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Review Article

Two-way Interaction Between Cerebrospinal Fluid and Brain Tumors

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Abstract

This review focuses on the role of Cerebrospinal Fluid (CSF) in brain tumor physiology and treatment. Recent studies indicate that brain tumors influence CSF, and CSF influences brain tumors. We begin by highlighting the critical function of CSF in the homeostasis of the Central Nervous System (CNS) and the role of the glymphatic system in waste clearance and nutrient distribution within the CNS. Next, this manuscript discusses alterations in CSF components, such as proteins, nucleic acids, and metabolic byproducts, that serve as biomarkers for tumor diagnosis, classification, and therapeutic response. In particular, tumor byproducts such as microRNAs (miRNAs) and circulating tumor DNA (ctDNA) could be used to determine tumor heterogeneity and treatment resistance via CSF sampling. Then, the role of brain tumors in disrupting CSF dynamics and the glymphatic system that can influence tumor progression is explored. Finally, the role of CSF flow in influencing brain tumor growth and invasion is discussed to highlight the two-way interaction between brain tumors and CSF. The review closes with promising preclinical studies that explore modulating the CSF to treat brain tumors and highlight CSF modulation as a promising therapeutic target. In conclusion, modulating CSF flow, flux, and composition could potentially enhance the delivery and efficacy of brain tumor drugs and, in the future, improve the treatment for this high-mortality disease.

Introduction

Cerebrospinal Fluid (CSF) movement within the brain is critical for metabolic homeostasis and protection of the Central Nervous System (CNS) [1,2]. CSF is predominantly produced in the choroid plexuses, located within the ventricular system, and circulates throughout the cerebral spaces and spinal column [3,4]. Respiration plays a pivotal role in facilitating the bulk flow of CSF, primarily moving nutrient-rich CSF produced in the choroid plexus through the ventricles towards the subarachnoid space, where CSF is excreted into the bloodstream [5]. Recent studies have expanded the field of CSF dynamics by studying CSF flux within the CNS to expand the field beyond the secretion of CSF and reabsorption into the bloodstream [6].

One recent result from studying CSF flux within the CNS is the discovery of the glymphatic system. The glymphatic system is a network of perivascular tunnels formed by astroglia cells and pericytes that shuttles CSF from the choroid plexus into the brain parenchyma and back to the ventricles. This system removes soluble proteins and metabolites from the CNS and circulates glucose, lipids, amino acids, growth factors, and neuromodulators throughout the brain parenchyma [7,8]. In addition to bulk and glymphatic flow, studies suggest that a third mechanism mediates the flux of CSF within the ventricles. This mechanism relies on ependymal cells, which line the ventricles and display cilia, microscopic hair-like structures, into the fluid-filled ventricular cavities. Ependymal cilia beat continuously and influence flow patterns within the ventricles that aid in CSF distribution throughout the CNS [9]. Understanding the extent to which ependymal cilia contribute to CSF dynamics is a burgeoning area of research in neurophysiology [10].

This review aims to dissect how the nuances of CSF composition and circulation affect brain tumors and how brain tumors affect CSF composition and circulation.

Impact of Brain Tumors on CSF Composition

Brain tumors release tumor-specific byproducts into CSF, including proteins, immunogenic factors, nucleic acids, such as circulating tumor DNA (ctDNA) and microRNAs (miRNAs), and metabolic byproducts [11]. Secreted tumor byproducts can serve as biomarkers to determine the presence, type, progression, and response to therapy of brain tumors. The impact of CSF changes mediated by brain tumors is discussed below.

Alteration in CSF Protein Levels Resulting From Brain Tumors: Elevated CSF protein concentration indicates a CNS pa-

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thology. Elevated Neuron-Specific Enolase (NSE) concentrations and Glial Fibrillary Acidic Protein (GFAP) in CSF are consistently observed in brain tumor patients [12]. Cytokines, which are normally absent from the CSF, are often elevated in the CSF of brain tumor patients. Elevated CSF IL-6 levels are associated with poorer prognoses in glioblastoma patients, suggesting IL-6 could be used as a prognostic biomarker to detect brain tumors [13]. Similarly, Tumor Necrosis Factor-alpha (TNF-alpha) and IL-1beta are also elevated in the CSF of patients with CNS tumors [14]. Finally, Soluble PD-L1 (sPD-L1), which "checks" the host immune response to a tumor, is often detected in the CSF of patients with glioma and correlates with poorer survival [15-17].

Alteration in CSF Nucleic Acid Levels Resulting From Brain Tumors: Recent studies demonstrate the presence of ctDNA and miRNAs in the CSF of patients with various brain tumors. The blood-brain barrier excludes serum nucleases, which degrade circulating free DNA resulting in an increase in the amount of ctDNA present in the CSF compared to plasma [18]. Thus, CSF can potentially provide a reservoir to identify genetic alterations in brain tumors via liquid biopsy to provide information on tumor heterogeneity, evolution, and treatment resistance [19,20]. Analysis of ctDNA from CSF allows a more comprehensive assessment of the genomic landscape of heterogeneous tumors compared to direct tissue sampling of a lesion via standard aspirate from a needle biopsy, which often reflects only focal changes in the sampled tumor region rather than information about the entire brain tumor.

Similarly, tumor-derived miRNAs are also found in CSF and used as biomarkers to differentiate between types of CNS cancers [21]. A recent study demonstrated elevated levels of metastatic tumor miRNAs, specifically miRNA-125a, miRNA-125b, and miRNA-1290 in the CSF, which correlated with the expression of these miRNAs in metastatic brain tumors [22]. Furthermore, miRNA-15b and miRNA-21 were observed only in the CSF of glioma patients compared to healthy individuals, indicating the utility of miRNA as a diagnostic biomarker [22-24].

Alterations in CSF Metabolites Resulting From Brain Tumors: The metabolic activity of brain tumors can lead to the accumulation of byproducts in the CSF. For example, Neopterin, a pteridine derivative, is significantly elevated in the CSF of patients with Primary CNS Lymphoma (PCNSL) and is used as a diagnostic marker [25]. This suggests that metabolic signatures in CSF could be leveraged for precise diagnosis and monitoring of CNS malignancies. Additionally, tumor-derived Extracellular Vesicles (EV) are present in CSF of brain tumor patients. A study found that exosomal miR-21 is significantly elevated in the CSF of glioma patients compared to controls [26]. The presence of miR-21 in CSF exosomes is also linked to metastasis within the spinal and ventricular systems and predicted tumor recurrence and site-specific reemergence of disease [26]. While still an evolving field, CSF EV could be used in the future to offer a window into the tumor type and microenvironment via quantitative analysis with high-resolution techniques [27,28].

Impact of Brain Tumors on CSF Movement

Brain tumors can significantly disrupt CSF dynamics, including the glymphatic system. Brain tumors, such as gliomas and meningiomas, alter glymphatic flow by impeding the normal perivascular movement of CSF [29]. A study of meningioma patients indicated an inverse correlation between the volume of Peritumoral Brain Edema (PTBE) and the glymphatic system efficiency [30]. Thus, tumors with significant edema compromise the glymphatic system function, which correlates with overall patient outcomes. Gliomas also demonstrate decreased Aquaporin-4 expression near the tumor, which correlates with reduced CSF influx and disrupted the glymphatic system clearance [31].

Table 1: Alteration in CSF from Brain Tumors.

CSF Modification	Description	Reference
Protein Levels	Elevated Neuron-Specific Enolase (NSE)	11
	Elevated Glial Fibrillary Acidic Protein (GFAP)	12
	Interleukin level 6 (IL-6)	13
	Tumor Necrosis Factor Alpha level (TNFa)	14
	Soluble PD-L1 (sPD-L1)	15-17
Nucleic Acids	Presence of ctDNA	18-20
	Prescence of miRNA-125a and miRNA-125b	22
	Elevated levels of miRNA-15b and miRNA-21	22-24
Metabolic Levels	Elevated Neopterin	25
	Cancer derived exosomes	26
CSF Flux	Impaired glymphatic system function	29-30
	Enhanced edema	33

Table 2: Alteration in Brain Tumors from CSF.

Brain Tumor Modification	Description	Reference
Tumor Grade	Glymphatic function correlates with Tumor grade mutation status	31
Metabolic Levels	Glymphatic removal of tumor metabolites	32
	Hypoxia conditions	37
Tumor Cell Migration	Migration and invasion of neuroblastoma tumor cells	36

In addition to primary brain tumors, metastatic brain tumors also alter the glymphatic system. A study comparing Apparent Diffusion Coefficient (ADC) values in tumors demonstrates that larger T2 MRI tumor volumes (indicating fluid levels in the tumor) impaired glymphatic flux, thus linking impaired glymphatic function, edema, and tumor volume in metastatic brain tumors [32].

The cognitive deficits observed in patients with brain tumors may also be related to glymphatic impairment. Pituitary tumors can induce alterations in glymphatic transport, indicated by Magnetic Resonance Imaging (MRI) and mathematical modeling, which could account for the accumulation of neurotoxic products and subsequent cognitive impairment [33].

Impact of CSF on Brain Tumors

CSF can also influence brain tumor growth and activity. A study of 201 glioma patients revealed that lower-grade gliomas (grade II/III) have significantly better glymphatic function than patients with grade IV gliomas. Gliomas with an isocitrate Dehydrogenase 1 (IDH1) mutation also displayed an enhanced glymphatic flux compared to wild-type counterparts, suggesting that glymphatic system performance correlates with the severity and mutation status of a tumor [31]. Further, enhanced glymphatic flux removes toxic metabolites and pro-inflammatory molecules, which may contribute to tumor progression [34]. Thus, enhanced CSF flux can reduce the build-up of neurotoxic substances, which intensify neuronal tissue damage and inflammation that can alter glioma progression.

Additional studies in pre-clinical models suggest that CSF flux is associated with the migration and invasion of tumor cells

[35]. Finally, altered fluid dynamics could interfere with the delivery of nutrients and oxygen to tumor cells, possibly leading to hypoxic conditions that can induce angiogenesis and further tumor growth [36].

Role of CSF in the Treatment of Brain Tumors

The role of the glymphatic system in the efficient clearance of metabolic waste from the brain parenchyma via CSF flux has introduced a novel therapeutic paradigm to treating brain tumors. Studies of CSF in glioma-bearing models indicate that restoring CSF flux by rerouting the glymphatic system may be a new treatment strategy for treating brain tumors [37]. Altering glymphatic function presents a promising strategy for managing or treating brain tumors. Recent preclinical studies demonstrate that pharmacological modulation of glymphatic activity can improve the efficacy of chemotherapeutic agents. A study demonstrated that co-administration of drugs that impair the motility of ependymal cell cilia along with Temozolomide (TMZ) enhanced TMZ retention in the CSF and parenchyma, which led to significantly improved survival in mice with glioblastoma [38]. Thus, targeting multiple aspects of CSF flux could enhance the treatment of malignant brain tumors.

In addition to CSF flux, CSF composition also affects the efficacy of therapeutic agents and the behavior of tumor cells. A recent study reveals that alteration in CSF composition can induce tumor cell plasticity and confer resistance to TMZ and radiation. This study identified NUPR1 as a critical mediator of tumor resistance to treatment. Administering trifluoperazine, an antipsychotic medication, to inhibit NUPR1-enhanced lethality of GBM treatments [39].

Challenges and Future Directions

The interaction between CSF and brain tumors is a burgeoning field of study. Manipulation of CSF movement and composition is a novel approach to hindering tumor growth and enhancing the delivery and potency of chemotherapeutic drugs.

One challenge to this approach is the dual nature of CSF and brain tumor interactions. The glymphatic system is vulnerable to disruption by brain tumors, and brain tumors rely on the system for nutrients and waste removal. Thus, impairment could both hinder or enhance brain tumor therapies that depend on CSF flux for efficacy based on the type, severity, and size of the tumor. Further exploration into how tumors influence the glymphatic system and how the glymphatic system influences the tumor may yield innovative approaches that exploit these complex interactions and improve patient outcomes. Finally, impairing CSF movement and solute clearance has profound implications for both the pathophysiology of brain tumors and the cognitive function of affected individuals. Thus, treatment strategies that modulate CSF require careful study and precise management before introduction to the clinic.

In conclusion, CSF impacts tumor behavior, and tumors impact CSF. Novel therapeutic approaches that alter CSF may enhance brain tumor treatments and improve patient outcomes. Additionally, monitoring CSF can provide biomarkers that indicate a patient's response to specific treatments, leading to more precise therapies. Thus, further understanding of the interaction between CSF and brain tumors could ultimately heighten survival rates and improve the quality of life for those suffering from brain tumors.

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