

Alerting the immune system via stromal cells is central to the prevention of tumor growth

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Anticancer immunotherapies are highly desired. Conversely, unwanted inflammatory or immune responses contribute to oncogenesis, tumor progression, and cancer-related death. For non-immunogenic therapies to inhibit tumor growth, they must promote, not prevent, the activation of anticancer immune responses. Here, the central immunoregulatory role of brain-specific stromal cells and neurons as well as their ability to maintain an immunological balance and prevent the development of glioblastoma is discussed.

Activating the immune system against cancer has been the objective of tumor immunologists for a long time. Several immunotherapeutic approaches, including the adoptive transfer of T cells as well as the administration of immunostimulatory cytokines or antibodies, may mediate partial or complete tumor regression in some patients. However, such approaches are often hampered by adverse events, dosing issues and/or an inability to precisely localize tumors. Although stimulating a physiologic inflammatory response against tumor cells is desired, paradoxically chronic inflammatory conditions may increase the risk of developing cancer and/or succumbing from disease.¹ An additional obstacle against the success of anticancer immunotherapy reflects the fact that the tumor microenvironment generally exerts a robust immunosuppressive activity and hence actively inhibits immune responses. Therefore, additional insights into the immunosuppressive nature of the tumor microenvironment, including stromal, endothelial, and immune cells, are needed to design strategies that increase the efficacy of anticancer immunotherapy and assist the development of beneficial immune responses.

The chronic inflammatory reactions that promote oncogenesis and tumor progression may have different origins. Indeed, inflammation can develop prior to or along with oncogenesis, but in both cases it affects the neoplastic tissue and/or the tumor microenvironment. Inflammation is not only required to promote tumor progression, but it is also a prerequisite for the acquisition by neoplastic lesions of a full-blown malignant phenotype, fostering contextually detrimental processes such as tissue remodeling, angiogenesis, metastasis, and the suppression of innate anticancer immune responses.¹ Although oncogenic signaling often initiates post-cancerous inflammation, smoldering inflammation can precede tumorigenesis and promote the accumulation of genetic and epigenetic alterations associated with malignant transformation.² Thus, local chronic inflammatory responses driven by tumor microenvironment can promote malignant transformation.

Presently, much attention has been dedicated at identifying the pro-inflammatory factors produced by malignant cells, which include growth factors and cytokines. These soluble mediators recruit a variety of cell types, including immune cells, to the tumor

microenvironment, hence facilitating the establishment of an inflammatory response. Conversely, the role that tissue stromal cells play in this process is less clear.

Glioblastoma multiforme (GBM) is a highly invasive tumor characterized by rapid growth, dismal prognosis, and resistance to standard treatments. Fortunately, GBM is a relatively rare neoplasm.³ We postulated that (1) brain-specific stromal cells are equipped to guard tissue homeostasis, and that (2) common genetic defects in regulators of the immune response as well as the instability of stromal cells may be central to the development of chronic inflammation (and hence to tumor progression). Genetic mutations resulting in the inability of the host to suppress tissue inflammation are the bedding for the accumulation of epigenetic alterations in cells. In agreement with our first hypothesis, we have reported that lack of interferon (IFN) β , a Type I IFN with anti-inflammatory, antiviral, and antitumor activities, leads to chronic tissue inflammation in several models of inflammatory diseases. We attributed such a chronic response to the inability of stromal cells to suppress local inflammation in the airway, joints,

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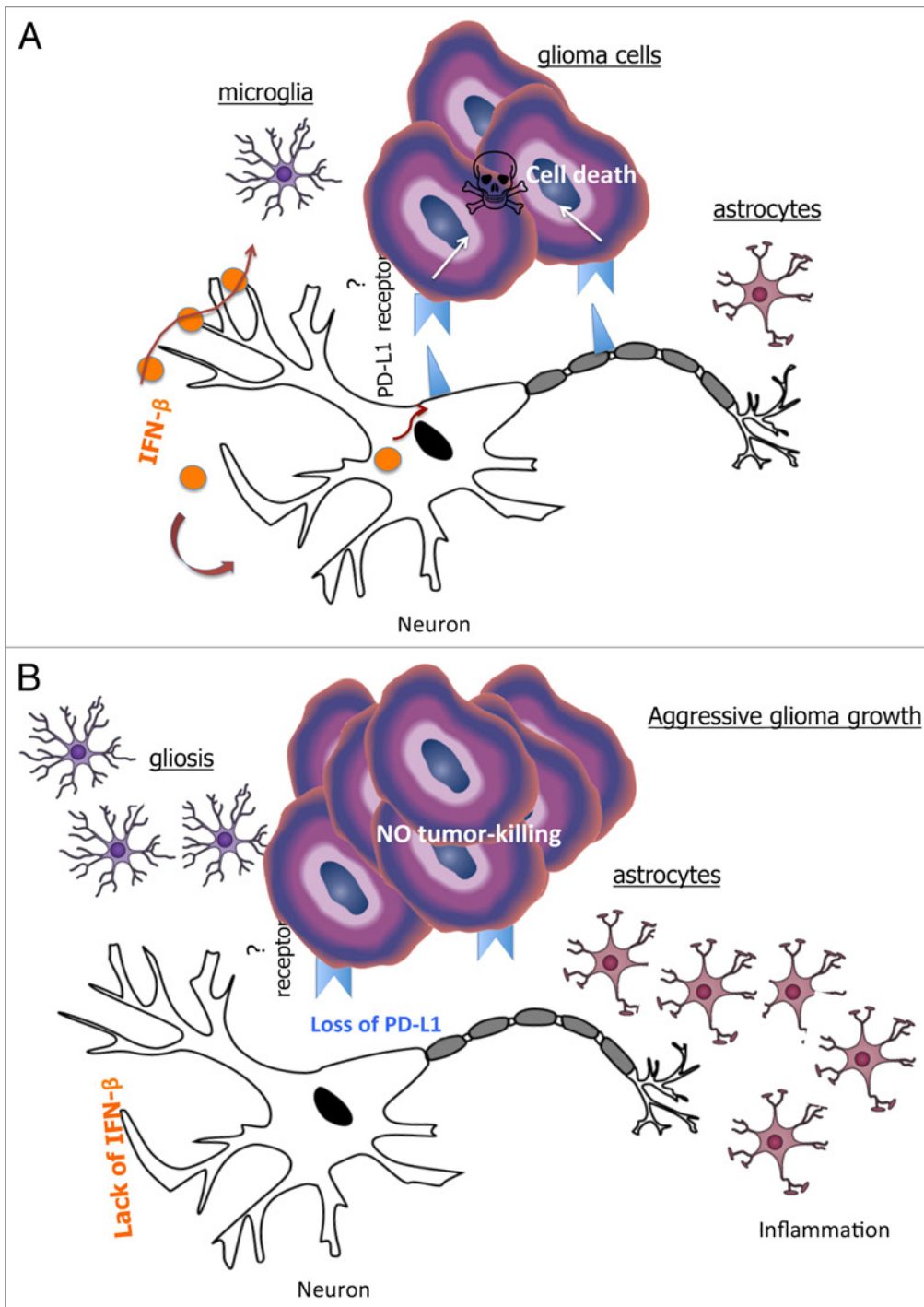


Figure 1. Neurons suppress central nervous system inflammation and glioma growth. **(A)** Immunocompetent neurons are capable of suppressing central nervous system (CNS) inflammation and oncogenesis because they can sense the danger posed by the autonomous proliferation of glial cells. This leads to the interferon β (IFN β)-dependent upregulation of programmed cell death 1 ligand 1 (PD-L1) on neurons, binding to a hitherto unknown receptor on glioma cells to induce their caspase-dependent demise. **(B)** *Ifnb*-deficient neurons lack the ability to prevent CNS inflammation and cancer growth as they fail to express PD-L1.

role in limiting chronic CNS inflammation.⁸

The next question for us to address was whether neurons also have an impact on CNS tumor growth. Given the importance of the *Ifnb* gene to the etiology of gliomas and CNS inflammation, it was reasonable to believe that IFN β functions to protect the CNS against development of gliomas. Indeed, the lack of *Ifnb* results in the loss of CD274 (best known as programmed cell death 1 ligand 1, PD-L1) expression by neurons. PD-L1 is a transmembrane protein that functions as a negative regulator of T-cell activation upon binding to programmed cell death 1 (PDCD1, best known as PD-1) and CD80 (also known as B7-1). PD-L1 may be harnessed by glioblastomas to evade immunosurveillance mediated by tumor-specific T cells, mainly upon the binding to PD-1.⁹ Our studies revealed that neuronal PD-L1 is instrumental in limiting the growth of gliomas by inducing the caspase-dependent death of malignant cells. However, none of the known receptors for PD-L1 was involved in the PD-L1-elicited caspase-dependent killing of glioma cells. One of central issues that remains to be addressed at this stage is which PD-L1 receptor expressed on gliomas mediates such an antineoplastic effect. Of note, mice lacking the IFN β -dependent expression of PD-L1 on neurons manifested accelerated glioma progression, suggesting that the immunocompromised milieu of these hosts allowed for the rapid growth of glioma cells, which would have been controlled

and central nervous system (CNS).⁴⁻⁶ In support of our second assumption, recent results demonstrated that defects in the Type 1 IFN receptor signaling pathway,

such as those manifested by *Ifnar1*-deficient mice, accelerate gliomagenesis.⁷ We have also shown that neurons are immunologically active and play a central

in an immunologically competent CNS microenvironment. In agreement with this notion, the expression levels of PD-L1 in tumor-associated neurons were

found to positively correlate with improved prognosis in GBM patients, while elevated amounts of PD-L1 on glioblastoma cells were negatively correlated with survival rate.¹⁰

Based on these findings, it is likely that immunocompetent neurons (and other tissue-specific stromal components of the tumor microenvironment) sense and inhibit tumor growth. At least in part, such an oncosuppressive mechanism appears to be mediated by the IFN β -dependent upregulation of PD-L1 on neurons, resulting in the activation of an unknown receptor on glioblastoma cells

that limits the expression of PD-L1 itself by the malignant compartment. Eventually, this process results in the activation of caspase-dependent cell death. Neurons with immunogenetic defects, such as those lacking the *Ifnb* or the *Cd274* gene, lack such an oncosuppressive capacity. In this scenario, the immunocompromised brain acts as a double-edged sword: it not only allows gliomagenesis and fosters local inflammation, but also tolerates tumor growth because neurons are unable to kill malignant cells (Fig. 1).

Our understanding of the complexity of the genetic and epigenetic changes

associated with oncogenesis and tumor progression will be complete only when the immunogenetic makeup of tissue-specific components of the tumor microenvironment is precisely characterized. This consideration highlights the need to appropriately classify groups of patients exhibiting various types of immunogenetic defects in order to design suitable, patient-specific immunotherapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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