Immunotherapy for glioblastoma: a long and winding road

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There has traditionally been discomfort with our current strategies to treat patients with gliomas, not only because their efficacy has remained limited despite undisputable progress, but also because a cure using a conventional combination of surgery, radiation therapy, and chemotherapy is still a distance away. This is, at least in theory, different for immunotherapy. In fact, clinical trials of immunotherapy, including various courageous local treatment approaches, have a long tradition in neurological surgery throughout the world. Accordingly, there are ongoing efforts to understand and circumvent the immunosuppression associated with glioblastoma and to design novel, more effective, but safe strategies of immunomodulation.

In the present issue of *Neuro-Oncology*, Rodrigues and colleagues (1) report that human monocytes from healthy donors acquire a myeloid-derived suppressor cell (MDSC) phenotype when co-cultured with human glioblastoma cells. Glioblastoma-conditioned monocytes exhibited reduced CD14 expression but increased expression of various immunosuppressive molecules, interleukin 10, transforming growth factor-β, and B7-H1; decreased phagocytic ability; and increased ability to induce apoptosis in activated lymphocytes. Direct contact between monocytes and glioblastoma cells was necessary for the complete induction of this phenotype. Moreover, the authors found elevated numbers of circulating MDSCs in the peripheral blood of glioblastoma patients, suggesting that these cells contribute to the cellular immunosuppression characteristic of glioblastoma.
Dendritic cell-based therapies are currently the most widely applied cellular immunotherapy for glioblastoma, although no controlled trial has been performed so far. Using a murine glioma model, the laboratory of G. Finocchiaro demonstrated that the intratumoral injection of pulsed dendritic cells increased survival significantly, either per se or in combination with subcutaneously administered dendritic cells. Further experiments suggested that intratumoral pulsed dendritic cells potentiated the anti-tumor immune responses elicited by subcutaneous dendritic cells by proimmune modulation of cytokines in the tumor microenvironment, a decrease of regulatory T cells, or a direct inhibition of tumor proliferation by tumor necrosis factor-α (2).

Finally, a third paper in this issue reports the results of a phase II trial in which 34 patients with recurrent glioblastoma were treated with intratumoral CpG oligonucleotides administered intratumorally via convection-enhanced delivery (3). Treatment was well tolerated, but progression-free survival at 6 months was only 19%. One partial response and 3 “minor responses” were observed. Predictors of a favorable response to this treatment await identification.

Despite these modest steps ahead, we are still waiting for the first breakthrough in the field of immunotherapy. Yet the field appears to be experiencing a revival, in part due to the heightened attention received by the vaccination strategy targeting mutant epidermal growth factor receptor in patients with glioblastoma (4).

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References

