

Brain Metastases in Patients with Kidney Cancer May Have Immune-Suppressive Tumor Microenvironments

Researchers applied single-nucleus RNA sequencing and spatial transcriptomics to identify potential therapeutic targets.

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In patients with renal cell carcinoma, brain metastases had distinct gene expression programs and lower antitumor immune cell infiltration than primary tumors or metastases in other organs, according to a study presented at the [AACR Annual Meeting 2023](#), held April 14-19.

Recent studies have suggested that brain metastases might occur in over 25 percent of patients with [renal cell carcinoma](#) who are treated with immune checkpoint inhibition, said Elshad Hasanov, MD, PhD, the presenter of the study and a medical oncology fellow at The University of Texas MD Anderson Cancer Center.

“The brain is becoming a common metastatic site of disease progression in patients treated with immune checkpoint inhibition, which may be due to the fact that it is an immune-privileged organ and might, therefore, allow tumor cells to escape the activity of immunotherapy,” he explained, adding that patients whose renal cell cancers have metastasized to the brain have lower rates of treatment response and worse outcomes.

“To develop better treatments for these patients, we first need to understand the biology of brain metastases and identify the factors that are driving immune suppression in the brain,” he said.

In this study, Hasanov and colleagues compared the tumor microenvironments of brain metastases with those of primary tumors and other sites of metastasis using tissue samples from patients with renal cell carcinoma collected via collaboration with researchers at MD Anderson, Emory University, and Hacettepe University in Turkey.

Collected samples were either frozen or formalin-fixed paraffin-embedded (FFPE) for preservation. The frozen samples included 14 brain metastases, eight matched primary kidney tumors, and five matched extracranial metastases; FFPE samples included 57 brain metastases. The researchers used a combination of single-nucleus RNA sequencing of frozen samples and spatial transcriptomics of FFPE samples to characterize gene expression and cellular interactions.

The analysis revealed that compared with primary tumors or extracranial metastases, brain metastases had greater infiltration of neuronal and glial cells into the tumor microenvironment. Hasanov explained that interactions between these brain cells and tumor cells were previously shown to enhance cancer growth and metastasis. They also observed that neuronal and glial cell interaction with immune cells potentially suppressed antitumor immune activity through known immunosuppressive ligand-receptor interactions.

The tumor microenvironment of brain metastases had fewer proliferating T cells, memory B cells, dendritic cells, and monocytes than primary tumors and extracranial metastases. Furthermore, T cells in brain metastases expressed higher levels of immune checkpoint proteins than T cells in other sites, and macrophages in the brain were more likely to express an immune-suppressing M2 gene signature.

In addition, tumor cells in the brain had greater expression of serum amyloid A1, which promotes immune-suppressive effects in macrophages; higher activity of the VEGFR and FGFR4 growth-promoting proteins; and greater expression of genes that allowed them to adapt to the brain environment, including MYC target genes and genes involved in mTORC1 signaling, epithelial-mesenchymal transition, fatty acid metabolism, oxidative phosphorylation, and the response to reactive oxygen species.

“Our study highlights the power of single-nucleus RNA sequencing and spatial transcriptomics to uncover facets of disease biology,” said Hasanov. “The immune-suppressive features identified in our analysis have the potential to serve as biomarkers or therapeutic targets for patients with renal cell carcinoma that has metastasized to the brain. We hope that the findings of this study will contribute to the design of better therapies for these patients.”

Based on the findings from this study, Hasanov and colleagues plan to initiate a multicenter clinical trial to evaluate lenvatinib (Lenvima) (a multi-target tyrosine kinase inhibitor of VEGFR, FGFR4, and other receptors) in combination with pembrolizumab (Keytruda) for patients with renal cell carcinoma who have brain metastases. While this regimen is currently approved for the first-line treatment of patients with metastatic renal cell carcinoma, prior trials testing this combination did not include patients with active brain metastases, Hasanov noted. In future work, Hasanov intends to pursue preclinical experiments and clinical trials to determine whether various combinations of tumor targeting agents and inhibitors of immune checkpoints in the tumor microenvironment of brain metastases could help overcome immune suppression.

Limitations of the study include its retrospective design and the small sample size. Additionally, all brain metastases were obtained from patients who had undergone dexamethasone treatment prior to craniotomy, which might have impacted the results. However, Hasanov noted that this treatment is common among patients with brain metastases, so the results likely reflect the microenvironments of most patients.

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