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ORIGINAL REVIEW

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The Sleep-Cancer Mystery: An Investigation of How Surgery Affects the Association Between Chronic Sleep Deprivation and Glioblastoma Progression Through Neuroinflammation and Immunosuppressive Modulation

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Abstract

Glioblastoma (GBM) is the most common and aggressive primary malignant brain tumor in adults. GBM progression is influenced by cytokines, chemokines, tumor-associated macrophages (TAMs), and other immune molecules that can lead to an immunosuppressive tumor microenvironment (TME) and infiltrate the blood-brain barrier. Chronic sleep deprivation is a pervasive and dangerous condition that is associated with systemic immunosuppression and neuroinflammation. Numerous studies have found links between sleep deprivation and elevated markers of systemic inflammation and impaired anti-tumor immunity; however, the direct impact on GBM progression remains poorly defined. This review examines whether and how chronic sleep deprivation contributes to neuroinflammation and immunosuppression that may facilitate GBM progression and whether surgical interventions can modulate these effects. While prior studies have explored individual therapeutic strategies, including surgery and immunotherapy, results have been limited. Rather than asserting causality, this review synthesizes evidence across five mechanistic links: (1) Chronic sleep deprivation and inflammatory biomarkers (Interleukin (IL)-6, Tumor Necrosis Factor Alpha (TNF-α), and C-Reactive Proteins (CRP)), (2) systemic neuroinflammation to Blood Brain Barrier (BBB) disruption, microglial activation and monocyte trafficking, (3) neuroimmune changes to TME remodelling, (4) TME remodeling and clinical outcomes, and (5) clinical treatments of surgical modulation and its effects on the BBB, TME and neuroinflammation. The current literature suggests there is a strong association between sleep deprivation and systemic neuroinflammation, and between neuroinflammation and GBM proliferation, but direct GBM-patient studies connecting measured sleep quality (actigraphy,

polysomnography (PSG), obstructive sleep apnea (OSA)) to inflammatory markers remain scarce. Given the challenging nature of directly addressing sleep deprivation and surgery's possible linkage to increased inflammation, combinative therapy could be more effective. By clarifying the current evidence and critical gaps, this review highlights the need for integrated clinical and translational studies examining how sleep therapy and combinative surgical-immunotherapeutic strategies could improve GBM outcomes. The implications of this review offer a greater understanding of the association between sleep deprivation and the proliferation and progression of GBM, and whether a combination therapy or surgery alone is the most feasible and effective approach in addressing this prevalent and dangerous disease.

Keywords: glioblastoma (GBM), sleep deprivation, neuroinflammation, immunosuppression, tumor microenvironment (TME), cytokines and chemokines, blood-brain barrier (BBB), neurosurgery, immunotherapy

1. Introduction

Chronic sleep deprivation is a widespread and severe condition that contributes to impaired immune function and neuroinflammation, promoting a pro-TME (Periasamy et al., 2015; Lanza et al., 2024; Berisha et al., 2022). Cytokines and other immune molecules influence this response and have made the treatment of GBM, a common form of brain cancer, very challenging (Lanza et al., 2024; Berisha et al., 2022).

Sleep is essential for maintaining homeostasis, supporting immune, neural, hormonal, and metabolic function (Periasamy et al., 2015; Lanza et al., 2024). Sleep deprivation, defined as reduced sleep below physiological needs, affects an estimated 50–70 million Americans across all ages and socioeconomic groups, and has become a growing issue (Lanza et al., 2024; Berisha et al., 2022; Garbarino et al., 2021).

Chronic sleep deprivation is associated with impaired immune responses, including lower cytotoxic activity (reduced CD8+ T cells and natural killer (NK) cells) and increased pro-tumor inflammation (Berisha et al., 2022). More specifically, sleep deprivation contributes to neuroinflammation, which is marked by proinflammatory cytokines (Lanza et al., 2024; Hurtado-Alvarado et al., 2013), promoting tumor-favorable conditions (Periasamy et al., 2015; Hurtado-Alvarado et al., 2013; Li et al., 2024). Furthermore, sleep deprivation weakens antitumor immunity and decreases T-cell activity and impairs the blood-brain barrier, leading to an influx of inflammatory agents (Lanza et al., 2024; Berisha et al., 2022). These immune alterations are connected to mechanisms implicated in cancer progression, but their specific relevance to GBM remains underexplored.

Patients with GBM, the most common and aggressive primary malignant brain tumor in adults (Berisha et al., 2022; Li et al., 2024; Yeung et al., 2013; Yeo et al., 2021), have a survival time of fewer than 15 months (Brettschneider & Terabe, 2021; Travers & Litofsky, 2021; Alghamri et al., 2021; Liu et al., 2016). The severity of GBM can be attributed to its anatomical location and the

disruption of the blood-brain barrier (Alghamri et al., 2021). GBM proliferation is complex and driven by epigenetic alterations and mutations in oncogenes, tumor suppressor genes, and DNA repair pathways (Alghamri et al., 2021; Liu et al., 2016; Alorfi et al., 2024; Dong et al., 2010; Saktikumar et al., 2020). Neuroinflammation promotes tumor growth, invasion, and therapy resistance by altering the TME (Alorfi et al., 2024). The TME is composed of tumor cells, immune cells (microglia, macrophages, T cells, NK cells), stromal cells, and the extracellular matrix (Lanza et al., 2024; Li et al., 2024; Yeo et al., 2021; Brettschneider & Terabe, 2021; Alghamri et al., 2021). Glioma-associated microglia/macrophages (GAMs) release TGF-β, IL-6, IL-10, and other molecules to inhibit T cells (Alghamri et al., 2021). Furthermore, CD8+ cells and NK cells, key to the anti-tumor response, are suppressed or exhausted in the GBM TME (Li et al., 2024).

Evidence from non-GBM populations indicates that sleep deprivation increases neuroinflammatory signaling and BBB permeability (Berisha et al., 2022; Hurtado-Alvarado et al., 2013); however, few studies have directly assessed whether chronic sleep deprivation correlates with inflammatory markers (IL-6, TNF-α, CRP) or survival outcomes such as progression-free survival (PFS) and overall survival (OS).

Multiple therapeutic strategies exist to combat GBM, including immunotherapy, pharmacological means, lifestyle and sleep management, and surgical interventions (Lanza et al., 2024; Li et al., 2024; Yeo et al., 2021; Alorfi et al., 2024). Surgery is especially vital in GBM treatment and can relieve symptoms by reducing tumor mass (Alorfi et al., 2024). Surgery, however, can disrupt the BBB by increasing the infiltration of inflammatory macrophages and decreasing the integrity of tight junctions (Yang et al., 2020). Given these contrasting effects, surgical intervention may serve as a modulator in the broader connection between sleep, neuroinflammation, and immune suppression.

Despite advances in neuroscience and oncology, treatment options for GBM remain uncertain and are only marginally effective. Recent studies have suggested that sleep deprivation plays a role in increasing neuroinflammation and immunosuppression facilitated through proinflammatory cytokines, macrophages, microglia, and T-cells (Berisha et al., 2022; Hurtado-Alvarado et al., 2013; Li et al., 2024).

While previous studies have associated sleep deprivation with neuroinflammation and immune suppression, and others have found a correlation between neuroinflammation/immune suppression and GBM progression, a direct association has yet to be identified.

This review, therefore, aims to answer these two key questions:

1. What evidence connects sleep deprivation with systemic neuroinflammatory and immunosuppressive markers that connect to GBM proliferation?
2. Can surgical or combinative interventions mitigate neuroimmune dysregulation associated with chronic sleep deprivation?

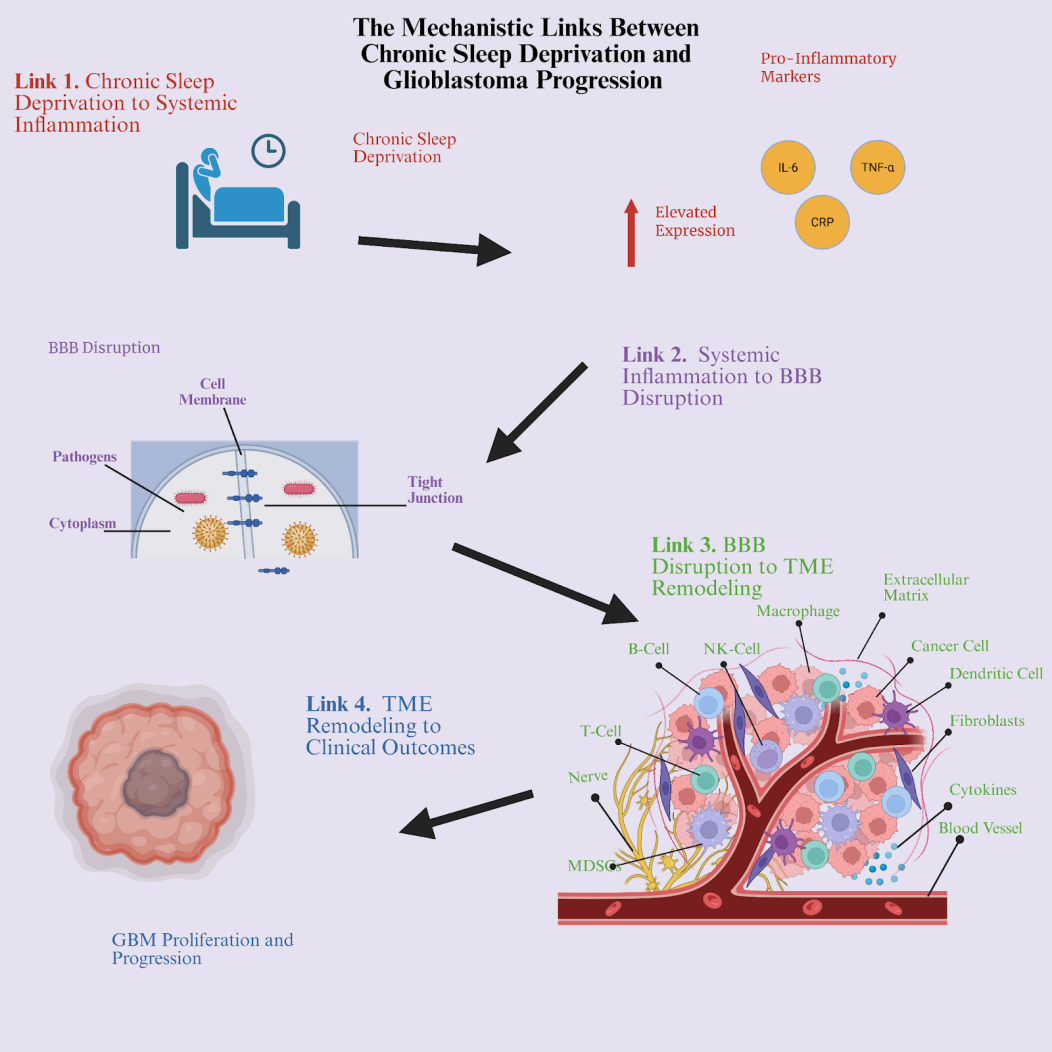

Figure 1: A graphical abstract illustrating the key mechanistic links of this review. (Chan, 2025)

2. Methods

2.1. Search Strategy and Databases

A comprehensive literature search was conducted through PubMed, Google Scholar, Scopus, Science.gov, Embase, BioMed Central, and Science Direct. Included entries were published from 1990 to 2025. Key words include "glioblastoma," "sleep deprivation," "circadian rhythm," "neuroinflammation," "blood-brain barrier," "cytokines," "surgery," "immunotherapy," and "tumor microenvironment." Boolean operators (AND/OR) were used to refine results.

2.2. Inclusion Criteria and Study Selection

Studies were included in this review if they:

- Were peer reviewed
- Involved human participants or relevant animal models
- Investigated at least one of the following: (a) effects of sleep deprivation or circadian disruption on immune or inflammatory signaling, (b) neuroinflammatory and immunosuppressive mechanisms in GBM, or (c) surgical modulation or other therapeutics involved in mitigating the effects of these pathways.

Excluded studies were non-English publications, sources without primary data, and papers that did not include measurable inflammatory, immune, or clinical outcomes.

2.3. Quality Assessment

Titles and abstracts were screened for relevance, and full-text articles were reviewed in depth. Study quality was determined based on methodological rigor, including sample size, control design, and clarity of variables. Potential biases and limitations of selected studies were noted in the results and discussion sections. When quantitative data were not feasible due to the nature of the study, results were assessed by mechanistic evidence and research gaps involving sleep deprivation, neuroinflammation, and therapeutic strategies.

3. Chronic Sleep Deprivation, Inflammation, and Immune Suppression: Investigating Sleep's Crucial Role in Immune Function

Adequate sleep ensures that the immune system is sufficiently regulated, controlling the spread of diseases. New studies highlight how insufficient sleep triggers neuroinflammation, characterized by elevated pro-inflammatory cytokine levels, and the impairment of key immune cells like T-cells and NK cells (Periasamy et al., 2015; Lanza et al., 2024; Berisha et al., 2022). Given the rising prevalence of sleep deprivation due to modern lifestyle changes, its immunological consequences must be addressed.

3.1. Sleep and Sleep Deprivation

Sleep is a fundamental physiological and neurological process that is crucial for maintaining immune, metabolic, and neural homeostasis (Lanza et al., 2024; Berisha et al., 2022). This process is shared among many organisms and is vital for healthy neural and brain functions (Berisha et al., 2022). Given the importance of sleep in immune function, sleep deprivation should be viewed as a serious health concern. In contrast, sleep deprivation, defined as the reduction in sleep time from the required amount (Berisha et al., 2022), has become increasingly common in modern society, driven by socioeconomic environment and lifestyle changes (Lanza et al., 2024; Berisha et al., 2022). Chronic sleep deprivation is excessive daytime sleepiness that occurs nearly every day for at least three months (Garbarino et al., 2021). Sleep deprivation affects an estimated 50–70 million Americans of all ages and socioeconomic classes (Garbarino et al., 2021). Alarmingly, the number of people getting sufficient

sleep, at least 6 hours of sleep a night, has continued to decrease over the last 25 years (Periasamy et al., 2015).

Beyond fatigue, sleep deprivation is associated with an increased risk of cardio/cerebrovascular diseases, accidents, hypertension, stroke, cancer, and neurodegenerative diseases (Garbarino et al., 2021; Czeisler, 2011). These associations underscore the necessity of researching sleep deprivation's interactions with the immune system, specifically, inflammatory and anti-tumor functions.

3.2. Sleep Deprivation and Immune Regulation

Sleep deprivation disrupts immune regulation, increasing susceptibility to infections and tumor proliferation (Garbarino et al., 2021). Individuals who are consistently sleep-deprived exhibit a higher susceptibility to common infections and are more vulnerable to diseases (Lanza et al., 2024; Hurtado-Alvarado et al., 2013). Past studies have shown that sufficient sleep leads to lower cortisol levels, allowing the immune system to function optimally, reducing the risk of inflammation (Lanza et al., 2024). Sleep deprivation triggers an inflammatory response characterized by increased levels of proinflammatory cytokines, supporting protumor conditions. Neuroinflammation is an inflammatory response in the brain marked by the release of cytokines, chemokines, and growth factors (Periasamy et al., 2015; Li et al., 2024).

Other markers with altered expression levels in sleep-deprived studies include IL-1α, IL-1β, IL-2, IL-8, IL-13, IL-15, IL-18, TNF-β, IFN-α, IFN-β, macrophage inhibitory protein (MIP)-1β, corticosterone, and homocysteine (Periasamy et al., 2015; Berisha et al., 2022). In multiple rodent models, sleep loss has been linked to an increase in IL-1, IL-6, IL-15, IL-17, and TNF-α (Hurtado-Alvarado et al., 2013).

In summary, sleep deprivation influences the balance between pro- and anti-inflammatory responses, leading to chronic inflammation. Chronic sleep deprivation also impairs the anti-tumor response by reducing T-cell activity. Adequate sleep enhances the activity of T-cells by increasing the expression of integrins on T cells, proteins that facilitate a cell's ability to attach to and destroy infected cells (Lanza et al., 2024). Therefore, sleep deprivation contributes to cytokine and immune alterations that favor tumor development and progression.

The correlation between sleep deprivation, neuroinflammation, and immune suppression must be further studied as sleep deprivation cases continue to increase. While chronic sleep deprivation is associated with elevated pro-inflammatory cytokines (e.g., IL-6, TNF-α) and impaired immune cells (e.g., T cells, NK cells), the specific molecular mechanisms, including downstream transcription factors and alterations in cytokine receptor signaling, are not fully understood. Nevertheless, sleep deprivation-induced immune imbalances create the immunosuppressive and pro-tumor environment that accelerates GBM progression. Future studies could investigate whether sleep quality or quantity is more impactful on immune regulation, as addressing these concerns could lead to targeted interventions involving sleep hygiene and sleep therapies.

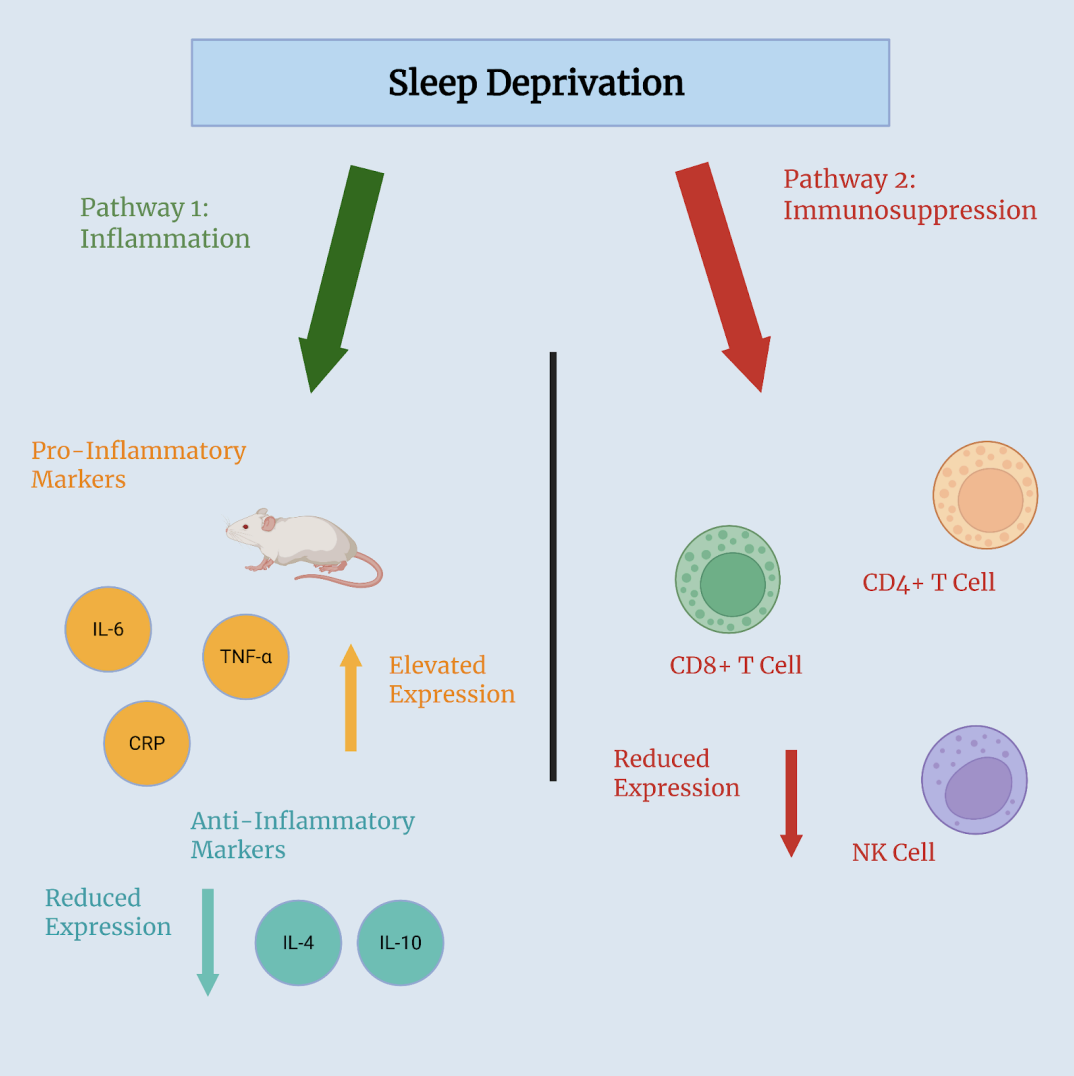

Figure 2: Sleep deprivation has been associated, in general physiological studies, with increased levels of pro-inflammatory markers, including IL-6, TNF-α, and CRP (Lanza et al., 2024; Berisha et al., 2022; Garbarino et al., 2021) and suppressed levels of anti-inflammatory cytokines IL-10 and IL-4 (Hurtado-Alvarado et al., 2013). Sleep deprivation also reduces immune cell activity, including CD8+, CD4+, and NK Cells (Berisha et al., 2022; Hurtado-Alvarado et al., 2013). While these immune alterations are well-characterized markers of sleep deprivation in non-tumor contexts, this figure extrapolates these mechanisms to the GBM TME, hypothesizing that these immune shifts may facilitate tumor immune evasion and progression. (Chan, 2025)

Table 1: Evidence Linking Chronic Sleep Deprivation to Inflammatory and Immune Markers

Study	Population/Model	Key Inflammatory Markers	Key Immune Markers	Limitations/Gaps
(Lanza et.al, 2024; Hurtado-Alvarado et.al, 2013)	Human Volunteers	IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-15, IL-18, TNF-α, TNF-β, IFN-α, IFN-β, IFN-γ	NK, monocytes, T, and B lymphocytes	Short-term studies; limited data on chronic deprivation
(Hurtado-Alvarado et.al, 2013)	Mouse and Rat Models (Forced Wakefulness)	IL-1α, IL-1β, IL-1, IL-6, IL-17, and TNF-α	NK, T lymphocytes	Inflammatory levels vary by sleep deprivation method

4. Understanding Glioblastoma: The Interactions Between Genetics, Neuroinflammation, and Immune Suppression

GBM is the most aggressive and lethal form of primary brain cancer and is associated with poor survival outcomes. This resistance is in large part due to GBM's highly immunosuppressive TME, which is a complex of inflammatory cytokines and immunosuppressive molecules. Key immune players, including TAMs, Myeloid-Derived Suppressor Cells (MDSCs), regulatory T cells (Tregs), and astrocytes, contribute to favorable tumor conditions. Molecular and cellular pathways play a decisive role in GBM proliferation and progression.

4.1. Glioblastoma & Mutations

GBM is the most aggressive and common primary malignant brain tumor that has been difficult to treat due to its location and immunosuppressive microenvironment (Berisha et al., 2022; Li et al., 2024; Yeung et al., 2013; Yeo et al., 2021). GBM arises from glial cells and accounts for 60–70% of all malignant gliomas, 50% of all gliomas that arise in the central nervous system (CNS), and about 15% of all brain tumors (Alghamri et al., 2021; Alorfi et al., 2024; Le et al., 2003). Patients with GBM have a median survival of 14.7 months, with only 6.8% of patients surviving past five years (Brettschneider & Terabe, 2021; Travers & Litofsky, 2021; Alghamri et al., 2021; Liu et al., 2016), and approximately 75% of affected patients die within two years of their diagnosis (Lee et al., 2015; Tafani et al., 2011). Although GBM represents roughly 1.4% of annual cancer incidences, it accounts for 2.5% of total cancer deaths. There are an estimated 10,000 new annual cases in the United States and 100,000 new cases globally (Yeo et al., 2021; Brettschneider & Terabe, 2021; Manrique-Guzman et al., 2017; Roesler et al., 2021). Hence, additional research into the molecular mechanisms involved in GBM proliferation and progression is required.

Neuroinflammation also plays a significant role in GBM progression by activating oncogenic signaling pathways and inducing genetic and epigenetic changes (Li et al., 2024; Alorfi et al., 2024; Roesler et al., 2021). GBM samples frequently express higher concentrations of pro-inflammatory proteins such as P2X7R, RAGE, NOS2, COX2, and PTX3 (Tafani et al., 2011). These genetic and epigenetic alterations are central to discerning the complex relationship between neuroinflammation and

immunosuppression in GBM. While mutations initiate GBM, sleep deprivation exacerbates these oncogenic pathways, fueling neuroinflammation and immune suppression.

Table 2: GBM progression is influenced by genetic mutations and epigenetic modifications that regulate cell cycle control, apoptosis, and DNA repair pathways. These alterations facilitate immune evasion and therapeutic resistance.

Genetic Alteration	Functional Alteration & Biological Role	Representative Sources
CDKN2A/p16^INK4a	A tumor suppressor that inhibits CDk4/6 and halts the cell cycle at the G1 phase. In GBM, CDKN2A is deleted or silenced.	(Liu et al., 2016; Medlineplus, 2018)
EGFR	The epidermal growth factor receptor is a transmembrane protein that controls cell growth and proliferation. In GBM, EGFR is amplified or mutated, leading to uncontrolled cell proliferation and tumor progression.	(Alghamri et al., 2021; Liu et al., 2016; Dong et al., 2010; Saktikumar et al., 2020; Medlineplus, n.d)
ERBB2	This gene codes for a receptor tyrosine kinase, ERBB2, to form heterodimers, enhancing cell proliferation. In GBM, ERBB2 is amplified or overexpressed, contributing to tumor growth.	(Dong et al., 2010; NIH, 2020)
PDGFR	Platelet-Derived Growth Factor Receptor is a tyrosine kinase that activates intracellular pathways, including MAPK, promoting cell proliferation. In GBM, PDGFR is amplified or overexpressed.	(Alghamri et al., 2021; Saktikumar et al., 2020; NIH, 2020)
EMP3	The Epithelial Membrane Protein 3 gene encodes a tetraspan transmembrane protein involved in cell proliferation. In GBM, EMP3 is often overexpressed or epigenetically dysregulated, exhibiting oncogenic behavior.	(Liu et al., 2016; NIH, 2025)

RASSF1A	The Ras Association Domain Family 1 gene encodes a RAS effector protein involved in cell cycle regulation and DNA damage response. In GBM, RASSF1A is inactivated by promoter hypermethylation, leading to cell cycle and DNA repair disruption.	(Liu et al., 2016; NIH, n.d.)
BLU	The BLU gene encodes a transcriptional repressor related to cell cycle regulation and apoptosis. In GBM, BLU is often silenced by promoter hypermethylation, leading to the loss of cell cycle control and apoptosis.	(Liu et al., 2016; Yoo et al., 2013)
TP53	The TP53 gene encodes the p53 tumor suppressor protein, which is involved in DNA repair and apoptosis. In the case of GBM, TP53 is functionally inactivated.	(Alghamri et al., 2021; Liu et al., 2016; Dong et al., 2010; Saktikumar et al., 2020; Medlineplus, 2020)
PTEN	The PTEN gene encodes a phosphatase enzyme that functions as a tumor suppressor, promoting genomic stability and apoptosis. In GBM, PTEN is often mutated, deleted, or epigenetically silenced.	(Alghamri et al., 2021; Liu et al., 2016; Dong et al., 2010; Saktikumar et al., 2020; Medlineplus, 2021)
NF1	The NF1 gene encodes for neurofibromin, a tumor suppressor protein expressed in neurons, oligodendrocytes, and Schwann cells. In GBM, NF1 is mutated, leading to uncontrolled tumor proliferation and enhanced survival.	(Alghamri et al., 2021; Liu et al., 2016; Dong et al., 2010; Saktikumar et al., 2020; Medlineplus, 2007)
RB1	The RB1 gene encodes the retinoblastoma protein (pRB), a key tumor suppressor that regulates the cell cycle, specifically the G1 S Phase transition. In GBM, RB1 is often deleted, mutated, or functionally inactivated, leading to G1/S checkpoint loss and tumor proliferation.	(Liu et al., 2016; Dong et al., 2010; Medlineplus, 2020)

MGMT	The MGMT (methylguanine-DNA methyltransferase) gene encodes a DNA repair enzyme, reversing damage caused by alkylating agents. In GBM, MGMT is silenced through promoter hypermethylation.	(Alghamri et al., 2021; Liu et al., 2016; NIH, n.d.)
MLH1	The MLH1 gene encodes a DNA mismatch repair protein that detects and repairs base-pairing errors during DNA replication. In GBM, MLH1 loss and hypermethylation lead to defective mismatch repair proteins.	(Liu et al., 2016; Medlineplus, 2020)
DAPK1	The Death-Associated Protein Kinase 1 gene encodes a calmodulin-dependent serine/threonine kinase regulating cytoskeletal dynamics and apoptosis. In GBM, DAPK1 is silenced, leading to reduced apoptotic signaling.	(Liu et al., 2016; NIH, n.d.)
TIMP3	The Tissue Inhibitor of Metalloproteinases 3 gene encodes a secreted extracellular matrix (ECM) protein that inhibits matrix metalloproteinases. In GBM, TIMP3 expression is reduced or inactivated, leading to enhanced invasion and metastasis and reduced tumor suppressive activity.	(Liu et al., 2016; NIH, n.d.)
CDH1	The CDH1 gene encodes E-cadherin, a transmembrane protein fundamental for cell-cell adhesion in epithelial tissues. In GBM, CDH1 is downregulated, disrupting cell adhesion and promoting enhanced invasion and metastasis.	(Liu et al., 2016; Medlineplus, 2017)

5. Neuroinflammation, Immunosuppression, and Blood-Brain Barrier Disruption

5.1. The Blood-Brain Barrier and Tumor Microenvironment

The BBB is essential for maintaining homeostasis, but it becomes compromised in GBM, contributing to immune suppression and inflammation. The BBB maintains normal brain function by preventing the absorption of toxins and pathogens, regulating transport and immune surveillance, and helping to maintain a stable environment (Li et al., 2024; Alghamri et al., 2021). However, when compromised, such as when an individual is sleep deprived, blood vessels in the brain are altered both anatomically and functionally (Alghamri et al., 2021). Hypoxia-inducible factor-α (HIF-1α) regulates the expression of inflammatory factors such as vascular endothelial growth factor (VEGF), which disrupts the cellular barrier around blood vessels by creating capillaries with fewer tight junctions (Alghamri et al., 2021). These alterations make the administration of medicine very challenging. Sleep deprivation can disrupt BBB integrity, increasing susceptibility to GBM proliferation and progression.

6. How Neuroimmune Changes Remodel the Tumor Microenvironment

Similarly, the GBM TME, a complex system, promotes tumor progression and immune suppression. The TME includes brain resident microglia, infiltrating macrophages, collectively known as GAM, and MDSCs (Yeo et al., 2021). Inflammatory cells are believed to make up between 30–50% of the tumor mass (Li et al., 2024).

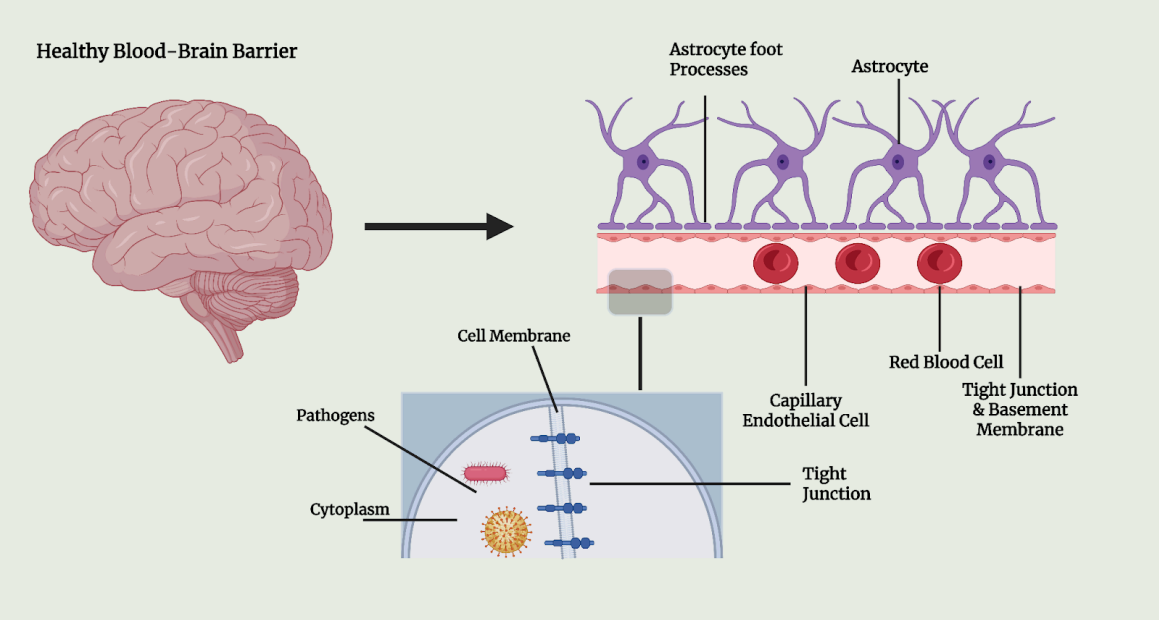

Figure 3: The healthy BBB is a selectively permeable barrier that is secured by endothelial cells linked by tight junctions and surrounded by astrocytes and basement membranes (Li et al., 2024; Alghamri et al., 2021). (Chan, 2025)

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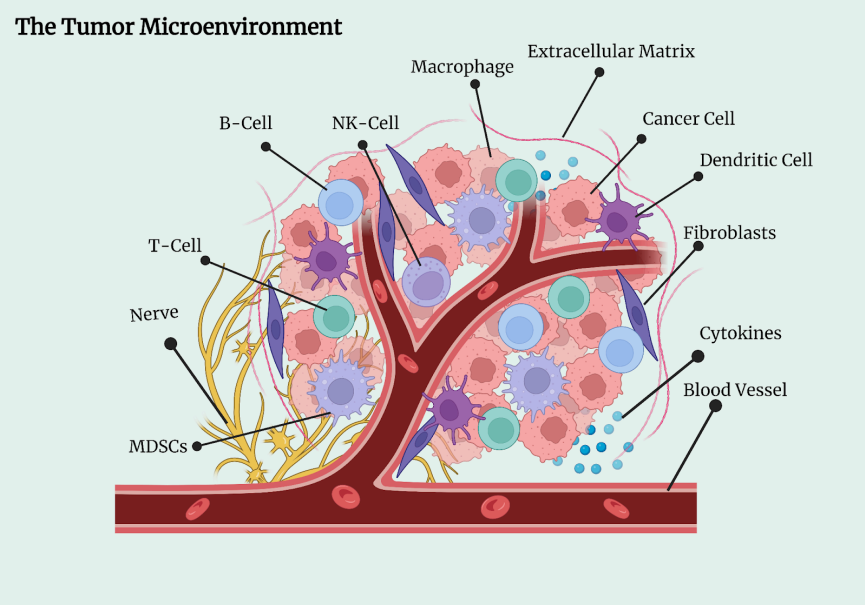

Figure 4: The TME accounts for up to 30% of the tumor's mass and is made up of cancer cells, immune cells, macrophages, dendritic cells, cytokines, fibroblasts, and extracellular matrix components (Lanza et al., 2024; Li et al., 2024; Yeo et al., 2021; Brettschneider & Terabe, 2021; Alghamri et al., 2021). (Chan, 2025)

6.1. Tumor-Associated Macrophages, Cytokines & Chemokines

TAMs and MDSCs are pivotal in immunosuppression and tumor progression in the GBM TME. Microglia cells are the resident macrophages of the CNS and respond to chemokines and cytokines (Geribaldi-Doldan et al., 2021). TAMs account for 30% of the tumor volume and are the main inflammatory cell components (Li et al., 2024). Pathological microglia, peripheral macrophages, and monocytes activate and contribute to a disrupted immune response by activating immunosuppressive pathways (Alghamri et al., 2021). MDSCs are immature myeloid cells that express higher levels of immunosuppressive molecules.

In GBM, microglia show increased expression of proinflammatory genes, including SPP1, HLA-DR, TREM2, APOE, CD163, and GPR56, which is elevated (Geribaldi-Doldan et al., 2021). Other inflammatory molecules include let7, tenascin-C (TNC), veriscan, IL-1β, TGF-β, TNF-α, stress-inducible protein (STI-1), prostaglandin E2, IL-6, IL-1β, IL-10, and epidermal growth factor (Alghamri et al., 2021). Interestingly, macrophages are divided into M1 and M2 phenotypes. M1 macrophages exhibit immune supportive and anti-tumor functions, while M2 macrophages are immune suppressive and pro-tumor (Li et al., 2024; Geribaldi-Doldan et al., 2021). Specifically, Gal-1 converts tumor-infiltrating macrophages to the immunosuppressive M2 variants (Alghamri et al., 2021). TAMs are critical components in immune suppression and GBM progression.

Cytokines and chemokines are key components in the promotion of immune suppression in the GBM TME by impairing anti-tumor responses. Cytokines are multifunctional molecules that control angiogenesis, proliferation, and immune cell

infiltration in the TME (Yeo et al., 2021; Alghamri et al., 2021). Cytokines are secreted by immune cells and include pro-inflammatory (IL-6, IL-8, TNF-α) functions and anti-inflammatory (IL-4, IL-10, TGF-β) functions (Li et al., 2024). Inflammatory cytokines significantly increase the proliferation and invasiveness of GBM cells as immune cells fail to recognize tumor cells (Yeung et al., 2013; Alghamri et al., 2021). Glioma cells express many cytokines, including TGF-β, IL-10, IL-4, IL-6, IL-13, colony-stimulating factor-1 (CSF-1), LDH5, galectin-1 (gal-1), and prostaglandin-E (Yeung et al., 2013; Alghamri et al., 2021; Zhu et al., 2012). IL-6 and TGF-β are especially important to GBM progression. High IL-6 expression is associated with poor survival and is produced by malignant cells in response to oncogenic mutations (Yeung et al., 2013; Yeo et al., 2021). TGF-β, meanwhile, is involved in the regulation of cell growth and differentiation (Yeo et al., 2021). TGF-β is expressed at low levels in the brain but is greatly increased in GBM, suppressing CD8+ T cell activity (Yeo et al., 2021). Likewise, chemokines are small proteins that manage the migration of various cells in the body. Chemokines that are highly expressed in TME include CXCL2, IL-8, and CCL2. The relationship between cytokines and chemokines facilitates neuroinflammation and immunosuppression, leading to GBM progression. Because cytokines and chemokines are elevated in patients with GBM and those who are chronically sleep deprived, sleep loss can compound the immunosuppressive TME, crucial to GBM progression.

6.2. T-Cells, Natural Killers & Astrocytes

The GBM TME impairs the immune functions of T-cells and NK cells through exhaustion and suppressed signaling. T cells are the largest group of lymphocytes that infiltrate the TME, preventing glioma immunity (Li et al., 2024; Alghamri et al., 2021; Yoon & Chung, 2023). However, low proportions of T-cells are found in most GBM patients (Li et al., 2024; Brettschneider & Terabe, 2021). The most common T lymphocytes in GBM are CD8+, CD4+ helper T cells, and Treg cells (Brettschneider & Terabe, 2021). Studies have shown that increased CD8+ T cell expression in the TME results in positive outcomes (Alghamri et al., 2021). However, a majority of CD8+ T cells infiltrating the TME are exhausted and ineffective (Alghamri et al., 2021). In GBM, Tregs, a subtype of CD4+ T cells, regulate immune homeostasis by inhibiting the anti-tumor response (Li et al., 2024). NK cells recognize and destroy tumor cells by detecting the presence of receptor ligands (Yoon & Chung, 2023). Despite only making up about 2% of the TME, NKs are critical in the antitumor response (Li et al., 2024). NK cells play an important inhibitory role in the metastasis of GBMs, regulating T cell-mediated immune responses (Lee et al., 2015). However, NK cells are hindered by the TME, limiting their effectiveness (Li et al., 2024).

Astrocytes, the most abundant glial cells in the brain, make up nearly 50% of all brain cells (Alghamri et al., 2021; Perelroizen et al., 2022). Astrocytes secrete factors that help maintain the tight junctions in the BBB (Alghamri et al., 2021; Perelroizen et al., 2022). They also promote the release of degradative enzymes, cytokines, and chemokines (Alghamri et al., 2021). When the CNS is impacted by tumors, astrocytes undergo reactive changes called astrogliosis and facilitate GBM proliferation (Le et al., 2003; Perelroizen et al., 2022). Reactive astrocytes were detected by increased glial fibrillary acidic protein (GFAP) expression levels (Le et al., 2003; Perelroizen et al., 2022). Thus, astrocytes support glioma pathogenicity by promoting immunosuppression, regulating immune cells, and contributing to the TME (Perelroizen et al., 2022). The GBM TME promotes immunosuppression through the activation of Tregs and MDSCs; reactive astrocytes, microglia, and endothelial cells secrete transforming growth factor (TGF-β) and metalloproteinases (MMP2 and MMP9) (Alghamri et al., 2021). GBM tumors can change the TME by increasing immunosuppressive cells, including Tregs and MDSCs, that promote inflammation (Lanza et al., 2024; Alghamri et al., 2021). The activation of these immunosuppressive molecules weakens the anti-glioma immune response (Yeo et al., 2021; Alghamri et al., 2021). Key components of the TME, TAMs, and MDSCs require further research.

7. How Neuroimmune Changes Associated with Chronic Sleep Deprivation Affect Clinical Outcomes

7.1. The Connection Between Chronic Sleep Deprivation and Glioblastoma Proliferation

A growing body of patient-based research demonstrates that measured sleep loss is associated with inflammatory activation. Sleep supports metabolic regulation, waste removal (glymphatic system), macromolecule synthesis, and immune function (Allgood et al., 2023). Studies linking sleep deprivation and inflammation focus on the hypothalamus, pineal gland, brainstem (especially the pons), thalamus, and basal forebrain, which regulate circadian rhythm, sleep induction, and NREM/REM control (Allgood et al., 2023).

Existing patient-focused sleep studies show an association between sleep loss and inflammatory markers in clinical cohorts. Studies incorporating clinical trials, twin studies, and the use of PSG support this link (Kuna et al., 2022). A 2017 cohort study of 378 adolescents using PSG found that adolescents with short sleep duration had elevated levels of CRP (Kuna et al., 2022). Similarly, a 2016 analysis of over 50,000 adults and a 2006 22-participant controlled clinical trial found that sleep deprivation was associated with increased IL-6 levels in addition to CRP (Kuna et al., 2022). Another 2006 study found through PSG and wrist actigraphy that short sleep duration (under 5 hours) led to prolonged blood oxygen desaturation and increased inflammation (higher CRP, IL-6, and TNF-α levels) (Sumagula et al., 2016). While median OS for adult GBM remains approximately 15 months, the existing literature contains virtually no studies in GBM patients that monitor both objective sleep deprivation and report Extent of Resection (EOR)-adjusted OS and POS. For example, the feasibility study of wearable sleep monitoring in primary brain tumor patients (n=54) demonstrated that obtaining physiologic sleep data (through a Fitbit) is correlated with patient-reported sleep loss, but it did not link sleep metrics to survival outcomes (Pascoe et al., 2024). Moreover, a Mendelian randomisation study reported a potential causal association between shorter sleep duration and increased GBM risk, but it did not report downstream survival data in diagnosed patients (Chen et al., 2025). Lastly, in a circadian clock gene review for brain tumors, circadian desynchronization is associated with poorer OS, but direct evidence in GBM is lacking (Albaqami, 2025). Thus, there is a major gap in this field: no large cohort study of GBM patients with baseline and peri-operative sleep monitoring and survival outcomes (OS/PFS).

GBM is a highly lethal brain tumor that is characterized by genetic mutations, chronic neuroinflammation, and immune suppression. Key contributors to GBM progression include MDSCs, TAMs, T-regs, astrocytes, cytokines, and chemokines. Additionally, BBB disruption and the TME promote neuroinflammation and immunosuppression. Advancing our understanding of these mechanisms, particularly the roles of other critical molecules along with strategies to restore BBB integrity, will be essential for developing targeted and effective GBM therapies.

Table 3: Evidence Linking Sleep Loss to Systemic Inflammation (General Population and Models)

Study	Model	Population	Sleep Assessment	Key Findings
(Fernandez-Mendoza et al., 2017)	Cohort Study	Adolescents from Penn State Child Cohort	Polysomnography	Adolescents with short sleep durations had elevated levels of CRP
(Burgos et al., 2006)	Controlled Clinical Trial	Patients	Polysomnography, PSQI, SF-A	Sleep deprivation was associated with increased IL-6 and CRP levels
(Yehuda et al., 2009)	Comparative experimental	Male Long Evans hooded rats	N/A	Increased IL-1α, IL-1β, IL-6, homocysteine, corticosterone, TNF-α, and IL-17A
(Taylor et al., 2017)	Controlled clinical trial	Young adult college students with Insomnia or No Insomnia	Questionnaires and self-reported sleep diaries	The insomnia group had lower baseline antibody levels than the control group
(Prather et al., 2015)	Controlled clinical trial	94 men and 70 women aged 18–55 years	Actigraphy and self-reported sleep diaries	Shorter sleep duration was associated with a higher risk for the development of a cold
(Sharpley et al., 2016)	Double-blind placebo-controlled study	16 healthy male and female adult participants	Polysomnography	IL-6 levels significantly increased
(Orzech et al., 2014)	Field-based study	56 adolescents aged 14–19 years	Actigraphy and In-Person interviews	Acute illnesses were more frequent in adolescents with shorter sleep durations

Note: None of the studies listed were conducted in GBM patients. These non-GBM human and animal models are included to establish a plausible association between sleep deprivation and systemic inflammation through modulating cytokine levels and inflammatory pathways.

8. Targeting Glioblastoma

8.1. The Surgical Approach

While GBM remains one of the most challenging cancers to treat, advances in surgical techniques have begun to alleviate this problem. Traditional approaches, including surgical interventions, only provide limited effectiveness due to GBM's highly invasive and immunosuppressive nature. As a result, research has focused on the development of advanced surgical techniques.

Surgical interventions are a vital component in GBM management through their ability to reduce tumor size and alleviate symptoms. Surgery can be a life-saving treatment for GBM, improving quality of life (Yang et al., 2020). The goal of surgery is to reduce as much tumor mass as possible, relieve symptoms, and obtain brain tissue for pathological analysis (Alorfi et al., 2024; Manrique-Guzman et al., 2017; Sales et al., 2022). Historically, surgery was the initial therapeutic approach for tumor debulking, including the use of cytoreductive surgery ranging from lobectomies to hemispherectomies (Manrique-Guzman et al., 2017; Patel & Chavda, 2024). Currently, common techniques include craniotomy and biopsies for histopathological analysis (Alorfi et al., 2024). Despite surgery's importance, GBM remains a dangerous disease; therefore, improvements in surgical intervention are necessary.

Advanced surgical techniques have led to improved outcomes. These techniques include fluorescence-guided surgery and intraoperative magnetic resonance imaging (iMRI) (Alorfi et al., 2024; Sales et al., 2022). Fluorescence-guided surgery utilizes fluorescent dyes (ie, 5-aminolevulinic acid), selectively taken up by tumor cells and visualized under a special microscope (Alorfi et al., 2024). 5-ALA is a photosensitizing agent that selectively accumulates in GBM cells (Manrique-Guzman et al., 2017; Patel & Chavda, 2024). Specifically, the tumor appears red, where normal tissue does not express fluorescence, helping surgeons differentiate tumors from healthy tissue in real time (Manrique-Guzman et al., 2017; Sales et al., 2022). This technique increases the rate of complete resection and improves patient outcomes and survival (Patel & Chavda, 2024). A meta-analysis of 20 studies, including 565 patients who underwent 5-ALA-guided resection, had a mean overall survival gain of 6.2 months (Sales et al., 2022). In a 2006 multiinstitutional study, a complete resection of malignant glioma was achieved in 65% of 5-ALA-guided resections compared to just 36% of procedures guided by white light (Roberts et al., 2012; Chavda, 2024). Furthermore, the six-month PFS was observed in 41% of 5-ALA-guided resections compared to 2.1% in white light treatments (Roberts et al., 2012). Another 2019 glioma study found that 5-ALA-guided resection resulted in a 26% higher gross total resection (GTR) rate as well as a 3-month additional OS and 1-month additional PFS, respectively, compared to control groups (Gandhi et al., 2019). However, as the majority of included studies were observational, causal interpretations should be made cautiously (Teixidor et al., 2016). Overall, evidence suggests that 5-ALA may improve EOR and PFS.

iMRI is another critical technique utilizing a specialized MRI machine for real-time imaging during surgery (Alorfi et al., 2024; Patel & Chavda, 2024). iMRI allows for the precise visualization of tumor boundaries and areas that may be confused with normal brain tissue (Patel & Chavda, 2024). From 3 randomized controlled trials with 384 patients, iMRI outperformed

conventional navigation-guided surgery, resulting in a 3.16 times higher rate in GTR and a 1.84 times higher PFS rate (Wach et al., 2024; Shah et al., 2020). Another study found that GTR rates increased from 30.7% in traditional treatments compared to 71.5% on iMRI (Shah et al., 2020).

In summary, the use of advanced techniques, including intraoperative MRI and fluorescence-guided surgery, can be associated with safer and more effective surgical resections (Manrique-Guzman et al., 2017). Like many of these potential therapeutic strategies, because few randomized trials exist, the survival impact remains less well defined, and thus, iMRI should be viewed as a technique that can enhance surgical precision rather than a guaranteed means of improving outcomes (Shah et al., 2020).

Surgical procedures can induce inflammation through the disruption of the blood-brain barrier. Globally, millions of patients undergo surgery that involves extensive tissue damage (Yang et al., 2020). These procedures, including those for GBM, are associated with systemic inflammation and can lead to major complications and even death (Yang et al., 2020). Surgical trauma can trigger endogenous factors, or damage-associated molecular patterns (DAMPs), which can activate immune cells (Yang et al., 2020). When activated, these cells contribute to systemic inflammation facilitated through molecules like IL-1β and IL-18 (Yang et al., 2020). Anesthesia and surgery can reduce tight junction protein expression in the brain, leading to increased migration of CCR2+ and other inflammatory macrophages into the brain (Yang et al., 2020). Lastly, GBM can infiltrate surrounding brain tissue, making a complete surgical removal of the tumor impossible (Alorfi et al., 2024; Patel & Chavda, 2024). Thus, the limitations of surgery can increase the risk of immunosuppression and inflammation, a side effect that can be mitigated through sleep therapies.

8.2. Peri-operative Sleep Inflammation Axis

Surgical interventions in GBM involve not only tumor debulking and neuroinflammatory tissue disruption, but also a host of physiological responses, including BBB disruption and DAMP signaling. However, what has been underresearched in many neuro-oncological studies is the sleep-inflammation axis during the perioperative period, specifically, how it may modulate the TME and increase the risk of recurrence.

Prior studies in non-oncological surgical groups have supported that major sleep and circadian disturbances occur prior to and following surgery. Pre-operative studies on aged mice found that sleep loss can trigger neuroinflammation and neuronal damage, potentially worsening outcomes post-surgery (Ni et al., 2019). Furthermore, IL-6 and IL-1β levels were elevated after surgery and were significantly higher when preceded by sleep deprivation (Ni et al., 2019). Microglial (IBA1) and astrocytic (GFAP) activation increased after surgery, in addition to increased expression of c-fos and caspase 3, in the sleep-deprived experimental group, indicating that preoperative sleep loss can exacerbate surgical side effects (Ni et al., 2019). Sleep deprivation before surgery was associated with increased BBB permeability and reduction of tight junction proteins (occludin, claudin-5) (Ni et al., 2019; Hurtado-Alvarado et al., 2016).

Likewise, post-operative surgical studies have shown that sleep loss is a frequent and underrecognized effect of surgery. This sleep loss, in turn, is associated with delayed recovery, impaired cognition, heightened pain sensitivity, and cardiovascular risk (Rampes et al., 2020; Du et al., 2025). Surgery induces systemic and neuroinflammatory responses involving molecules such as TNF-α, IL-1β, and IL-6 (Rampes et al., 2020). IL-6 is correlated with poor sleep quality, while IL-1β and TNF-α suppress

REM sleep (Rampes et al., 2020). Moreover, sleep deprivation post-operation has been associated with increased pain sensitivity and a bidirectional feedback loop linking pain to increased sleep interruption (Rampes et al., 2020). In summary, sleep loss post-neural surgery is associated with increased catabolism, recovery delays, prolonged hospitalization, and a worse quality of life (Rampes et al., 2020; Du et al., 2025; Campbell & Figueiro, 2024). Circadian misalignment is often compounded by the effects of anesthesia, the ICU environment, and light interruptions (Campbell & Figueiro, 2024).

Surgical trauma and sleep deprivation can shape postoperative immune responses. Across surgical cohorts, IL-6 rises within 6–12 hours, peaks at 24–48 hours (Jawa et al., 2011; Vacas et al., 2017). TNF-α spikes early (around 2 hours post trauma) but stabilizes quickly, while CRP peaks on postoperative days 2–3 (Liu & Tang, 2014; Larsson et al., 1992). Sleep disturbances are closely tied to foundational surgical and environmental variables. While patients after brain tumor resection commonly experience insomnia, there are no studies to date that have evaluated whether the EOR is associated with longer-term sleep disturbances or prolonged CRP elevation (Rampes et al., 2020; Alessandro et al., 2022; Liang et al., 2025). Finally, steroids, including Dexamethasone, disrupt circadian rhythms, raising neutrophil and monocyte counts (Jia & Zhang, 2022; Liu et al., 2022). Although these links must be acknowledged, there is a major gap in these factors being measured in GBM sleep studies.

In response to these gaps, this review proposes a standardized peri-operative framework measuring sleep, in addition to inflammatory and immune signal peaks. A pilot randomized controlled trial is proposed in which GBM patients undergoing surgical resection receive perioperative cognitive behavioral therapy for insomnia (CBT-I) intervention. Objective sleep metrics would be captured using wrist actigraphy for two weeks preoperatively and four weeks postoperatively, in addition to optional PSG to characterize baseline OSA and REM sleep metrics. These measurements aim to quantify sleep continuity and circadian disruption during a period of intensified vulnerability.

Primary outcomes include neuroinflammatory and immune signaling measurements that focus on markers implicated in surgical stress responses and sleep loss. These markers include IL-6, TNF-α, CRP, and cortisol, selected based on documented peri-operative dynamics and established roles in sleep and immunity. Additionally, CCR2+ monocytes and lymphocytes will be tracked to evaluate sleep-related shifts in immune trafficking. Secondary clinical outcomes include quality of life, PFS, and EOR.

To complement this approach, a prospective cohort is proposed in which GBM patients undergo longitudinal sleep monitoring through actigraphy, PSG, serial cytokine panels, and immune profiling of blood and tumor tissues. This design would enable the evaluation of naturalistic sleep-inflammation, helping to distinguish baseline associations from treatment effects. Lastly, mechanistic insight could be gained through a preclinical orthopedic chronic sleep fragmentation GBM model. In this model, sleep disruption would be used to assess astrocyte activation, microglial polarization states, monocyte infiltration and trafficking, and BBB permeability, helping to link sleep disturbances to empirical changes in the TME.

Although direct data on GBM craniotomy patients are virtually absent, data from other major surgical populations can be used to support that craniotomies disrupt sleep patterns through pain, hospital environments, and cytokine-induced neuroinflammation. That being said, future studies should study sleep loss and circadian disruption pre- and post-craniotomy in GBM patients, incorporating BBB integrity markers, inflammatory biomarkers, and recovery rate measurements. This proposed framework provides measurable and responsible parameters for evaluating how perioperative

sleep deprivation can reshape the neuroimmune landscape and influence GBM outcomes.

8.3. Alternative Approaches: Immunotherapy, Pharmacology & Lifestyle Management

Given the limitations of surgical resection, GBM management increasingly depends on multimodal strategies that intersect inflammatory, immune, and metabolic pathways. Rather than acting independently, immunotherapies, including checkpoint inhibitors, chimeric antigen receptor T-cell (CAR-T) therapy, and oncolytic viruses that aim to bolster the body's anti-tumor immune response, pharmacological strategies, and lifestyle and sleep changes can be combined to reduce neuroinflammation, restore circadian rhythm, and improve immune surveillance.

8.4. Immunotherapy in the Neuroimmune Context

Immunotherapy strategies have provided some breakthroughs in targeting GBM tumor cells, but have been limited by the TME. Some immunotherapies include peptide vaccines, dendritic cell therapy, adoptive T cell therapy, CAR-T cells, oncolytic viruses, and immune checkpoint inhibitors (Li et al., 2024; Yeo et al., 2021). The specific use of immune checkpoint inhibitors and CAR-T-cell therapy can be employed to attack GBM cells (Alorfi et al., 2024). Other methods include programmed death ligands (PD-L1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), HSC transplantation, gene therapies and virotherapies, dendritic cell vaccines, and high-density lipoprotein nanoparticle vaccines (Li et al., 2024; Alghamri et al., 2021).

Checkpoint inhibitors, including ICIs (anti-CTLA-4, anti-PD-1, and anti-PD-L1), have revolutionized GBM treatments. Checkpoint inhibitors work by blocking inhibitory pathways that suppress T-Cell activation, promoting antitumor immune responses (Ser et al., 2024). Anti-vasculature therapy specifically blocks the VEGF/VEGFR signaling pathways, reducing angiogenesis, but has failed to demonstrate significant clinical benefits in improving progression-free or overall survival (Li et al., 2024). Past mouse studies have shown a synergy between checkpoint inhibitors and radiotherapy, specifically radiation therapy followed by checkpoint inhibitors (Ser et al., 2024). Furthermore, Laser interstitial thermal therapy (LITT), a minimally invasive surgical treatment, is a strong candidate for combination therapy with checkpoint inhibitors (Ser et al., 2024). Future studies should move forward with combination therapies including checkpoint inhibitors, suggesting synergies with vaccines, oncolytic viruses, and CAR-T cell therapy (Ser et al., 2024).

CAR-T cell therapy is a novel and promising immunotherapeutic strategy. CAR-T Cells are T cells that have been removed from patients and modified to have tumor antigen-binding receptors that are specific. They are then reinserted, increasing T Cells' ability to recognize and destroy cancer cells (Li et al., 2024; Alghamri et al., 2021; Bagley et al., 2018). Mouse and vivo models show tumor-killing abilities; however, CAR-T Cell therapy in a clinical context is limited by the heterogeneity of target antigen expression and difficulty in maintaining the activity of injected CAR-T cells (Li et al., 2024; Yoon & Chung, 2023; Brown et al., 2016). Preclinical trials have shown that checkpoint inhibitors, blocking PD1, could help overcome CAR-T cell exhaustion and enhance the activation and efficacy of this treatment option (Ser et al., 2024).

Similarly, Oncolytic Virus Therapy infects cancer cells with antigens that can lyse the tumor cells in preclinical trials. But in clinical settings, oncolytic viral therapies face safety and delivery constraints in clinical trials (Li et al., 2024). These viruses can activate macrophages, enhancing the infiltration of T-cells into the TME, leading to reduced immunosuppression (Li et al., 2024). That being said, studies have tested combining checkpoint inhibitors with oncolytic virotherapies (Ser et al., 2024).

Mouse GBM models demonstrated increased tumor-infiltrating CD8+ T cells after combined treatment (Ser et al., 2024).

Neuroimmune interventions that modulate systemic neuroinflammation, such as increasing sleep duration or reducing corticosteroid dependence, can enhance immunotherapeutic success and checkpoint inhibitor efficacy (NCI, 2020). For instance, improved sleep is associated with reduced IL-6, TNF-α, and CRP, cytokines linked to neuroinflammation (Garbarino et al., 2021). Preclinical human studies suggest that combining CBT-I or continuous positive airway pressure (CPAP) therapy for OSA with immune checkpoint therapy may enhance immunity in GBM patients with sleep deprivation (Xie et al., 2013). Similarly, oncolytic viral therapy can synergize with sleep-based chronotherapy to restore melatonin rhythms, optimizing interferon-mediated antiviral signaling and macrophage polarization (Xia et al., 2022; Quist et al., 2024; Boga et al., 2012). This approach reframes immunotherapy not as an isolated intervention, but as one component of a coordinated circadian-immune approach in mitigating the effects of GBM.

8.5. Pharmacological Coordination

Pharmacologically based sleep interventions can lead to improved immune function and reduced inflammation (Lanza et al., 2024). Physicians can prescribe sedative-hypnotic drugs: benzodiazepines and non-benzodiazepines used to improve sleep (Lanza et al., 2024). Furthermore, orexin agonists and antagonists can be implemented to manage sleep cycles (Lanza et al., 2024; Berisha et al., 2022). Their use must be balanced against risks of dependence, cognitive impairment, and next-day sedation, especially in neuro-oncologic populations.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) decrease prostaglandin synthesis and inhibit microglial activation, reducing the production of pro-inflammatory cytokines, chemokines (Alorfi et al., 2024). However, the incorporation of NSAIDs into GBM care must consider clinical contraindications, including gastrointestinal toxicity and perioperative bleeding risk (Tai & McAlindon, 2021; Sohail et al., 2023). While preclinical models support anti-inflammatory and antitumor effects, human survival data remain mixed and insufficient.

Corticosteroids, including dexamethasone and prednisone, are widely used to reduce neuroinflammation in GBM patients (Alorfi et al., 2024; Vrendenburgh et al., 2010; Pitter et al., 2016; Swildens et al., 2022). High doses of corticosteroids have been shown to rapidly decrease tumor-associated edema and improve clinical symptoms (Manrique-Guzman et al., 2017). Corticosteroids inhibit the production of inflammatory mediators such as prostaglandins and cytokines, suppressing inflammation and restoring BBB integrity, but can also induce hyperglycemia, weight gain, infections, myopathy, diabetes, immunosuppression, and osteoporosis (Alorfi et al., 2024; Geribaldi-Doldan et al., 2021; Vrendenburgh et al., 2010; Swildens et al., 2022; Scheffler et al., 2024). Therefore, corticosteroids such as dexamethasone can reduce vasogenic edema but could at the same time also impair immune activation and limit the effectiveness of immunotherapies (Scheffler et al., 2024). As a result, current studies are evaluating alternatives to dexamethasone, which can enable some patients to reduce or discontinue corticosteroid doses (Vrendenburgh et al., 2010; Scheffler et al., 2024). Furthermore, limiting steroid use through gradual tapering supported by NSAIDs, or sleep-targeted anti-inflammatory agents, should be a clinical priority. The use of orexin receptor agonists or short-term hypnotics to establish sleep structures could reduce cytokine load and indirectly lower the steroid requirement for edema management (Xiong et al., 2013). Additionally, melatonin could serve as both a chronobiotic to realign circadian rhythms and as an antioxidant and immunomodulator (Moretti et al., 2020; Li et al., 2020). Hence, the use of corticosteroids and other pharmacological medications must take into account synergies and antagonisms

with other therapeutic strategies in managing GBM.

8.6. Lifestyle and Metabolic Modulation

While immunotherapies and pharmacological approaches may alleviate symptoms, they must be considered alongside lifestyle interventions. The management of sleep deprivation and maintenance of a balanced lifestyle can help reduce immune suppression and inflammation associated with GBM development. Lifestyle interventions complement molecular therapies by addressing metabolic substrates of GBM. Experts have recommended routine screening for sleep disorders and sleep interventions (Lanza et al., 2024). Lifestyle changes may therefore reinforce circadian stability and mitigate sleep-related immune dysfunction.

Preclinical GBM mouse models demonstrate robust tumor growth reduction and increased survival on the ketogenic diet (KD), characterized by a high fat-to-carb ratio (Travers & Litofsky, 2021). Preclinical models showed that GBM cells grown in high-glucose media replicate significantly faster than those grown in normal media (Travers & Litofsky, 2021). KD slows tumor growth and increases survival due to changes in immune response, gene expression, and amount of reactive oxygen species (Travers & Litofsky, 2021). Thus, KD remains a promising but not yet proven approach to mitigating the effects of GBM. In the non-cancer population, KD has been shown to alter sleep efficiency, REM cycles, and circadian signaling (Pasca et al., 2024; Masi et al., 2022; O'Hearn, 2021; Kouki & Hajri, 2024). Whether similar effects occur in GBM patients remains an important unanswered question.

Although human evidence remains limited, small-scale clinical studies show that approximately 44% of ketogenic diet studies reported improved health-related quality of life, a fundamental component of GBM management (Wassef et al., 2024). In fact, case studies show that KD, when combined with chemotherapies and immunotherapies, can lead to additive effects (Sims et al., 2023). A single-arm phase 1 trial at the Cedars-Sinai Medical Center found that GBM patients on the ketogenic diet had a median PFS of 12.9 months compared to the baseline 6.9 months, and a median OS of 29.4 months compared to 14.6 months (Amaral et al., 2025). Furthermore, a 2024 patient trial found that the ketogenic diet reduces tumor glucose uptake by 22% and resulted in a 38-month mean survival compared to just 20 months in the control group (Valerio et al., 2024). Notably, however, none of these studies assessed sleep duration or circadian disruption, representing a critical gap in the literature. KD implementation in GBM patients can be challenging due to strict nutrient requirements, gastrointestinal side effects, and weight loss (Tuck & Staudacher, 2019; Basolo et al., 2022). These challenges underscore the importance of understanding how KD may interact with sleep, as sleep disruption could offset potential immunological gains. In fact, KD has been associated with improved sleep quality and reduced levels of insomnia (O'Hearn, 2021; Tereshko et al., 2024; Patel & Cheung, 2025). Thus, while promising, KD remains only a possible adjunct as opposed to a validated therapy.

Other metabolic interventions include calorie restriction and short-term fasting. In rodent and primate models, calorie restriction and short-term fasting can also have a major impact on glioma survival (Travers & Litofsky, 2021). Calorie restriction has been proven in preclinical glioma studies to extend life span in yeast, mice, and primates by selectively protecting normal cells over cancer cells (Travers & Litofsky, 2021). That being said, clinical data are sparse, and feasibility concerns, including weight loss and cachexia, limit broad application. Current findings suggest that dietary patterns can influence sleep quality and circadian alignment through modulating serotonin, melatonin, and tryptophan levels (Alruwaili et al., 2023).

Observational studies link caffeine to reduced glioma risk and inhibition of tumor invasion/migration, but causal inference is limited (Travers & Litofsky, 2021). Meanwhile, excessive intake worsens sleep and overall health, undermining circadian therapeutic goals (Travers & Litofsky, 2021). That being said, excessive caffeine intake can worsen insomnia, elevate stress responses, and disrupt circadian rhythms (Sherman et al., 2011; Segu & Kannan, 2023; Lane et al., 1990). Thus, caffeine use should be considered cautiously. Epidemiological studies have found that consuming coffee and tea every day is associated with a 54% lower risk of glioma (Holick et al., 2010). Another study found that every one cup of coffee per day decreases the risk of glioma by 3% (Pranata et al., 2022).

Exercise represents one of the most beneficial lifestyle interventions, with preclinical models demonstrating reduced tumor proliferation and enhanced immune function (Travers & Litofsky, 2021). In GBM mouse studies, exercise significantly reduces tumor proliferation, and up to 41% of glioma patients complete recommended exercise during treatment (Travers & Litofsky, 2021; Liu et al., 2024). Clinical evidence supports improvements in GBM outcomes, though direct survival benefits remain unproven. Furthermore, exercise is associated with enhanced antitumor immunity and immunotherapeutic efficacy (Patel & Cheung, 2025). Preclinical models demonstrate that combining exercise with immune checkpoint inhibitors can lead to reduced tumor volume and increased apoptosis (Patel & Cheung, 2025). Furthermore, exercise, especially when performed earlier in the day, can improve sleep quality and circadian alignment, thus reinforcing its role as both an immune and sleep modulator (Alruwaili et al., 2023; Gururaj et al., 2024; Shen et al., 2025).

Micronutrients and chronobiotic compounds link metabolism to sleep and tumor regulation. Vitamin A, especially retinoic acid, has been shown to inhibit the proliferation of tumor cells in some human GBM cell lines (Travers & Litofsky, 2021). Additionally, micronutrients including iron, magnesium, zinc, omega-3 fatty acids, vitamin B6, and vitamin D may influence sleep quality and circadian synchronization (Ji et al., 2017; Zhang et al., 2025; Conti, 2025). Likewise, melatonin, an antioxidant produced by the pineal gland, has an anticancer effect on many cancer types (Berisha et al., 2022; Travers & Litofsky, 2021). Although human clinical evidence, safety, and dosing are limited, melatonin's central role in circadian signaling positions it as a relevant adjunct in a sleep-centered therapeutic framework (Travers & Litofsky, 2021). Integrating these approaches within sleep optimization frameworks may result in additive effects. For instance, early-day exercise and time-restricted feeding reinforce circadian rhythm stability, enhancing melatonin secretion and improving responsiveness to CBT-I or CPAP (Leerssen et al., 2022; Zhao et al., 2024). Moreover, vitamin A supplements and caffeine, when appropriately used, can modulate oxidative stress and glial activation, supporting neuroimmune restoration (Navidhamidi et al., 2022).

8.7. Sleep Therapy as the Central Bridge

Interventions aimed at improving sleep quality and duration are thus the centerpiece in connecting multiple therapeutic strategies and reducing GBM proliferation and progression. In fact, sleep interventions have been promising in their objective of reducing oncogenic pathways.

For instance, therapies such as CBT-I have been effective in treating insomnia and, by extension, are associated with improvements in immune function (Lanza et al., 2024; Diggens et al., 2025). CBT-I is a multicomponent intervention that targets sleep deprivation using sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, and relaxation strategies (Diggens et al., 2025; Ma et al., 2021). When paired with treatments like CPAP, therapy for OSA not only alleviates sleep deprivation but also reduces levels of inflammatory markers, which are crucial in GBM growth (Lanza et al., 2024).

Ultimately, restoring adequate sleep duration and quality can enhance the activity of immune cells, bolstering immune surveillance against cancer (Lanza et al., 2024). These insights highlight the strong association between sleep, immune function, and GBM, underscoring the importance of addressing sleep disorders in cancer prevention and treatment (Lanza et al., 2024). Sleep therapies can be combined with other therapies, including cancer screening, immunotherapy, and lifestyle management. Oncology clinics can adopt approaches that include sleep specialists who collaborate with oncologists to assess and manage sleep-related issues (Lanza et al., 2024).

Similarly, integrating sleep management strategies and pharmacological treatments into immunotherapy protocols may help optimize immune function and enhance treatment efficacy (Lanza et al., 2024). Diets rich in fruits, vegetables, lean proteins, and whole grains can enhance sleep quality by providing essential nutrients that support the body's natural sleep–wake cycle (Lanza et al., 2024). Therefore, sleep interventions are not only a promising yet overlooked therapeutic, but they also enhance the efficacy of other strategies. Sleep interventions are foundational in recalibrating the immune and endocrine systems upon which other therapies depend, thus improving quality of life and therapeutic responsiveness, especially when coordinated with immunotherapy or pharmacological drugs.

In summary, integrated therapy for GBM requires optimizing multiple therapies in tandem, involving both immunological and physical components. Surgical interventions remain an effective treatment for reducing tumor mass but may increase the risk of neuroinflammation. While immunotherapies benefit from cytokine stabilization achieved through sleep and metabolic regulation, pharmacological drugs can be regulated to minimize immune disturbances. Lifestyle interventions can reinforce circadian and inflammatory homeostasis. This mechanistic synergy links sleep, immune modulation, surgery, and metabolism. Future research should test the effectiveness of combinative therapies and discover new and more effective synergies.

9. Conclusion

The complex relationship between sleep deprivation and GBM proliferation has been largely overlooked. Chronic sleep deprivation is associated with a pro-TME through increased neuroinflammation and immune suppression, which is fundamental in GBM progression. Sleep plays a vital role in immune regulation, and chronic sleep deprivation contributes to increased expression of pro-inflammatory cytokines and a reduction in T and NK cell function (Berisha et al., 2022; Hurtado-Alvarado et al., 2013). The severity of GBM is driven by genetic mutations, an immunosuppressive TME, and the impairment of the blood-brain barrier. Key components include Tregs, TAMs, MDSCs, cytokines, and chemokines (MedlinePlus, 2018). Thus, sleep deprivation is strongly hypothesized to contribute to GBM progression through immune regulation.

Current evidence strongly supports that chronic sleep deprivation promotes systemic inflammation and immune suppression, and that these processes contribute to GBM progression. However, direct clinical studies linking measured sleep duration to inflammatory biomarkers or survival metrics are largely absent. Moreover, the investigation of surgical intervention has resulted in mixed results in which surgery can both alleviate symptoms and exacerbate neuroinflammation (Yang et al., 2020), consequently warranting consideration of a combinative therapeutic strategy. Given the severity of GBM and limitations of individual treatment, a combined approach involving surgery, immunotherapy, pharmacology, and lifestyle changes could overcome these individual limitations.

Each therapeutic approach, including surgery, immunotherapy, pharmacology, and lifestyle interventions, has its limitations. Surgery, while critical for tumor debulking and relieving symptoms, can worsen neuroinflammation and disrupt the blood-brain barrier (Alorfi et al., 2024; Yang et al., 2020; NIH, 2025). Likewise, immunotherapies, including CAR-T cell therapy and checkpoint inhibitors, are promising but are largely ineffective as a result of the immunosuppressive TME (Li et al., 2024; Yoon & Chung, 2023; Yehuda et al., 2009). Pharmacological interventions, including corticosteroids and NSAIDs, and lifestyle changes (KD and sleep hygiene), may be unrealistic or lack long-term success.

When put together, these findings suggest that a combinative approach should be considered as a method to overcome individual limitations. At the forefront of this approach is addressing sleep deprivation through sleep therapies. Likewise, surgery should not be used in isolation but in conjunction with other therapeutic strategies. By connecting sleep deprivation to GBM progression, treatment plans address the interplay between lifestyle, immunity, and surgical interventions.

Nevertheless, questions remain. Is the timing or quality of sleep more important in maintaining sufficient immune function? What other key molecules contribute to immune suppression and neuroinflammation that haven't been discovered or researched? How can surgical advancements bypass current neuroinflammatory limitations? Future research should

1. prioritize GBM-patient studies incorporating objective sleep metrics (actigraphy/PSG/OSA) and immune profiling (IL-6, TNF-α, CRP), and
2. evaluate combinative strategies integrating sleep management, surgery, and immunotherapy to address GBM proliferation and progression.

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Author Biography

Nathaniel Chan is a 17-year-old student researcher at Basis Independent Brooklyn in New York City, where he specializes in neuroscience, biology, and psychology. Nathaniel is eager to explore the connection between sleep deprivation and the development of various cancers. He hopes to go to college on the pre-med track. Nathaniel is an aspiring neurosurgeon who aims to bridge technology and medicine in the service of empowering people with disabilities and the elderly. He also aspires to contribute to groundbreaking medical research focused on developing new treatments for developmental disorders related to the brain.

Beyond this project, Nathaniel has engaged in various projects, including estimating the economic burden of Antimicrobial resistance in underdeveloped regions in the United States and evaluating the correlation between sleep deprivation and academic recall ability of adolescents across STEM and Humanities subjects. Nathaniel is also actively engaged in Robotics, having co-founded his school's inaugural robotics team. He also mentors peers in Biology, Chemistry, and Math.

Mentor Contribution Statement

Dr. Jorge Avila served as the primary academic mentor for this manuscript and contributed to its intellectual development, methodological rigor, and scholarly presentation. He provided instruction through twice-weekly, three-hour lessons focused on research strategies in neurogenetics and functional neurosciences. These lessons directly relate to this manuscript's conceptual framework, specifically the discussion of gene expression, cell cycle control checkpoints, cytokines, and the blood-brain barrier. His instruction on orexin modulators, sleep regulation, mouse studies, and microglial and astrocytic function shaped the manuscript's focus on sleep biology, neuroinflammation, and disease progression.

Dr. Avila also trained the author in advanced research practices that were fundamental to the writing of this manuscript. This includes systematic literature searches across major academic databases, evaluation of source credibility, mining citations, and managing references and annotations using Zotero. He provided guidance on review paper structures, including abstract construction, thesis refinement, introduction structure, and ethical paraphrasing. His teachings emphasized identifying gaps in the literature and presenting the manuscript as a contribution that advances understanding rather than compiling prior work.

Furthermore, through one-on-one feedback sessions, Dr. Avila offered critiques on structure and concepts. He advised condensing long gene lists into a table, replacing descriptive sections with original figures, strengthening thesis linkage in every section, and reducing wordiness to improve the argument. He also encouraged the development of figures using Biorender and provided guidance on where to place these figures for optimal clarity. Lastly, Dr. Avila also advised journal selection and completed a formal review of the final manuscript, scanning for academic rigor, originality, and presentation fit for a peer-reviewed journal.

Bre Calhoun served as the course teaching assistant and provided mentorship that shaped the manuscript's clarity, organization, and scientific accuracy. Through one-on-one feedback sessions and weekly assignment evaluations, she guided the author in refining the paper's scope, central argument, and adherence to the scholarly writing in the field of neurogenetics and biomedical sciences. Bre played a critical role in helping the author create a focused, scientifically accurate research question and thesis. She provided guidance on choosing between a review paper and an empirical study, specifically clarifying that while original methods were optional, the author needed to understand and interpret the methodologies used in cited studies. Her feedback emphasized concise and succinct phrasing, the appropriate use of terms including "association" and "correlation" and abstaining from using informal or insensitive language in titles and abstracts.

Throughout the drafting process, Bre emphasized identifying gaps in the literature in both a global and domestic context. She advised the consolidation of background information, reduction of jargon in the introduction, and saving evidence for the body section that could be critically analyzed rather than simply listed. Her guidance encouraged the author to avoid summaries and instead prioritize synthesizing findings across studies and proposing future research directions. Bre also provided detailed stylistic feedback on abstracts, outlines, and drafts focused on clarity, flow transitions, citation adherence, and formatting consistency. She recommended the use of visuals, tables, and abbreviations to improve precision and appeal. Her feedback across multiple assignments resulted in a draft with a focused aim, narrative, and argument fit for publication.