European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2023 vol. 12, ISSUE N. 2, May-August

THE RESPONSE OF IMMUNE SENTINELS CAUSING INFLAMMATION IN GLIOMA AND GLIOBLASTOMA

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ABSTRACT

Glioma is a type of central nervous system (CNS) tumor originating in glial cells. Glioblastoma, the most severe form of glioma, is the most common and malignant form of glial tumors. Astrocytoma, which takes its name for having star-like cells, also belongs to this group of glial tumors and is distinguished in various forms. Gliomas are tumors of various types and of unknown etiology and are difficult to cure. The tumor microenvironment is made up of stromal cells, normal fibroblasts, epithelial cells, and T cells. In these tumors, immune cells invade the tumor tissue and may play an important role in prognosis and therapy. Microglia, which constitute about 20% of the total glial cell population, are macrophage-like cells of innate immunity and express CD11b, CD68, and CD163, amongst other markers. Microglia are activated in gliomas and glioblastomas and produce pro-inflammatory molecules, such as the chemokines CCL2 and CCL5, which attract immune cells. The chemokine CXCL8 attracts neutrophils, while CXCL12 is implicated in glioma post-radiotherapy resistance. Pro-inflammatory cytokines such as IL-1, tumor necrosis factor (TNF), and IL-6 are also produced in the tumor environment. In this article we highlight the importance of immune cells in gliomas and glioblastomas, and the role of pro-inflammatory chemokines and cytokines.

KEYWORDS: *glioblastoma, glioma, astrocytoma, CNS, inflammation, tumor, cytokine, chemokine, immunity*

INTRODUCTION

Primary brain tumors are those that arise directly in or near the brain, and secondary brain tumors are the result of metastases from a tumor originating elsewhere. The glial cells, which includes astrocytes, oligodendrocytes, ependymal cells, and Schwann cells, perform the following biological functions: support of the pyrenophores, participation in the myelination of nerve fibers, isolation function towards neurons and nerve fibers, injury repair, trophic functions, and indirect participation in the transmission of the nerve impulse. Gliomas are very common tumors of the central nervous system (CNS) (1,2). There are several types of gliomas that affect the brain and marrow. The most serious is glioblastoma which has a high growth rate and severity, with a median survival rate of approximately 15 months (3). The presence and type of glioma in the CNS and spinal cord is detected with specific laboratory tests.

Glioma derives from glial cells which act as support and nutrition for neuronal cells and form the CNS together with blood vessels, and gliomas are classified based on the presupposed cell of origin (4). Gliomas are divided into

Received: 03 June 2023
Accepted: 02 July 2023

2974-6345 (2023)

astrocytoma, involving astrocytes, oligodendrogliomas, involving oligodendrocytes, ependymomas, affecting the ependymal cells, and mixed gliomas, affecting both oligodendrocytes and astrocytes (5). In addition, brain tumors can be classified according to growth rate, infiltration, and metastasis capacity, and range from I to IV, where III and IV are more severe and with rapid growth, while tumor cells I and II are with a low and localized growth index (6).

The causes of the onset of gliomas are still obscure, even if they are often attributed to a genetic mutation of unknown origin (7). Exposure to ionizing radiation is also an environmental risk factor (8,9). The study of tumor tissue through genome sequencing can highlight new mutations that may take part in the pathogenesis of cancer. Mutations are diagnosed through analysis of cancer DNA in both brain fluid and peripheral blood, as well as liquid biopsies (10,11).

Even though glioma and glioblastoma look similar, there are differences between them; glioma is the general term to describe a primary tumor of the CNS, while glioblastoma, which is also called glioblastoma multiforme (GBM), is the most malignant and most common tumor of the glial neoplasms, accounting for almost 60% of cases (12). Astrocytoma, which also includes glioblastomas, is the most common type of glioma which affects the brain and, at times, the spinal cord as well. There are various types of astrocytoma including diffuse astrocytoma, diffuse wild type non-mutated astrocytoma, gemistocytic astrocytoma, anaplastic astrocytoma, and anaplastic wild type non-mutated astrocytoma. Glioblastomas also exist in various types such as glioblastoma multiforme, primary wild-type non-mutated glioblastoma, giant cell glioblastoma, gliosarcoma, epithelioid glioblastoma, and secondary mutated glioblastoma multiforme.

Gliomas are brain tumors of unknown etiology and are difficult to cure. Diffuse midline glioma (DMG) develops more frequently near the brain stem, concentrating around the pons and sometimes also invading the cerebellum and hypothalamus (13). GBM shows a genetic heterogeneity that prevents a clear diagnosis, as well as an effective therapy, while in DMG, the most evident mutations can be highlighted, facilitating diagnosis and therapy. The therapy for DMG involves radiotherapy and chemotherapy which can give the patient only transient relief with an extension of survival by only a few months (14,15).

DISCUSSION

The blood-brain barrier (BBB) hinders anticancer therapies in patients with brain cancer, demonstrating that its functionality is not impaired by the tumor (16). In recent times, research has focused on immune cells that invade the tumor microenvironment. For example, T cells, although with low infiltration into the tumor site, can play an important role in both prognosis and therapy (17). T cells that contact activated astrocytes or glioma cells in brain tumors exhibit TCR-CD3 for antigen recognition and T lymphocyte activation (18). The tumor microenvironment consists of stromal cells, normal fibroblasts, epithelial cells, and immune cells (19). The latter influences tumor development by the production of growth factors, cytokines, and chemokines. CD8+ cytotoxic T lymphocytes and Treg regulatory cells play a key role in tumor dynamics (20). Cytotoxic lymphocytes oppose tumor pathogenesis and are present, albeit too few, in greater numbers than CD4+ T helper cells (21). The greater the number of infiltrated CD8+ T cells, the longer the patient's survival is, demonstrating that the immune response at the tumor site is important for survival (22). T lymphocytes help fight the tumor but are also cells that provoke inflammation in the brain, causing negative effects for the patient. However, some gliomas, such as DMG, have much less T-cell infiltration than others (15). Gliomas often show increased expression of growth factor mRNA (TGF-ß1), as well as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (23). The natural killer (NK) cells of the innate immune system, which we know are responsible for killing tumor cells, are drastically suppressed at glial tumor sites (24,25). While the lymphocyte response in glial tumors is inhibited, the gene expression of inflammatory cytokines and chemokines generated by lymphocytes and macrophages is increased, explaining the cerebral inflammatory state (26).

Microglia distributed in the brain and spinal cord are sentinels of the CNS and defend the brain from damaged cells and infectious agents. Microglia, which comprise up to 20% of the total glial cell population (27), are also part of the innate immune system and represent a collection of primary brain macrophage-like cells expressing CD11b, CD68, and CD163, and other specific markers which have recently been highlighted (28,29). These cells are activated in cerebral gliomas and produce pro-inflammatory molecules, such as cytokines and chemokines, which makes them protagonists in the cerebral inflammatory system.

Macrophages are divided into anti-tumor M1 and pro-tumor M2 categories. In gliomas, they appear to play a part in the immunosuppression due to the increased level of M2 cells and decreased expression of TGF-β1 and TNF (30), while some cytokines such as macrophage colony stimulating factor (CSF) and chemokines attract monocytes to the tumor site (31). In addition, some cells of these tumors express the chemokine ligand CCL2 [also called monocyte chemoattractant protein (MCP)-1] and CCL5 (32,33). CCL2 mediates the inflammatory process by recruiting macrophages and pro-

inflammatory lymphocytes, causing immunosuppression, and it appears that the higher the level of CCL2 is, the more aggressive the tumor is (34).

In gliomas, CCL5 is also involved in inflammation, where it is overexpressed causing the recruitment of macrophages, granulocytic cells, and T lymphocytes (35). The pro-inflammatory chemokine CCL5 is expressed by both glioma and stromal cells and contributes to the migration and proliferation of microglia cells (33). Inhibition of this chemokine appears to reduce the migration of pro-tumor M2 monocytes (36).

Another chemokine of the CXC family, CXCL12, is implicated in the post-radiation therapy resistance of glioma (37). CXCL12 attracts tumor hypotoxic areas to molecules that play a large role in tumor development (38). CXCL8, or IL-8, is a chemokine involved in the recruitment of neutrophil granulocytes, which participates in cell invasion and angiogenesis. The CXCR2 receptor antagonist causes a reduction in glioma expansion, improving patient survival (39).

Astrocytes, taking their name from resemblance to a star, are cells located in the CNS that make-up neuroglia and are divided into fibrous astrocytes that are found in white matter, and protoplasmic astrocytes located in gray matter and form the neurovascular unit. Astrocytes are activated by inflammatory stimuli, leading to modification of their phenotype and overexpression of some proteins including cytokines and chemokines (40). Proteins expressed by astrocyte activation participate in various pathophysiological processes such as cell proliferation, neural growth, motility, autophagy, synaptic plasticity, myelination, immune defense, and BBB formation (41). Astrocytes communicate with each other through cyclic-AMP and following the loss of ATP, the damaged cells activate the P2 receptors of astrocytes, an effect that leads to their modification. In these reactions, the release of proteins stimulates cytokine receptors on astrocytes (42).

Glial-mediated inflammatory immunoreactivity occurs in glial tumors and brain lesions. Gliomas are brain tumors with cells that originate from neuronal stem cells, progenitors of oligodendrocytes, astrocytes, or differentiated neurons. However, since glioma cells and normal astrocytes reside in the same sites, their cell morphology appears similar. In gliomas and other brain pathologies, glia-mediated inflammation involves astrocytes with responsive morphological changes and blood cell recruitment, including immune cells (43). *In vivo*-activated astrocytes can release chemokines into the parenchyma and blood, exerting a recruitment effect for other inflammatory cells. In *in vitro* experiments, astrocytes can be activated to release cytokines by various pathogens, including the bacterial product lipopolysaccharide (LPS) which causes the secretion of various chemokines such as CCL2 (MCP-1), CCL3 (MIP-1α), CCL5 (RANTES), CXCL1, and CXCL2 (44). In addition, tumor necrosis factor (TNF)-treated astrocytes in vitro release other chemokines such as CCL2, CCL5, and CXCL8 (IL-8) (45), demonstrating that these cells are true mediators of brain inflammation.

CONCLUSIONS

In conclusion, even if the immune reaction in glioma and glioblastoma is low, it causes the secretion of cytokines and chemokines which mediate the inflammatory reaction.

Conflict of interest

The author declares that they have no conflict of interest.

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