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Invited Review

Tumor infiltrating immune cells in gliomas and meningiomas

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ABSTRACT

Tumor-infiltrating immune cells are part of a complex microenvironment that promotes and/or regulates tumor development and growth. Depending on the type of cells and their functional interactions, immune cells may play a key role in suppressing the tumor or in providing support for tumor growth, with relevant effects on patient behavior. In recent years, important advances have been achieved in the characterization of immune cell infiltrates in central nervous system (CNS) tumors, but their role in tumorigenesis and patient behavior still remain poorly understood. Overall, these studies have shown significant but variable levels of infiltration of CNS tumors by macrophage/microglial cells (TAM) and to a less extent also lymphocytes (particularly T-cells and NK cells, and less frequently also B-cells). Of note, TAM infiltrate gliomas at moderate numbers where they frequently show an immune suppressive phenotype and functional behavior; in contrast, infiltration by TAM may be very pronounced in meningiomas, particularly in cases that carry isolated monosomy 22, where the immune infiltrates also contain greater numbers of cytotoxic T and NK-cells associated with an enhanced anti-tumoral immune response. In line with this, the presence of regulatory T cells, is usually limited to a small fraction of all meningiomas, while frequently found in gliomas. Despite these differences between gliomas and meningiomas, both tumors show heterogeneous levels of infiltration by immune cells with variable functionality. In this review we summarize current knowledge about tumor-infiltrating immune cells in the two most common types of CNS tumors–gliomas and meningiomas–, as well as the role that such immune cells may play in the tumor microenvironment in controlling and/or promoting tumor development, growth and control.

1. Introduction

Tumor development and growth typically requires an appropriate microenvironment, in addition to genetic/molecular alteration of tumor cells. Such tumor microenvironment consists of a complex network of distinct cell types and extracellular matrix components, in which neoplastic cells interact with fibroblasts, vascular endothelial cells, a variety of infiltrating immune cells (including a network of cytokines and chemokines released by these cells) and extracellular matrix proteins, among other components. Although tumor development and growth largely depend on an adequate microenvironment, the tumor cells *per se* also induce significant changes in the tissue where they home and grow (Whiteside, 2008). Because of this, patients may show behavioral changes including neuropsychiatric symptoms and/or cognitive effects depending on the affected region of the brain and/or the local immune response (Taphoorn and Klein, 2004).

Immune cells present in the tumor typically include T lymphocytes, natural killer (NK) cells, macrophages, dendritic cells (DC), polymorphonuclear leukocytes and occasional B cells (Whiteside, 2008; Fridman et al., 2012). Overall, infiltration by immune cells is a hallmark of virtually every tumor (Quail and Joyce, 2013), and it is frequently associated with tumor behavior and patient outcome (Fridman et al., 2012). In this regard, while multiple reports in the literature have linked the presence of inflammatory infiltrates in human tumors with an improved prognosis and a better patient outcome (Fridman et al., 2012; Pages et al., 2009; Mahmoud et al., 2011), many others have found no significant

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association, or they have even linked immune cell infiltration with a poorer prognosis (Fridman et al., 2012). Such apparent discrepancy may be due to the type and functional state of immune cells infiltrating the tumor. In fact, the different types of infiltrating immune cell populations vary not only according to the type of cancer, but also from patient to patient within the same type of tumor or at different time points within a patient (e.g. at diagnosis *vs.* recurrence); these observations suggest that different immune cell microenvironments may have distinct effects/roles in tumor control and progression (Fridman et al., 2012). In addition, the same immune cells present in the tumor microenvironment may modulate their anti-or pro-tumoral functions, being able to play dual roles with potential to either suppress or promote malignancy (Shiao et al., 2011);usually, the latter predominates as the tumor cells acquire mechanisms for 'immune evasion'. Thus, in such circumstances the tumor, not only manages to escape from the host immune system, but it also develops a phenotype capable of manipulating immune cells (e.g. via secretion of chemokines and cytokines), and modifying their function to create a microenvironment that would favor tumor progression (Mantovani et al., 2008). To date, many mechanisms of immune evasion by tumor cells have been identified (Table 1), including inhibition of immune cell functions or apoptosis of anti-tumor effector cells, together with production of both growth factors and angiogenic factors that stimulate tissue repair and vascularization, and consequently also, tumor growth (Whiteside, 2008). In case of CNS tumors, immune responses may also contribute to induce changes in patient symptoms and behavior, depending on tumor localization and the specific types of immune cells and mediators involved. In this regard, it is considered that younger patients presenting with acute signs and symptoms of neurologic disease are investigated earlier, and consequently, referred more promptly for treatment (Yuile et al., 2006). Conversely, patients with organic brain lesions in neurologically silent brain areas might present with milder symptoms and/or isolated psychiatric symptoms such as depression, anxiety disorders, schizophrenia, anorexia nervosa, or cognitive dysfunction (Cheema et al., 2010; Bunevicius et al., 2008). In such later cases, differential diagnosis between a brain tumor *vs.* a psychiatric disorder is required, final diagnosis being frequently delayed for variable periods of time (Taphoorn and Klein, 2004; Gehring et al., 2009).

Table 1
Mechanisms that have been frequently associated with immune escape by tumor cells.

Cell feature	Mechanism of immune escape	Tumor cell-associated	Immune cell-associated
↓Expression of TAA	Lack of susceptibility to effector immune cells	+	–
↓HLA expression on tumor cells	Immune selection of resistant variants	+	–
↓Co-stimulatory molecules	Activation of signaling pathways for tumor cell survival	+	+
↑Death-receptor/ligand signaling	↑Immune cell death/apoptosis	+	+
Defective antigen presentation by DC	Altered T cell function	–	+
Altered T-cell receptor (TCR) signaling	Suppression of immune cells (e.g. T cells) by Tregs or MDSC	–	+
Secretion of chemokines and cytokines	Suppression of immune response	+	+

TAA, tumor associated antigens; Treg, regulatory T-cell; MDSC, myeloid-derived suppressor cell.

2. Diagnostic subtypes of glioma and meningioma

CNS tumors are rather heterogeneous and they vary widely by site of origin, morphological and histopathological features, growth potential and extent of invasion. At present, classification of gliomas is mainly based on the existence morphological evidence of differentiation of tumor cells along the astrocytic (70% of the cases) and less frequently the oligodendroglial and mixed astrocytic-oligodendroglial cell lineages in addition to ependymal tumors (Louis et al., 2007). The specific cell(s) targeted during neoplastic/malignant transformation of gliomas currently remains unknown, although tumor cells from primary brain tumors mimic the morphologic and phenotypic profiles of glial cells, or their precursors, from which they potentially originate. Because of their distinct cell appearance, gliomas are therefore classified into four major groups: astrocytomas, oligodendrogliomas, oligoastrocytomas (tumors presenting morphological features of both astrocytes and oligodendrocytes) and ependymomas, depending on their differentiation-associated features and their morphological similarities with normal/reactive glial cells. These tumors are further subclassified according to their histopathological grade into grade I to grade IV tumors, >80% of all diffuse gliomas being high-grade (grade III/IV) tumors, from which glioblastoma (GBM) is the most common in adults. Thus, according to the WHO criteria, patients are distributed into: (i) astrocytomas (grade I pilocytic astrocytomas, grade II diffuse astrocytomas, grade III anaplastic astrocytomas, grade IV glioblastomas, and grade IV gliosarcomas; (ii) oligodendrogliomas (grade II oligodendroglioma, and grade III anaplastic oligodendrogliomas); (iii) mixed oligoastrocytomas (grade II and grade III anaplastic oligoastrocytomas) and; ependymal tumors (subependymoma and myxopapillary ependymoma grade I; ependymoma grade II and anaplastic ependymoma grade III) (Table 2).

Conversely, all meningiomas originate from the meningeal coverings of the brain and the spinal cord. The vast majority of meningiomas are considered to be benign and slow-growing neoplastic lesions. However, these tumors present with a great clinical heterogeneity as regards the symptoms of the disease, histopathology, recurrence rates, clinical aggressiveness, and outcome. Overall, the majority of meningiomas are intracranial tumors, with up to 60% being located in the convexity, parasagittal, tuberculum sellae, and sphenoid wing regions, the clinical signs and symptoms associated with an underlying meningioma being directly related to the size and localization of the tumor. Despite this, general CNS-associated symptoms such as personality changes, neuropsychological deficits, headache, aphasia, sensory-motor or visual symptoms, as well as seizures, also occur rather frequently (Fathi and Roelcke, 2013). From the histopathological point of view, meningiomas are currently classified according to the WHO grading system into three major (prognostic) categories which include: benign (WHO grade I), atypical (WHO grade II), and anaplastic (WHO grade III) meningiomas, with several histopathological variants. Such variants include: (i) grade I meningothelial, fibroblastic, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich and metaplastic meningiomas; (ii) grade II atypical, clear-cell and chordoid tumors and; (iii) grade III anaplastic, rhabdoid and papillary meningiomas (Louis et al., 2007). WHO grade I/benign meningiomas represent around 90% of all meningiomas, the meningothelial, fibroblastic, and transitional variants being the most common ones (Domingues et al., 2014). By definition, these meningiomas do not invade the brain and they display a benign clinical behavior (Table 2); despite this, a significant proportion of cases show recurrence of the disease after complete tumor resection, with different recurrence rates (range: 7–20% of cases) for distinct histopathological subtypes.