1484 AN INTERPLAY BETWEEN INNATE/ADAPTIVE/HUMORAL IMMUNITY LEADS TO INCREASED IMMUNOGENICITY OF MELANOMA VS. NON-MELANOMA DERIVED BRAIN METASTASES

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Background Brain metastases (BrMs) are a devastating complication of solid tumors. Despite improvements in tumor detection and local treatment as well as the introduction of new therapies including immune checkpoint blockade (ICB) and targeted therapies, the clinical benefit is observed only for a subset of BrMs patients.[1–3] A better understanding of this disease is needed to develop more effective patient selection strategies and therapeutics.

Methods In this study, multidisciplinary molecular and proteomic approaches were applied on to the peripheral blood and tumor tissues derived from primary lesions and BrMs from patients with melanoma, lung, breast, and renal cancer to evaluate in depth the tumor immune portrait behind BrMs biology.

Results The tumor microenvironment (TME) of melanoma brain metastasis (MBM) appeared to be less immunogenic when compared to the TME of primary melanoma (PM), based on less infiltration of NK and NKT cells. However, higher infiltration of $CD8^+$, antigen presenting cells, and B cells was observed in MBM when compared to BrMs derived from other solid tumors (non-MBM). Conversely, increased infiltration of Tregs and neutrophils was found in non-MBM compared with MBM. Interestingly, the presence of immature early tertiary lymphoid structures (TLS), as another hallmark of the TME of MBM, was supported by molecular and proteomic evaluations. Furthermore, proteomic analysis revealed higher infiltration of $CD8^+$ and $CD20^+$ cells in MBM to be associated with longer overall survival (OS). Curiously, the presence of immature early TLS structures in a MBM patient with longer OS compared to a MBM case with lower OS also emphasizes the potential influence of TLS formation in MBM patient survival and/or response to immunotherapy. These observations suggest that presence of TLS may have a strong association or even play a functional role in the immune control of MBM.

Conclusions Taken together these results suggest that the TME of BrMs plays a pivotal role in the pathogenesis and therapeutic resistance of BrMs derived from different solid tumors.

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Ethics Approval Samples were procured under studies approved by Providence Saint Joseph Health Institutional Review Board or Western Copernicus Group Institutional Review Board. All specimens evaluated were derived from consenting patients.

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