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Abstract

ELUCIDATING CELLULAR AND MOLECULAR DETERMINANTS OF SYSTEMIC IMMUNE SUPPRESSION IN GLIOBLASTOMA PATIENTS.

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Glioblastoma (GBM) is the most aggressive primary tumour that afflicts the brain and the inefficacy of the standard treatment raises the need of novel therapeutic approaches. Recently, immune-based therapies have been tested in GBM, without significant improvement of patient prognosis. This poor outcome is mainly attributed to prominent local and systemic immunosuppression, mostly driven by GBM cells but also tumour-associated myeloid cells. Despite tumour microenvironment has been deeply characterised, the diversity of the blood immune constituents has only been partially addressed. Hence, we here conduct a comprehensive profiling of GBM patient's peripheral blood mononuclear cells (PBMCs) combining single cell RNA-sequencing (scRNA-seq) and flow cytometry analyses. By analysing PBMCs from our cohort composed by 10 GBM patients and 5 healthy donors, we uncovered that patient-derived myeloid cells display phenotypic trajectories linked to immune suppression. GBM patient-derived classical monocytes show decreased sensitivity to

pro-inflammatory stimuli and pathways related to T cell activation capacity. Additionally, GBM-derived monocytes express S100A family cytokines that have been correlated to immune suppression and poor prognosis in GBM. Transcriptional regulator inference demonstrated dampening of programs prototypically related to immune cell activation, such as NFκB and AP-1. Moreover, GBM patients show depletion of pro-inflammatory non-classical monocytes, thus demonstrating altered myelopoiesis. Moreover, patient-derived classical monocytes show high inter-individual transcriptional heterogeneity, thus reflecting tumour heterogeneity. Collectively, our results suggest that the immunological profile of the patient's PBMCs represents a potential source for biomarker discovery and personalized patient management in clinical settings. Additionally, the identification of immunosuppressive pathway in blood monocytes can lead to the development of novel immune-activating targeted therapies to improve GBM prognosis.