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Immunology

## The role of human glioma-infiltrating microglia/macrophages in mediating antitumor immune responses<sup>1</sup>

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Little is known about the immune performance and interactions of CNS microglia/macrophages in glioma patients. We found that microglia/macrophages were the predominant immune cell infiltrating gliomas (~1% of total cells); others identified were myeloid dendritic cells (DCs), plasmacytoid DCs, and T cells. We isolated and analyzed the immune functions of CD11b/c+CD45+ glioma-infiltrating microglia/macrophages (GIMs) from postoperative tissue specimens of glioma patients. Although GIMs expressed substantial levels of Toll-like receptors (TLRs), they did not appear stimulated to produce pro-inflammatory cytokines (tumor necrosis factor  $\alpha$ , interleukin 1, or interleukin 6), and in vitro, lipopolysaccharides could bind TLR-4 but could not induce GIM-mediated T-cell proliferation. Despite surface major histocompatibility complex class II expression, they lacked expression of the costimulatory molecules CD86, CD80, and CD40 critical for T-cell activation. Ex vivo, we demonstrate a corresponding lack of effector/activated T cells, as glioma-infiltrating CD8+ T cells were phenotypically CD8+CD25-. By contrast, there was a prominent population of regulatory CD4 T cells (CD4+CD25+FOXP3+) infiltrating the tumor. We conclude that while GIMs may have a few intact innate immune functions, their capacity to be stimulated via TLRs, secrete cytokines, upregulate costimulatory molecules, and in turn activate antitumor effector T cells is not sufficient to initiate immune responses. Furthermore, the presence of regulatory T cells may also contribute to the lack of effective immune activation against malignant human gliomas.

**Key Words:** costimulation • human glioma • macrophages • microglia • regulatory T cells • tumor immunotherapy

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