Central Nervous System Tumor Immunity Generated by a Recombinant Listeria monocytogenes Vaccine Targeting Tyrosinase Related Protein-2 and Real-Time Imaging of Intracranial Tumor Burden.

Experimental Studies

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Abstract:
OBJECTIVE: Previously, we demonstrated that a recombinant Listeria monocytogenes (rLM) vector encoding the melanoma-associated antigen, tyrosinase related protein (TRP)-2, could successfully treat subcutaneous B16 melanomas. The purpose of the present study was twofold: 1) to test whether this rLM-nucleoprotein (NP)/TRP-2 could generate antitumor immunity to a B16 tumor challenge in the immunologically privileged central nervous system (CNS) and 2) to develop a noninvasive imaging modality to monitor tumor progression in the brain after immunotherapy.

METHODS: Mice were vaccinated with either a control rLM strain expressing only a viral antigen (rLM-NP) or a strain expressing both the viral epitope and TRP-2 (rLM-NP/TRP-2). These mice were then analyzed for their ability to mount tumor-specific T-cell responses, to generate protective antitumor immunity to a CNS tumor challenge, and for the localization of T cells at the tumor site. To noninvasively measure tumor growth within the CNS in vivo, we developed a B16 cell line expressing firefly luciferase that could be readily detected via bioluminescent imaging.

RESULTS: Vaccination with rLM-NP/TRP-2 induced a robust, tumor-specific CD8+ T-cell response to the dominant cytotoxic T lymphocyte epitope of TRP-2 and selective interferon-[gamma] secretion when cocultured with B16 melanoma cells in vitro. Significant decreases in CNS tumor sizes were easily visualized in mice vaccinated with rLM-NP/TRP-2 compared with mice that received a control rLM expressing the NP epitope alone (rLM-NP). The subsequent decreased tumor size and extension of survival induced by rLM-NP/TRP-2 was similarly associated with an early increase of tumor infiltrating T cells.

CONCLUSION: The ability to treat tumors arising within the CNS is difficult because of the nature of the anatomic confines of the brain and a microenvironment that may not promote immune responsiveness. These studies describe an in vivo bioluminescent imaging system to monitor CNS tumor growth in mice, which we successfully used to document decreased intracranial tumor progression and size after vaccination with rLM-NP/TRP-2. The results suggest that metastatic tumors in the CNS can be targeted immunotherapeutically without overt autoimmune toxicity.