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FUNCTIONAL PRESENCE OF M2 MACROPHAGE MARKERS IN GBM TUMOR CELLS

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BACKGROUND: Tumor associated macrophages (TAMS) have been suggested to be key players in the tumor microenvironment. The M2 activation phenotype is believed to be the predominant TAM phenotype in solid tumors. To further define the role of M2 TAMs and analyze the cross-talk between tumor cells and TAMs, we examined the presence of macrophage markers in glioblastoma (GBM) tumors, their responses to various treatments, the genetic profile of M2 macrophages and also potential mediators of tumor cells communication with TAMs. METHODS: GBM tumor specimens were assayed for macrophage/microglia and M2 activation markers via immunohistochemistry and immunofluorescence. GBM tumor lysates and glioma tumor cell lines were assayed for M2 macrophage activation markers, CD163, CD204 and CD206 via immunoblotting. Gene expression analysis in a THP-1 model of macrophages was performed using Affymetrix Human Gene 1.0 ST Array. Proteins released by GBM cells were analyzed by mass spectrometry (LC-MS). Cells were cultured under various conditions of hypoxia or stem-like cells promoting or they were exposed to irradiation. RESULTS: Pan-macrophage CD68, microglia CD11b, and monocyte marker CD14 were all readily detected in GBM. CD163 + , CD204 + , and CD206+ cells were found to be richly present throughout GBM tumors. To confirm the M2 activation phenotype marker expression pattern, THP-1 monocytic cells model polarized by IL-4/IL-13 expressed CD163, CD204 and CD206. We also isolated the CD163+ cells from the resected specimens that, interestingly, expressed also an astrocytic cell marker, GFAP. Unexpectedly, GBM cells in culture were also found to express macrophage markers. Macrophage markers expression was differential in response to hypoxia, stem-like cells conditions and irradiation. In situ staining of GBM tumor specimens showed the co-localization of M2 macrophage markers and GFAP. We also found two groups of gene expression patterns in THP-1 M2 macrophages that differ from M1 and M0 types, with potential individual candidates for new M2 and also M1 markers. Among the proteins specifically picked by LC-MS, several are known to be associated with activated astrocytes (CTGF), immune cells (CCL2) or other stromal cells (periostin), and to some extent with tumor cells. CONCLUSIONS: GBM cells express macrophage activation markers CD163, CD204 and CD206, which is a novel observation. This finding implies the existence of a subset of GBM cells with a potential important functional role in the tumor microenvironment. Also, more specific markers for M2 macrophages are needed. Moreover, GBM cells release an abundance of factors enabling communication with TAMs. SECONDARY CATEGORY: Immunobiology & Immunotherapy.

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