REVIEW ARTICLE

Updates in Microglial Research with Respect to Brain Cancer

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ABSTRACT

Microglia resides in the microenvironment of the central nervous system (CNS) and is thought to play a key role in the development and progression of brain cancer. This is because it was shown that microglia comprised a large portion of the total brain tumour mass. Besides, the origin of microglia cells in brain tumours is worth understanding as it is important to distinguish the resident macrophages from the circulating macrophages when discussing the pathology of brain tumours. Activated microgliosis has been linked to increased inflammatory mediators like cytokines, growth factors, matrix metalloproteinases (MMPs) and many more, which would facilitate tumourigenesis. Brain tumour cells also proliferate under the influence of signalling pathways, such as the toll-like receptor 2 signals. Vascular endothelial growth factor (VEGF) which is an angiogenic factor aids in the growth of tumour cells. Brain cancer cells rely on suppressing the effector arm of immune system to evade attacks by downregulating major histocompatibility complexes (MHC) class II molecules and inducing the conversion of microglia to an immunosuppressive phenotype. Glioblastoma stem cells (GSCs) that give rise to brain cancers communicate with microglia cells, which determines their growth and invasion potential. Understanding the molecular interactions of brain cancer and microglia cells would help unlock novel treatments via means of immunotherapy, immunosuppressants and utilising microglia cells to deliver nanoparticle drugs to effectively target and treat brain cancer.

Keywords
Microglia, Brain Tumour, Immune Evasion, Cancer Stem Cells, Brain Cancer Treatment

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INTRODUCTION

The conception of microglial (small glue) cells was introduced by Pio del Rio-Horteg.[1] Microglia is an immune macrophage cell of the central nervous system (CNS) that supervises the microenvironment of the CNS in order to encounter injuries and foreign substances in the body.[2] During the early development of the brain of a human, microglial cells appear as ~~an~~ amoeboid-shaped. In a fully-fledged developed brain, these cells modify into a more branched and ramified phenotypic shaped. At this stage, these cells will be evenly distributed throughout the CNS and will be ready to face pathological events, as they are equipped with properties of migration, multiplication and phagocytic skills.[3] The number of microglial cells complements the number of neurons found in the CNS which is around 100–200 billion cells, the condition of the body whether healthy or diseased affects the amount too.[1]

Brain cancer, brain tumour or intracranial tumour is a disease where there is an emergence of abnormal growth of cells in the brain or spinal cord of the CNS, which can be either benign or malignant.[4] In a benign tumour, these cells proliferate slowly and compresses neighbouring areas of the brain and spinal cord. Whereas when the tumour proliferates at a high rate and spread to other immediate surrounding tissues, the tumour becomes malignant. The compression of the tumour on the brain region will inhibit the function and blood supply of that region leading to ischemia. If the tumour arises from the brain, then it is known as a primary brain tumour. As for secondary brain tumours, it originates from a different organ of the body and spreads to the brain causing metastatic brain tumour, where this is more common compared to primary brain tumours.[5] Globally, around

250,000 people are afflicted by primary brain tumour which is less than 2% of all cancers. In children under the age of 15, brain tumours are usually the second most common type of cancer affecting them, next to acute lymphoblastic leukaemia. It has been shown that primary malignant brain tumours (PMBT) most commonly affect people in the age group of 20–60 with a male to female ratio of 2:3 by as reported by Krishnatreya and associates.[6] Brain tumour occurs when the genes involved in the regulation of cell division, fixing of other malformed genes that fails in differentiating between self and non-self are defective. Environmental factors such as exposure to vinyl chloride, ionising radiation and Epstein-Barr Virus (EBV) can also contribute to the destruction of regulatory genes in humans.[7]

Besides tumour cells, non-neoplastic cells such as microglial cells are found abundantly in the microenvironment of brain tumours, where it accounts for 30-50% of the total brain tumour mass.[8] The tumour cells and microglial cells interact with each other in the formation of tumourigenesis and invading the tumour. The high population of microglial cells observed indicates that they play a crucial role in tumourigenesis and metastasis.[9] For this reason, this paper focusses on the current updates in microglial research regarding brain cancer.

Physiology and Origins of Microglia in Brain Tumour

A copious amount of microglia infiltration was consistently observed within the human brain tumour tissues while performing immune-histological studies. Hence, it is said that the extent of stimulation of microglia certainly influences the grade of the brain tumour.[10] This stimulation indicates that the neoplastic progression correlates with the microglia activation. Recent studies have shown that microglia and macrophages are acquired from two different myeloid groups of cells. Even though older reports show these cells have resemblances in the surface biomarkers and physiological functions, microglia and macrophages have distinct origination where microglia are the parenchymal resident and macrophages arises from hematopoietic stem cells.[11] The microglial cells will inhabit the brain continually in order to strengthen the population of local microglia. Latest research have proven that the surface antigens of microglia and macrophages are discrete and specific too, where microglial cells are positive for chemokine receptor CX3CR1 and negative for chemokine receptor CCR2 ($CXC3R1^{+}/CCR2^{-}$), while it is the opposite for macrophages, which are $CX3CR1^{-}/CCR2^{+}$.[12] This clearly points out the differences in origins of microglial cells and macrophage populations. In brain cancers, microglia and macrophages are elucidated as $CD45^{low}$ and $CD45^{high}$ cells individually.[13] Flow cytometry analysis revealed that microglial cells are abundantly prominent at the site of tumour, consisting about 13-34% tumour mass, whereas macrophages are less evident, comprising of around 4.2-12% of the tumour mass.[11] These findings demonstrate that microglial cells play a pivotal role in facilitating an inflammatory reaction specific to the tumour. Studies have also shown that microglia-derived enzymes, cytokines and growth factors contribute to tumour expansion and colonization, immunodeficiency and angiogenesis in primary brain cancer.[10] In addition, activated microglial cells are found at various phases of primary and metastatic brain tumours. Microglial induction frequently exists in the primary tumour mid-phase with instant microglia or macrophage response to metastatic brain tumour cells.[14]

Cross-Talk Between Microglia and Tumour Cells by Multiple Factors That Stimulate Brain Tumour Progression

Due to the role of microglia in neuronal DNA damage and neuron death via secretion of proinflammatory mediators or reactive oxygen species (ROS), activated microgliosis is a feature of neurodegenerative diseases, neuron destruction and brain cancer.[15,16] Severe microgliosis, by comparison, raises the release of cytokines and chemokines that boost tumour growth, providing a conducive brain microenvironment for tumour progression and results in self-sustaining autocrine inflammatory reaction in the brain.[17] The crucial molecules involved in microgliosis leading to the worsening of brain tumour are cytokines, chemokines, prostaglandins, transforming growth factor-β (TGF-β), growth factors and matrix metalloproteinases (MMPs).[18]

Chemokines and receptors, including monocyte chemoattractant protein-1 (MCP-1), granulocyte/ macrophage-colony stimulating factor (GM-CSF), CX3CL1 and CCLL, have been shown to be highly expressed in brain tumours.[19-21] MCP-1/CCL2 is thought to be a significant contributor to microglia recruitment in brain metastases of breast cancers, causing higher microglial proliferation in glioma. It demonstrates that MCP-1 expression links favourably with higher grades of malignant glioma.[22] In promoting microglial proliferation, GM-CSF has a similar impact to MCP-1. Also, in GM-CSF, elevated levels of the granulocyte colony stimulating factor (G-CSF) receptor are released by brain tumour tissues.[23] In comparison to GM-CSF, G-CSF does not support microglial proliferation. However, autocrine pathways have shown to facilitate the differentiation of brain tumours.[24] Besides that, it is understood that MMPs weaken the extracellular matrix, which facilitates the invasion and metastasis of tumours. Nearly 80 percent of brain metastases from lung adenocarcinomas and 50 percent of breast cancers that metastasise to the brain are positive in MT1-MMP immunostaining.[25] Moreover, when MMP-2 and MMP-9 is upregulated, it causes loss of function to astrocyte end-feet, which in turn makes the blood-brain barrier more permeable to cancer cells, macrophages and T cells in the brain.[26]

Signaling Pathways of Microglia for Brain Tumour Growth and Invasion

Mutual microglia-tumour cell interactions activate several key signalling pathways that play a vital role in the development and invasion of brain tumours such as toll-like receptor 2 signal, S100B-RAGE-STAT3 signal, angiogenic factor and signalling in other brain residential cells. Numerous Toll-like receptors (TLRs) on microglia cells can identify the soluble substances released from a glioma.[27] In a recent research, it was shown that versican produced from glioma was demonstrated as TLR 2 ligand, which is capable of activating the p38 MAPK signalling pathway that gives rise to membrane type 1 metalloproteinase (MT1-MMP) in microglial cells.[28] Interestingly, impeding the activity of microglia by the Wnt inhibitor substantially decreases overall tumourigenesis. As such, the WnT signal is vital in the interaction between microglia and neural-metastasis tumour cells. In patients with breast cancer with brain metastasis, Wnt signalling is elevated, compatible with the analysis.[29] Triggering of Wnt signalling in microglia thus facilitates brain metastasis in part through the increased expression microglial cytokines.[30] Other than that, the development of the vascular network is required for the metastatic spread of cancer cells where they can provide oxygenated blood to tumour cells to support their development and infiltration.[31] At vascular branching points, microglia are found to be positioned there and release vascular endothelial growth factor (VEGF) that aids the endothelial $VEGFR^+$ cells to form effective vascular channels.[32]

Immune Evasion of Brain Tumours with Relation to Microglia

A common hallmark of cancer is immune evasion by means of inducing local or systemic immunosuppression. In brain cancers, for example, gliomas employ a variety of immunosuppressive mechanisms, which include reducing the expression of major histocompatibility complex (MHC) class II antigens on microglia cells. Immunophenotyping of these microglial cells help in determining tumour grades in the case of astrocytic gliomas, as high-grade astrocytomas often contain microglial cells with diminished expressions of MHC class II antigens.[33]

Immunohistochemical markers like CR3/43 were used to study microglia cells in human glioma and revealed a surprising finding that these microglia cells and the tumour cells were neighbouring each other. Despite being present in large quantities and in close approximation with the tumour cells, microglia cells are somehow unable to eliminate these cancerous cells, which is explained by the compromised efferent arm of the immune response involving microglia cells.[34] Immunosuppressive factors have been found to be abundant within the microenvironment of glioblastomas, particularly the transforming growth factor β (TGF- β) produced by the glioblastoma cells, which aids in converting resident or infiltrating immune cells like the microglia cells into a state of immunosuppressive phenotype. As a result, the

cancerous cells create an immune barrier that these immune cells are unable to break through and attack.[35]

For the preservation of local immunosuppression, the amplification of M2 microglia cells is essential. Thus, tumours develop an immunosuppressive microenvironment to encourage their growth while attracting microglia.[36] Several recent studies have suggested that S100B-RAGE-STAT3 signalling initiation induces the polarisation of M2 microglia cells. S100 calcium binding protein B (S100B) secreted tumour stimulates an advanced glycation on microglia, which triggers the activation of STAT3, resulting in the repression of M1 microglial activity, which inhibits the secretion of TNF-α and IL-1β.[37]

Interaction Between Microglia Cells and Cancer Stem Cells in The Brain

It is abundantly clear that tumour formation, aggression, and virulence factors can be driven by cancer stem cells (CSCs). Brain tumours are thought to originate from glioblastoma stem cells (GSCs), specifically glioblastomas. A research showed that the tendency of GSCs to attract microglial cells was greater than that of other tumour cells.[38] GSCs expressed higher levels of CCL2, CCL5, and CCL7 in contrast with non-GSC glioma cells, and also higher levels of VEGF and neurotensin.[39] In addition, GSCs were discovered to positively affect microglia polarisation. GSC-secreted periostin has recently been found to serve as a new powerful cancer treatment to recruit macrophages by integrin alpha-vβ3 signal induction. The alpha-3 signal was observed to regulate the morphology of microglia in the M2 genotype, leading to GSC proliferation in brain tumours.[40] Additionally, IL-6 has indeed been described as a growth factor for GSC, meaning that IL-6 originating from microglia may enhance the growth of GSCs. A recent study showed that naïve microglial cells curb GSC invasion. Moreover, growth- and differentiation-related genes were significantly down-regulated in GSCs when they were treated with naïve microglial-conditioned medium.[41] These results suggest that the crosstalk between GSCs and microglia/macrophages promotes GSC growth and invasion. According to a latest study, GSC interference is hindered by naïve microglial cells. Besides, when treated with naïve microglial-conditioned medium, growth- and differentiation-related genes were substantially downrated in GSCs.[42] These findings indicate that GSC development and intrusion are supported by the crosstalk between GSCs and microglia.

Inhibiting Microglia Activation as Therapeutic Strategy for Brain Tumour

A possible antitumour-targeted treatment to suppress brain tumour development is thought to be the modulation of signals arising from microglia. Immunotherapy, immunosuppressants, antibiotic disruption and drug distribution by microglia are many techniques that regulate and alter the functionality of microglia. A recent research has shown that immunotherapy with natural killer (NK) cells combined with the mAb 9.2.27 antibody decreased tumour growth by blocking tumour replication and encouraging cell death.[43] It was reported that a recombinant immunotoxin drug blocks the β-folate receptor on microglia, inducing microglia degradation and reducing the emergence of glioma in nude mice.[44] Evidently, microglial cytotoxic effect and phagocytosis that removed cancer cell expansion were effectively improved by IL-12, LPS and INF-γ. By inhibiting the expression of MT1-MMP and p38 MAP kinase in microglial cells, antibiotic drugs such as minocycline hydrochloride have been shown to slow down tumour invasion.[45] Cyclosporine greatly lowered IL-10 and GM-CSF levels, which in turn decreased microglia accumulation and slowed the proliferation of glioma.[46] Recent experiments have used polymer nanoparticle (CDP -NP) to regulate the activity of microglial cells in tumours without poisoning, due to the benefits from the microglial phagocytic mechanisms. In malignant brain tumours, microglial cells bound with CDP-NP might theoretically be used as nanoparticle drug delivery system.[47]

CONCLUSION

It is now evident that signalling cascade between cancer and microglial cells have a significant effect on microglial pro- and anti-tumour functions, contributing to the advancement and repression of brain tumours respectively. Nevertheless, there are still several issues that

remain unanswered. The key factors and pathways that mediate microglia's association with cancer cells in the brain tumour, for example, remain largely unexplored. Microglia and astrocyte associations can also lead to tumour formation, but the precise processes involved in their contact remain uncertain. Consequently, brain metastasis is a complex process and it is unclear how metastatic cells survive microglia's immune threat to populate the internal environment of the brain. These lingering questions require more studies on the role of microglia in brain tumour which may lead to the development of new brain cancer therapeutic agents. And early halting of the activity of microglia could also provide a promising therapeutic path for metastasis of brain tumours.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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