Inflammation of human body tissues and cells is described as an immune reaction of the human body towards any abnormal activity that occurs within it. The inflammation process involves swelling, an increase in body temperature, and the release of cytotoxic substances to the surrounding cells, resulting in the injury or degeneration of body tissues.

Inflammatory substances, such as those produced by activated immune cells, can be cytotoxic and lead to neurodegeneration. The skull acts as a physical barrier, preventing inflammation-induced brain swelling from affecting the brain function. However, in scenarios of chronic damage, tumour-infiltrating immune cells produce inflammatory mediators instead of engaging in tumoricidal action.

With the inflammation process, cells are injured, and inflammatory markers are released into the plasma, as shown in Figure 1. Chronic inflammation results from persistent inflammation, and any failure of control mechanisms within the brain tissues will promote the development of cancer cells.

An inflammatory biomarker is an indicating substance that facilitates the process of cell injury and promotes the development of cancer cells. The brain structure naturally protects the extracellular matrix (ECM), which consists of microglia, astrocytes, and neurons, by separating them from harm with the blood–brain barrier (BBB). Yet, the inflammation process damages the brain cells, thus releasing inflammatory markers into the plasma. Chronic inflammation results from persistent inflammation, and any failure of control mechanisms within the brain tissues will promote the development of cancer cells. Previous studies showed that several proinflammatory biomarkers, which included interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and C-reactive protein (CRP), were observably higher in patients with glioblastoma compared to those with healthy brain tissues. However, the relationship between proinflammatory factors and glioma development remains unclear. Against such background, this review discusses the potential association between inflammatory markers and a brain tumour, along with the importance of these parameters.

**INTRODUCTION**

A brain tumour is one of the most lethal forms of cancer, with a relatively low survival rate. Glioma is the most prevalent type of tumour, arising from glial cells from the central nervous system (CNS). Gliomas account for almost 14.6% of CNS tumours and 48.3% of all primary malignant tumours of the CNS, according to the Central Brain Tumour Registry of the United States of America (CBTRUS) statistical report for 2012–2016. Gliomas are categorised as astrocytomas, oligodendrogliocytes, or ependymal cells, depending on their histological resemblance to astrocytes, oligodendrogliaomas, or ependymomas.

Within the brain tumour tissues, there are tumour microenvironments (TMEs) that contain different brain cells, such as endothelial cells, pericytes, fibroblasts, and immune cells. The brain structure naturally protects the extracellular matrix (ECM)-consisting of microglia, astrocytes, and neurons-by separating it from harm with the blood–brain barrier (BBB). Inflammation of human body tissues and cells is described as an immune reaction of the human body towards any abnormal activity that occurs within it. The inflammation process involves swelling, an increase in body temperature, and the release of cytotoxic substances to the surrounding cells, resulting in the injury or degeneration of body tissues. Inflammatory substances, such as those produced by activated immune cells, can be cytotoxic and lead to neurodegeneration. The skull acts as a physical barrier, preventing inflammation-induced brain swelling from affecting the brain function. However, in scenarios of chronic damage, tumour-infiltrating immune cells produce inflammatory mediators instead of engaging in tumoricidal action. With the inflammation process, cells are injured, and inflammatory markers are released into the plasma, as shown in Figure 1. Chronic inflammation results from persistent inflammation, and failure of control mechanisms within the brain tissues will promote the development of cancer cells.
Meanwhile, inflammatory factors also create an immunosuppressive tumour microenvironment within the tumour tissue area by promoting immune surveillance.9 Figure 2 presents a simplified case of inhibition of tumour development through both the JAK-STAT pathway and NF-κB pathway in relation to their pro- and anti-inflammatory biomarkers. In both pathways, the release of IL-10 in the nucleus during the transcription stage functions as an anti-inflammatory biomarker and inhibits the pathway's tumorigenic activity. IL-6 initially serves as a proinflammatory biomarker in the promotion of the JAK-STAT pathway, but it may become anti-inflammatory when bound to a soluble IL-6 receptor, in which case it promotes transactivation of the membrane-bound signalling receptor protein. Accordingly, interleukins may act as both pro- and anti-inflammatory biomarkers for glioma development.

As set out in Figure 2(a), IL-12 activates the phosphorylation of macrophages and promotes STAT4 to translocate to the nucleus and further promote the proinflammatory process. Yet, the release of IL-10 inhibits that translocation and creates an anti-inflammatory cascade. Figure 2(b) reveals how, meanwhile, macrophages activate NF-κB when TNF-α binds to receptors TNFR1 and TNFR2, producing IKK complexes that bind with and phosphorylate IκB. IκB then degrades and releases NF-κB into the nucleus for transcription, prompting IL-10 to inhibit the transcription as its anti-inflammatory response to the pathway.

Currently, the diagnosis of brain tumour depends mainly on brain histopathology and radiological examination. Yet, inflammatory biomarker analysis now offers a non-invasive procedure for identifying the earlier stage of
brain tumour cases.\textsuperscript{10,11} Previous research has discussed the potential of inflammatory biomarkers in the early diagnosis of brain tumours for differentiating those tumours into different grades and monitoring their growth.\textsuperscript{12} This review paper highlights the relationship between those factors and the metabolic pathways of inflammatory biomarkers in brain tumours, which may thus be valuably utilised as a potential diagnostic and therapeutic target of brain tumours.

**Overview of inflammatory biomarkers**

Inflammation is a protective immune reaction that eliminates damaged cells, irritants, infections, and sterile lesions to maintain tissue homeostasis. Yet, the function of chronic inflammation in cancer aetiology is well-established.\textsuperscript{13} Recent investigations have identified cytokines as crucial factors in inflammation-mediated cancer development. Cytokines can directly affect various tumorigenic processes, including tumour–stromal cell communication, immune cell recruitment, cellular differentiation, migration, and invasion.\textsuperscript{14} Inflammatory factors have been proven to promote the complexity and lethality of glioblastoma multiforme (GBM), also referred to as a grade IV astrocytoma, which can evade immune surveillance by creating TMEs.\textsuperscript{15} The inflammatory response results in the degranulation of neutrophils with the activation of macrophages. Macrophages release all inflammatory biomarkers and signal the activation of monocytes and lymphocytes, which concentrate at the injured site of the tumours. Proinflammatory markers stop anti-tumour immunity and release tumour-promoting signals, while anti-inflammatory markers promote immunosurveillance.\textsuperscript{16}

Multiple immune-suppressive cytokines are expressed by glioma cells, including transforming growth factor-beta (TGF-\(\beta\)), interleukin-10 (IL-10), interleukin-4 (IL-4), interleukin-6 (IL-6), and interleukin-13 (IL-13).\textsuperscript{15} This condition is supported by the elevated levels of these inflammatory biomarkers in serum and plasma.\textsuperscript{9,17} Previous studies showed that several proinflammatory biomarkers, which included interleukin-6 (IL-6), tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\), and C-reactive protein (CRP), were observably higher in patients with glioblastoma compared to those with healthy brain tissues.\textsuperscript{9,18,19,20,21}

Available evidence also shows that these markers may be involved in the risk faced by glioma patients and thus their survival.\textsuperscript{18,22} Researchers have found that high levels of circulating IL-6 and CRP are associated with a worse prognosis in patients with glioma than those with lower levels of both.\textsuperscript{9} However, the relationship between circulating inflammatory markers and glioma development, risk, and prognosis remains unclear, making it challenging to determine the markers’ predictive significance. Yet, there are a few commonly investigated inflammatory biomarkers in brain tumour patients, as shown in Table I.\textsuperscript{1,23}

<table>
<thead>
<tr>
<th>Type</th>
<th>IL6</th>
<th>CRP</th>
<th>TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine</td>
<td>Cytokine</td>
<td>Cytokine</td>
<td>Cytokine</td>
</tr>
<tr>
<td>Signalling molecule</td>
<td>Signalling molecule</td>
<td>Signalling molecule</td>
<td>Signalling molecule</td>
</tr>
<tr>
<td>Monocytes and macrophages</td>
<td>Hepatocytes</td>
<td>Macrophages and T-cells</td>
<td>Nuclear factor kappa light-chain enhancer of activated B cells (NF-(\kappa)B)</td>
</tr>
<tr>
<td>Mitogen-activated protein kinase 3 (MAPK3)</td>
<td>Human platelets express (Fcy-RIIA)</td>
<td>Binds to polysaccharides such as phosphocholine (PCh) and triggers the classical complement pathway of innate immunity by activating C1q</td>
<td>Regulates immune cells and induces apoptosis</td>
</tr>
<tr>
<td>Induces synthesis of acute phase protein, inhibits TNF and IL-1 production</td>
<td>Fluorescence polarization immunoassay, nephelometry, ELISA</td>
<td>Fluorescence polarization immunoassay, nephelometry, ELISA</td>
<td>ELISA</td>
</tr>
</tbody>
</table>

**Table 1:** The common biomarkers investigated in brain tumour patients and their role, sources, functions, and analysis technique.

Abbreviations: C1q, complement component 1q; ELISA, enzyme-linked immunosorbent assay; MAPK3, mitogen-activated protein kinase 3; Fcy-RIIA, fragment gamma receptor IIa; NF-\(\kappa\)B, nuclear factor kappa-light-chain-enhancer of activated B cells; PCh, phosphocholine; TNF, tumour necrosis factor.

The above information leads us to conclude that several relatively non-invasive techniques may now be utilised to analyse inflammatory biomarkers not only in brain tissue but also in body fluids such as serum and plasma. The diverse roles played by various inflammatory biomarkers and metabolic pathways are essential to tumour development, but further research is yet required to improve our understanding of those roles and thus leverage their therapeutic value.
Association of interleukins with brain tumours

Interleukins (ILs) are a group of cytokine proteins usually secreted by inflammatory cells. Interleukins can promote or inhibit carcinogenesis.9 The glial tumours may create a pro-tumour environment by actively secreting or recruiting microglia to stimulate the secretion of cytokines with pro-tumorigenic functions. Among primary brain tumours in adults, glioblastoma (GBM) is both the most common and the deadliest (Glioblastoma WHO grade IV). GBM has one of the lowest survival rates of any malignancy, and it is notoriously unresponsive to treatment, which typically consists of a combination of chemotherapy and radiation after maximal surgical resection.24 Figure 3 illustrates the immunosuppressive environment in GBM cells and the release of cytokines resulting from inflammation.

Figure 3 The immunosuppressive environment in GBM cells and the release of cytokines resulting from inflammation.

Abbreviations: CSF-1, colony stimulating factor 1; EGF, epidermal growth factor; GBM, glioblastoma; IGF, insulin-like growth factor; IL-6, interleukin-6; IL-10, interleukin-10; IL-33, interleukin-33; TGF-β, transforming growth factor-beta; TNF-α, tumour necrosis factor-alpha; TAA, tumour-associated antigen.

Circulating IL-6 may serve as a diagnostic or predictive biomarker for glioma formation. However, its role in brain tumours is still far from clear. Altered serum profiles of inflammatory factors IL-6 and TNF-α have been observed in glioma patients and have been closely related to brain tumour behaviour.25 IL-6 also plays a significant role in glioma progression and apoptosis resistance, according to the Cancer Genome Atlas.26 Meanwhile, high levels of IL-6 have been linked to tumour growth and poor survival in glioma and other malignancies.27 Nevertheless, one study could not find a significant difference in IL-6 concentrations between patients with higher and lower glioma grades.17

Brain tumours and C-reactive protein (CRP)

CRP is an acute-phase protein found in the blood, which is synthesised in the liver in response to inflammation. Once activated, the complement system aids in clearing the injured or dead cells from tissues.28 Yet, CRP assists the inflammation process by promoting cytotoxic T-lymphocyte recruitment, causing cell retention and tumour cell lysis, and creating a pro-tumourigenic microenvironment. Accordingly, CRP may act not as a causal protein but as a marker of systemic inflammation. Elevated CRP levels have also been correlated with other elevated inflammatory markers.28 High CRP levels, that is, more than 10 µg/ml, are proven to be related to the development of different malignancies, including lung, breast, gastrointestinal, head and neck, sexual and reproductive organs, renal, pancreas, and blood cancer.29 A prior study demonstrated elevated CRP levels in patients with meningioma, glioma, and brain metastases. Still, the increase was not statistically significant.4 Another study showed serum CRP levels were increased in patients with GBM, and patients with GBM who had a serum CRP level between 50 and 29 mg/l had a poor prognosis.30 High levels of CRP have, furthermore, been associated with reducing the efficiency of chemotherapy.31

When conducting research on this topic, since-as with other inflammatory markers-CRP has a relatively short half-life, proper sample processing is essential. Transient conditions such as a common cold or mild injury/trauma can drastically alter individual CRP levels.32 Such variability of CRP levels may lead to issues with analyses and biased statistical estimates. As a result, single studies with single measurements can easily be affected by transient conditions. One investigation into the efficacy of a single CRP measurement in epidemiologic studies suggested that conducting a single measurement could largely attenuate observed effect sizes, leading them to err from the accurate effect sizes. Multiple measures are, therefore, beneficial for tracking changes in levels over time.
Brain tumours and the TNF protein superfamily

Tumour necrosis factor (TNF) has been reported to be a major mediator of cancer-related inflammation and shown to be elevated in cancer patients with poor prognoses. TNF is a type of multifunctional cytokine that activates the distinct signaling pathways of NF-κB and c-Jun N-terminal kinase (JNK). NF-κB is one of the most important transcription factors, which signals JNK to activate and promote cell death. NF-κB also promotes the development of proinflammatory biomarker TNFα, which is encoded in the major histocompatibility complex with a single copy gene in human chromosome 6, with three introns and four exons. TNF-α is promoted as a 27-kDa precursor and binds to the tumour cell membrane for new cell development via proteolysis with TNF alpha-converting enzyme, to produce a 17-kDa subunit. In pathological conditions, microglia release significant levels of TNF, and this de novo synthesis of TNF is related to various neurological diseases.

In vitro studies with glioma cells have shown that TNF can promote the growth of cancer tissues by stimulating angiogenesis, downregulating the tumour suppressor phosphatase and tensin homolog gene (PTEN), and increasing glioma cell invasiveness. TNF and its receptor families have been shown to play key roles in GBM progression, with the study in question showing that TNF-α, which is elevated in GBM cells, is associated with GBM growth.

Peripheral blood analysis of inflammatory biomarkers in brain tumours

Investigations into how we can conduct peripheral blood analyses for inflammatory biomarkers in brain tumours will aid in supporting diagnoses for inoperable tumours, where safe biopsy may be difficult or impossible. Such peripheral blood analyses should offer a non-invasive approach that can be carried out rapidly. The ability to obtain glioma information from the peripheral blood will provide advanced opportunities to study the evolution of tumours and mechanisms of treatment resistance, as well as enable us to monitor tumours to identify any mutational changes in response to the therapy. It is suggested that combining different biomarker analyses may promote more specific and compelling methods of tumour analysis in the future than considering them separately. However, further investigations are needed to ensure that these biomarkers are tumour-specific and their results are consistent across every stage of brain cancer. Confounding factors should also be addressed; for example, patients undergoing chemotherapy and radiation may have altered levels of these biomarkers. Furthermore, while there are various methods for analysing peripheral blood inflammatory markers, there are not yet specific cut-off levels or standard assays to confirm the diagnosis and prognosis of a brain tumour. Moreover, the effectiveness of this approach to conducting tumour-specific analysis is still the subject of debate, with further experimental research needed before it can be widely implemented in clinical practice.

CONCLUSION

In conclusion, brain tumours remain among the deadliest forms of cancer, with a high risk of treatment failure. Much research has been conducted to support the potential of inflammatory biomarkers in diagnosing and treating brain tumours. However, their roles are still the subject of debate, meaning the biomarkers have limited therapeutic value for patients. This aimed to elucidate a potential association between inflammatory biomarkers and the pathophysiology of cancer cells, highlighting relevant findings that may shed light on the relationships between these inflammatory markers and progress and prognosis of brain tumours, which may support future interventions enabling us to better manage brain tumour patients.

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