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Characterization of tumor-infiltrating lymphocytes and tumor-associated macrophages within the tumor microenvironment of primary tumors and matched brain metastases

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Background

Tumor-associated macrophages (TAMs) and tumor-infiltrating lymphocytes (TILs) have recently been postulated to impact the brain metastatic seeding of solid cancers. Therefore, we aimed to investigate differences of TILs and TAMs between matched primary tumor and brain metastasis (BM) samples regarding cell densities and entropy.

Methods

Patients who received a resection of the solid primary tumor and matched BM between 01/1990 and 10/2022 were included. Cell density quantification of TAMs (CD163+, CD68+) and TILs (CD3+, CD8+, FOXP3+, CD45RO+) was performed semi-automatically with QuPath software. Heterogeneity of the tumor microenvironment (TME) was measured by Shannon Entropy from generated heatmaps. Time-to-BM (TTBM) was defined as time from diagnosis of primary tumor until first diagnosis of BM.

Results

In total, 104 patients (46.2% females, 53.8% males; median age 57.3 years at BM diagnosis) were included. Of these, 78/104 (75%) presented with BM from non-small cell lung cancers (NSCLC), 18/104 (17%) from breast cancers (BC), and 8/104 (8%) from renal cell carcinomas (RCC). Higher densities of $CD3^+$ ($p<0.001$) and $CD8^+$-TILs ($p<0.001$) were present in primary tumors compared to BM, while $CD68^+$ ($p=0.035$) and $CD163^+$-TAM densities ($p<0.001$) were higher in BM. Higher $CD3^+$-TILs and $CD163^+$-TAMs densities in primary tumors were associated with shorter TTBM ($p=0.039$ and $p=0.024$, respectively). Higher entropies of CD3+ ($p<0.001$) and FOXP3+ ($P=0.011$) TILs were observed in primary tumors compared to BM. Longer TTBM was associated with higher entropy in FOXP3+ TILs ($p=0.031$) and lower entropy in CD163+ TAMs ($p=0.040$).

Conclusions

In our unique cohort of matched intra- and extracranial specimen, intracranial cell densities of TAMs were significantly higher compared to primary tumors, whereas TILs are less present in matched BM, indicating potentially diverting impact of the innate and the adaptive immune system in the brain metastatic spread. Cell densities but not the entropies of TILs correlates with TTBM, indicating that further in-depth analysis of the spatial distribution is warranted.

Legal entity responsible for the study

The authors.

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