Localized Cytokines Protect Neuronal Integrity and Drive Potent Anti-Cancer Immunity

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Over the last two decades, life expectancy for aggressive melanoma patients has risen 10-fold, whereas adult glioblastoma (GB) patient life expectancy remains largely unchanged. Despite nearly half a century of research into systemically administered chemotherapy, intracranial chemotherapy, slow-eluting intracranial chemotherapy, photodynamic therapy, radiation, and tumor-treating fields, GB patient outcomes remain exceedingly poor, which suggests that relying on modalities which seek to disrupt cell division alone is a poor therapeutic strategy.

By contrast, immunotherapy has fundamentally altered melanoma patient care, owing to the adoption of immune checkpoint blockade (ICB) with drugs such as nivolumab. Despite their success in peripheral cancers, nivolumab and other immunotherapies have not fared well in clinical trials for adult GBs. A large suppressive myeloid compartment (MDSCs) and the unique immune environment of the central nervous system (CNS) are obstacles that limit effector immune cells in the brain. Furthermore, it remains difficult to characterize the protective or degenerative effects of anti-cancer inflammation on neurons *in vivo*.

In this thesis, we report a new neuroimmune modality which can induce potent and programmable neuroinflammation against brain tumors. We find this modality, an intratumoral depot of cytokines, creates an artificial brain-immune border that enables infiltration of T lymphocytes and other peripheral immune cells into the brain parenchyma. This triggered potent innate and adaptive inflammatory cascades which lead to significant survival benefit in tumor-bearing mice.

We then further developed a framework to delineate the effects of tumors and neuroinflammation on neural activity *in vivo*. We created a new class of bioelectronic neural interfaces which are modular, soft, and hydrogel-based. These neural interfaces revealed that brain tumors disrupt the electrophysiology and calcium firing characteristics of the brain and establish their own signaling networks. Furthermore, we saw that while cytokines alter the brain tumor immune microenvironment, they leave endogenous neuronal networks intact. This thesis shows that programmed inflammation can be neuroprotective and establishes a framework to evaluate neuronal activity in the context of cancer and inflammation within deep brain structures *in vivo*.

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