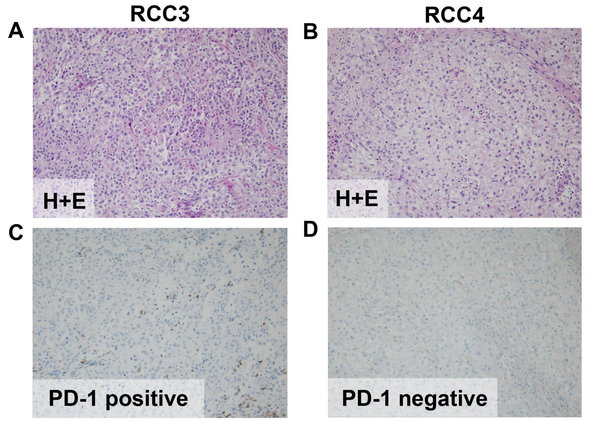
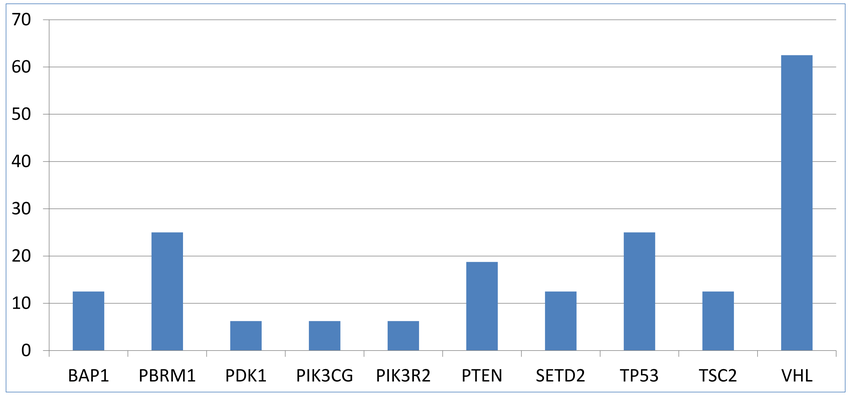


Figure 2. Representative immunohistochemical staining (×20 magnification) of PD-1 expression in sRCC and ccRCC. (A and C) PD-1$^+$ TILs in RCC with sarcomatoid features. (B and D) PD-1 negative lymphocytes in ccRCC. H + E, hematoxylin and eosin.

Results, Gene mutations

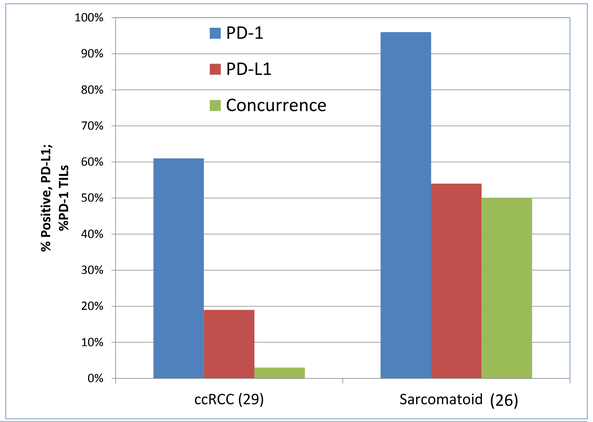
Figure 3. Alterations identified in listed genes as percent cases with mutation of all cases tested.

Direct sequence analysis was performed on genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina NextSeq platform. An Agilent custom-designed SureSelect XT assay was used to enrich 591 whole-gene targets. The test has a sensitivity to detect as low as approximately 10 % population of cells containing a mutation and all variants are detected with >99% confidence.



Results, Immunohistochemistry

Figure 4. PD-L1 expression, presence of PD-1$^+$ TILs, or concurrence in sRCC and ccRCC. RCC with sarcomatoid differentiation had higher occurrence of PD-1/PD-L1 when compared to ccRCC. PD-1/PD-L1 was available for 29 ccRCC and 26 sRCC.



Conclusions

- Multi-platform molecular profiling of sRCC identifies numerous predictive biomarkers to cytotoxic agents and immunotherapies.
- In other solid tumors, overexpression of TOPO2A and loss of RRM1 are associated with sensitivity to anthracyclines and gemcitabine, respectively.
- sRCC have increased infiltration of PD-1+ TILs and may respond to PD1/PD-L1 targeted immunotherapies.
- Further evaluation of TOPO2A, RRM1 and PD-1/PD-L1 as predictive biomarkers in sRCC is warranted.

References

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