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Understanding the relationship between gliomas and T cells: Paving the way for effective immunotherapy

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Tumor-reactive cytotoxic T cells are often seen as critical to achieving successful antitumoral immune responses. In this context, functional T cells' tumor tropism, infiltration, and survival are essential to mounting effective immunotherapies.

Robust evidence supports that the innate and adaptive immune system surveils the central nervous system (CNS) under physiological and pathological conditions. For instance, CNS local immune-depletion (ie, multiple sclerosis patients treated with lymphocyte CNS migration blocker natalizumab) or systemic immunodeficiency (ie, HIV patients) can lead to the occurrence of opportunistic infections, such as progressive multifocal leukoencephalopathy,[1] a potentially severe neurological condition caused by the replication of a neurotropic form of the human polyomavirus 2, commonly known as the JC virus. While the JC virus usually is harmless, found in a "dormant" state within 50% of the population, the virus can escape local immunosurveillance upon T-cell depletion in the CNS. Furthermore, despite the lack of conventional lymphatic channels in the CNS, both the cerebrospinal fluid (CSF) and the interstitial fluid (IF) can drain into the peripheral compartment via the deep cervical lymph nodes.[2] This route of communication can drain soluble CNS-associated antigens where dendritic cells uptake and present CNS-associated antigens to T and B cells.

Although the immune system regularly surveils the CNS to ensure its homeostasis, the profound immunosuppressive nature of gliomas and their metabolically harsh microenvironment[3] contribute to the exclusion of functional T lymphocytes and subsequent dominance of tumorigenic myeloid cells.[4] These characteristics have contributed to the poor results obtained from immunotherapies for treating high-grade gliomas and glioblastoma.[5,6] Even though immunotherapy remains an attractive approach, understanding glioma-associated T-cell biology and how these cells interact with the tumor and its microenvironment is crucial to elucidate how primary brain tumors escape the tumor immunosurveillance. Answers to these questions will indeed lead us to optimize current and future clinical approaches. Along these lines, in this issue of *Neuro-oncology*, Cordell et al provide an elegant overview of the role of T cells in shaping low- and high-grade gliomas.[7] Interesting aspects of T-cell biology are highlighted in this manuscript, such as T cells' pro- vs anti-tumorigenic roles (ie, regulatory CD4 T cells vs cytotoxic CD8 T cells). In addition to the direct role of T cells in regulating glioma growth, the authors highlight how the tumor microenvironment evades immunosurveillance by the expression of inhibitory ligands such as PD-L1, secretion of immunoregulatory factors such as IL10 and TGFβ, or production of myeloid-favorable factors such as G-CSF. This study also examines (dis)functional T-cell stages, such as tolerance, ignorance, anergy, and exhaustion, and how these stages regulate gliomas' survival and expansion. This information serves as an introduction to an exhaustive literature compilation of current T-cell-focused immunotherapeutics.

Most immunotherapy strategies are designed to activate cytotoxic T cells. Among these cells, effector $CD8^+$ T cells have centralized scientific attention. However, an efficacious response to immunotherapy might rely on the optimal activation of broader immune components to orchestrate the antitumor immunity. One candidate is the CD4 T-cell compartment.[8] CD4 T cells in brain tumors are best known for their protumoral effect driven by regulatory $Foxp3^+$ T cells. However, differentiated $CD4^+$ T cells are essential coordinators of the adaptive antitumoral immunity. Helper $CD4^+$ T cells (Th) promote cytotoxic CD8 T cells function via activation of dendritic cells and regulate the myeloid compartment and tumor cells via secretion of immune-modulatory factors, such as interferon (IFN) gamma and tumor necrosis factor (TNF) alpha. Importantly, helper $CD4^+$ T cells can modulate the antitumoral humoral response by inducing plasmablast differentiation. $CD4^+$ T cells are necessary to build a humoral response against tumor antigens by providing help via CD40 ligand signaling to CD40 on B cells to drive their differentiation and maturation into affinity-matured, class-switched plasma cells. In support, intratumoral B-cell gene signature and formation of tertiary lymphoid structures (TLS) are the best predictors of overall survival (even when combined with CD8, PD-1, or CTLA-4 gene signatures) in soft-tissue sarcoma and metastatic melanoma patients treated with neoadjuvant pembrolizumab (PD-1 blockade). In advanced metastatic melanoma, TLS and B-cell signatures, but not T-cell signatures, predicted therapeutic

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responses to pembrolizumab and ipilimumab (CTLA-4 blockade). Intratumoral B cells of immunotherapy responsive patients showed more B-cell receptors oligoclonality than B cells of nonresponding patients. In support of this observation, antitumoral functions of B cells upon immune-checkpoint blockade therapy have been attributed to their differentiation into plasmablasts[9] and the subsequent production of tumor-reactive antibodies. These observations suggest that B-cell infiltration and TLS formation could serve as criteria for checkpoint blockade response, and patients could be enrolled based on these parameters. Nevertheless, the potential relevance of $CD4^+$ T cells and B cells in gliomas remains to be fully elucidated.

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