Tumor evolution of brain-specific tropism in metastatic renal cell carcinoma

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Background: Brain metastases (BMets) pose a clinical challenge in the management of patients (pts) with metastatic renal cell carcinoma (RCC), leading to significant morbidity and mortality. Herein, we sought to comprehensively characterize the molecular landscape of BMets in RCC.

Methods: We performed panel-based DNA (DNAseq) and whole transcriptome (RNAseq) sequencing to analyze BMets, matched non-BMets (nBMets), and matched primary renal tumors (PRTs) from pts who underwent surgical resection of BMets in RCC at our institution.

Results: Our cohort consisted of 95 samples from 53 patients (BMets = 54, nBMets = 14, PRT = 27) with clear cell histology in 45 pts (84.9%). DNAseq was available on 85 samples (50 pts). Patient-level mutations revealed recurring mutations in VHL (18 pts, 36%), TP53 (n = 12 pts, 24%), PBRM1 (12 pts, 24%), SETD2 (12 pts, 24%), and BAP1 (4 pts, 8%). Mutations within the MTOR signaling pathway were enriched, with 25 pts (50%) having at least one mutation in PTEN (12 pts, 24%), TSC1 (4 pts, 8%), TSC2 (5 pts, 10%), or MTOR (9 pts, 18%). Copy number analyses revealed frequent deletions in chr14q21 (34 pts, 68%) and chr9p21 (35 pts, 70%) and gains in chr20q13 (n = 31, 62%) and chr7p15 (n = 31, 62%).

At the sample-level, PTEN mutations were more common in BMets (11 pts, 22.9%) vs nBMets (0 pts) and PRTs (3 pts, 12%, p = 0.124), as were deletions in chr13q22 (BMets = 13pts [26.5%], nBMet = 1pts [8.3%], PRT = 1 [4%]; p = 0.036) and gains in chr20q13 (BMets = 30pts [61.2%], nBMet = 4pts [33.3%], PRT = 8 [32%]; p = 0.03). Deletions in chr9p21 were enriched in BMets (32, 65.3%) and nBMets (8, 66.7%) relative to PRTs (7, 28%, p = 0.006), whereas other copy number alterations and somatic mutations exhibited similar proportions across specimen sites.

Differential expression analysis performed on 86 samples (51 pts) identified 806 differentially expressed genes (DEGs) between BMets and PRT (adjusted adj. p < 0.05) and 399 DEGs between BMet and nBMets (adj. p < 0.05). Gene set enrichment analysis of MSigDB Hallmark gene sets revealed upregulation of MTORC1 signaling, glycolysis, and MYC targets in BMets compared to PRT and nBMets (adj. p <0.0001). In contrast, immune-related gene sets, such as interferon-alpha, interferon-gamma, and tumor necrosis factor-alpha, were enriched in PRT relative to BMets (adj. p <0.0001), but not nBMets (adj. p > 0.05).

CIBERSORT cellular deconvolution analysis comparing BMets with PRT revealed decreased proportions of M1 macrophages (p = 0.0003) and CD8+ T-cells (p = 0.0106), but an increased proportion of M2 macrophages (p = 0.0009).

Conclusions: RCC with brain metastases are characterized by distinct copy number alterations, enrichment of MTOR pathway mutations, MTOR pathway hyperactivation, and an immunosuppressive tumor milieu. These findings may hold therapeutic implications of MTOR pathway inhibition and immune modulators in treating RCC BMets.

Keywords: Metastasis, MTOR