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BRAIN TUMOR AND INFLAMMATION

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ABSTRACT

Innate immunity generates cytokines, including IL-1, which are important in controlling tumor development. Excessive synthesis and secretion of pro-inflammatory cytokines causes inflammation that promotes tumor development and progression. Immune cells are present in tumor tissue, including lymphocytes and monocytes that generate cytokines. These immune cells are recruited to the tumor site to fight the new tumor tissue which is not recognized as self. However, this process leads to a production of chemokines which attract immune cells, producing an excess of inflammatory cytokines that favor tumor development. Mast cells (MCs) are ubiquitous immune cells that also reside in brain tissue and participate in the brain tumor process by generating neuroinflammation. MCs are recruited by chemokines into brain tumor tissue where they become activated and produce several cytokines including IL-8, growth factors, vascular endothelial growth factor (VEGF), and also chemical mediators such as histamine and heparin, and tryptase and chymase that favor the formation of new blood vessels and mediate the production of metastases. However, MC accumulation in cancer tissue can be either beneficial or detrimental for tumor development.

KEYWORDS: *brain, tumor, inflammation, cytokines, chemokines, immune response*

INTRODUCTION

Chronic brain inflammation is mediated by cytokines and chemokines, which are generated by innate immunity and can have effects on the growth of tumors (1,2). This demonstrates the close connection between cancer and inflammation (3). Neuroinflammation and pain are characteristic and fundamental symptoms of the central and peripheral nervous systems. The brain has non-neuronal cells such as glial cells and keratinocytes that play an important role in the pathogenesis of diseases, including cancer. In recent years, much has been learned about the immune response to brain tumors and it has been seen that inflammation plays an important role both in the central nervous system (CNS) (4) and in other areas of the body.

Experimental and clinical studies have shown that tumor development is related to the host's immune response (5,6). In fact, histological analyses of tumor tissue shows the presence of immune cells surrounding the tumor mass (7). Immune cells, such as lymphocytes and monocytes, generate inflammatory cytokines in tumor tissue, including brain tissue (8). The inflammation produced by the excessive production and secretion of pro-inflammatory cytokines promotes the development and progression of tumors.

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DISCUSSION

In brain tumor tissue, there are immune cells such as lymphocytes and monocytes that are recruited to the tumor site in response to new tissue that is recognized as non-self. These immune cells generate cytokines and produce chemokines which attract further immune cells, producing an excess of inflammatory cytokines that exacerbates tumor development (9).

In brain tumors, immune cells, and particularly Th1 cells which physiologically monitor and maintain neuronal integrity, are activated (10). In glioma tumors, microglial cells and macrophages make up approximately 30% of the inflammatory cells in the brain (11). Inflammation in brain tumors manifests with edema (containing inflammatory proteins) which causes an increase in intracranial pressure and compromises the circulation of cerebrospinal fluid (CSF) (12). This phenomenon can give rise to hydrocephalus, resulting in headaches, hypertension, and shock, a life-threatening event. CNS tumors are often accompanied by fever and headache which represent the response to the inflammatory state (13,14).

Immunotherapy is a biological strategy that trains the immune system to recognize tumor neoantigens generated by genetic mutations. The activation of effector T lymphocytes plays an important role in homeostasis and in combating specific antigens, although excessive stimulation can induce an autoimmune phenomenon (15). In tumors, fever is caused by brain inflammation (called sterile inflammation), which should not be confused with fever that is induced by microorganisms. It has been reported that pro-inflammatory cytokines promote tumor cell development and play an important role in brain pathogenesis. Inflammatory cytokines contribute to brain tumor invasion and metastasis through the induction of metalloproteinases (16). In addition, inflammatory cytokines such as IL-1 and tumor necrosis factor (TNF) can have an autocrine effect, aggravating tumorigenic activity (17).

In the brain, proliferative and invasive tumors develop using non-transforming cells and chemoattracting molecules such as chemokines (18). These molecules are a subfamily of cytokines that have the ability to migrate and exert their biological effects through their specific transmembrane receptors (19). They are classified into C, CC, CX3C, and CXC categories based on the cysteine position on their molecular structure (20). The chemokines CCL2 and CXCL8 belong to the CXC subgroup and are produced by glial cells that express their receptors. These chemokines mediate diverse biological effects, including angiogenesis, invasiveness, proliferation, and cell survival (Table I).

Table I. *Some of the biological effects that are mediated by certain chemokines.*

Chemokine	Biological effect
• CXCL1	Reepithelization
• CXCL8	Tissue remodeling
• CXCL10	Inflammation
• CXCL12	Reepithelization, inflammation, angiogenesis
• CCL2	Inflammation, mast cell (MC) chemoattractant
• CCL5	Fibroblast migration
• CCL27	Keratinocyte chemoattractant, effector cell recruitment to sites of epithelial injury
• CCL28	Effector cell recruitment to sites of epithelial injury

Mast cells (MCs) are ubiquitous immune cells that are involved in innate and adaptive immunity. They are classic cells known to mediate allergic diseases and also participate in the development of brain tumors (21). The accumulation of MCs in cancer tissue can have dual effects, as it can be either beneficial or detrimental for the development of tumors.

These cells are present in brain tissue and can generate neuroinflammation that promotes tumor growth (22). Chemokines recruit MCs into brain tumor tissue where they become activated and generate different cytokines such as IL-8, growth factors, and vascular endothelial growth factor (VEGF), chemical mediators such as histamine and heparin, and tryptase and chymase that support the formation of new blood vessels and mediate the production of metastases (21). At the same time, MCs can be detrimental for tumor cells by producing several cytokines, including IL-1, IL-4, IL-6, and TNF, which limit the growth of the tumor mass and the formation of metastasis (23).

CONCLUSIONS

The immune system plays an important role in the brain and in tumors of the CNS. After they are recruited by chemokines released *in situ*, immune cells release inflammatory cytokines that may be beneficial or detrimental to tumor growth and the formation of metastasis.

Current research has focused attention on the use of immunotherapies for treating cancer, including brain tumors. Chimeric antigen receptor (CAR) T-cell therapy utilizes reconstructed patient T-cells that express CAR proteins directed toward surface-exposed tumor-associated antigens (TAAs). The use of CAR T-cell therapy has shown promising results in hematologic cancer studies (24) and for lymphoma (25,26); however, more research is needed to discover the role for this therapy in brain tumors, and for its utilization in clinical practice.

Conflict of interest

The author declares that they have no conflict of interest.

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