Distinct genomic and microenvironmental profiles of brain metastases in renal cell carcinoma: Insights into hypoxia-driven adaptation and therapeutic vulnerabilities.

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Background

- Brain metastases (BM) in renal cell carcinoma (RCC) are linked to poor prognosis.
- BM may show unique genomic and tumor microenvironment features influenced by the brain niche, differing from primary RCC and extracranial metastases (ECM).

Objective: Characterize genomic and microenvironmental differences in BM vs. primary RCC/ECM and identify therapeutic vulnerabilities.

Methods

Retrospective analysis of RCC samples that underwent NGS (WES, WTS) analysis from Caris Life Sciences database.

Assessed: prevalence, demographics, genomic alterations, treatment patterns, survival (Cox regression), and Tumor micro-environment (Gene Set Enrichment Analysis), hypoxia Score (Buffa, et al, 2010).

Statistical tests: chi-square/Fisher's exact, Kruskal-Wallis, adjusted p-values (Benjamini-Hochberg. P-values: * < 0.05, ** < 0.01, *** < 0.001, **** < 0.0001.

Results

Total	3913	100%	
Primary	1775	45.40%	
BM	138	3.50%	
ECM	2000	51.10%	
Gender (Male)			
Primary	1210	68.17%	P = 0.488
BM	98	71.01%	
ECM	1438	71.90%	
Average age ± standard deviation			
Primary	60.7 ± 13.6		P < 0.0001
BM	63.8 ± 9.5		
ECM	64.4 ± 12.0		

Tumor Histology (Clear Cell)			
Primary	1456	82.03%	P < 0.0001
BM	91	65.94%	
ECM	1278	63.9%	
Radiation Treatment before collection			
Primary	212	11.9%	p = 0.571
BM	35	25.4%	
ECM	33	23.2%	
Survival: Median (95% CI) months			
Primary	49.4 (45.8 – 54.8)		P < 0.0001
BM	30.3 (19.3 – 47.5)		
ECM	30.3 (28.0 – 32.3)		

Figure 1. Biomarker alterations in primary RCC, BM and ECM

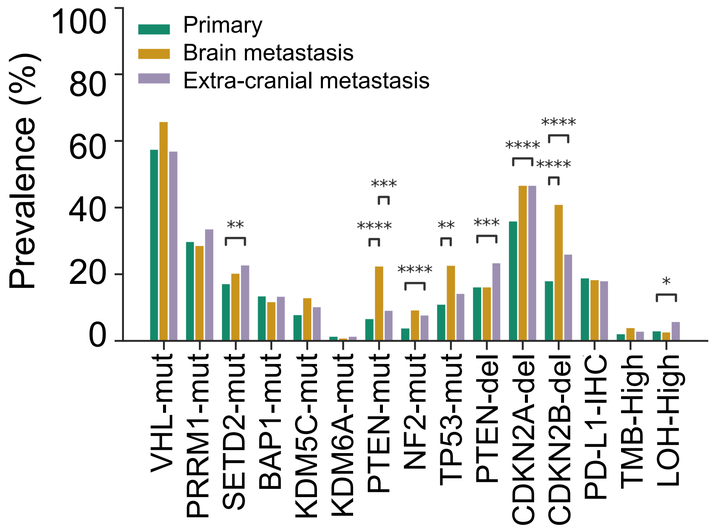


Figure 2. RNA expression of therapeutic target genes in RCC

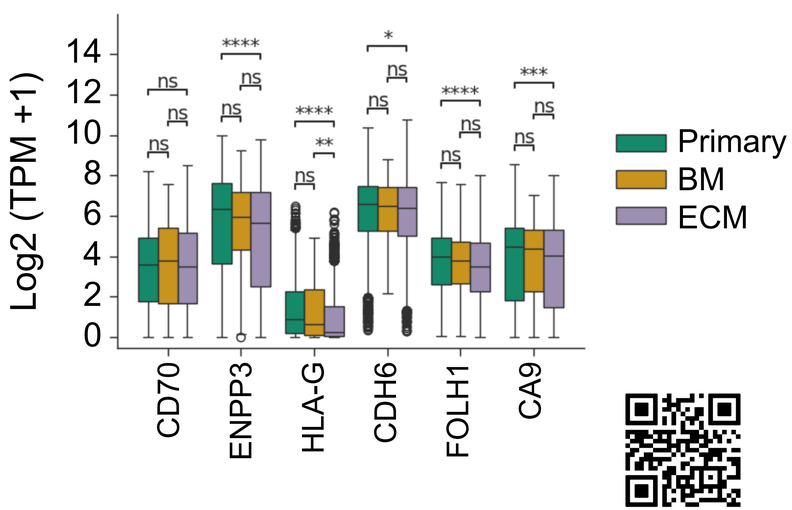


Figure 3. GSEA pathway enrichment

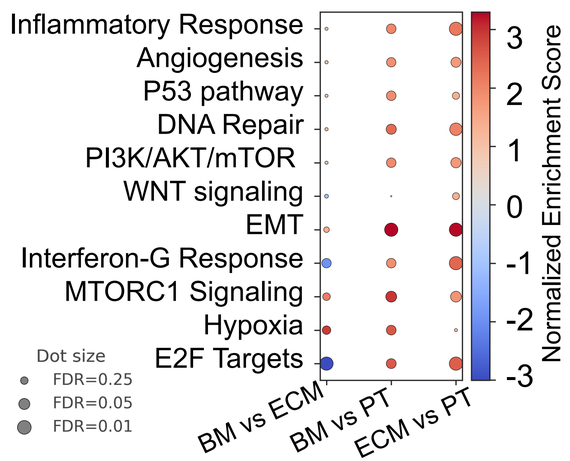
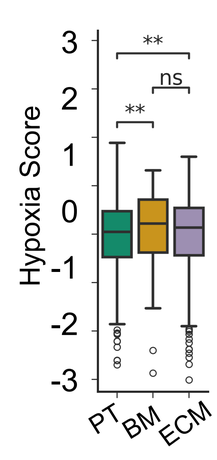


Figure 4. Hypoxia



Conclusion:

BM in RCC exhibit distinct genomic and microenvironmental profiles with hypoxia-driven adaptation, and mTOR/HIF activation.

Future Directions for Research

Studies with paired primary–ECM–BM samples to map disease progression.
Target hypoxia/mTOR pathways in BM.

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