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# Intra-tumoral dendritic cells increase efficacy of peripheral vaccination by modulation of glioma microenvironment.

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## Abstract

Pilot data showed that adding intratumoral (IT) injection of dendritic cells (DCs) prolongs survival of patients affected by glioblastoma multiforme (GBM) treated by subcutaneous (SC) delivery of DCs. Using a murine model resembling GBM, we investigated the immunological mechanisms underlying this effect. C57BL6/N mice received brain injections of GL261 glioma cells. Seven days later, mice were treated by 3 SC injections of DCs with or without 1 IT injection of DCs. DC maturation, induced by pulsing with GL261 lysates, was necessary to develop effective immune responses. IT injection of pulsed (pDC), but not unpulsed DCs (uDC), increased significantly the survival, either per se or in combination with SC-pDC ($P < .001$ vs controls). Mice treated by IT-pDC plus SC-pDC survived longer than mice treated by SC-pDC only ($P = .03$). Injected pDC were detectable in tumor parenchyma, but not in cervical lymph nodes. In gliomas injected with IT-pDC, CD8+ cells were significantly more abundant and Foxp3+ cells were significantly less abundant than in other groups. Using real-time polymerase chain reaction, we also found enhanced expression of IFN-gamma and TNF-alpha and decreased expression of transforming growth factor-beta (TGF-beta) and Foxp3 in mice treated with SC-pDC and IT-pDC. In vitro, pDC produced more TNF-alpha than uDC: addition of TNF-alpha to the medium decreased the proliferation of glioma cells. Overall, the results suggest that IT-pDC potentiates the anti-tumor immune response elicited by SC-pDC by pro-immune modulation of cytokines in the tumor microenvironment, decrease of Treg cells, and direct inhibition of tumor proliferation by TNF-alpha.

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