Glioblastoma's Effect on Brain Circuitry

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Abstract

Research over the past few decades has reshaped our understanding of glioblastoma. Rather than existing independently in the brain and physically disrupting brain function, glioblastoma integrates and modifies neuron communication and vasculature to its advantage. Glioblastomas can leverage neuronal signaling, respond to synaptic activity, and remodel their microenvironment to promote their growth. This review consolidates findings from electrophysiology, blood oxygenation level-dependent functional magnetic resonance imaging (BOLD fMRI), magnetoencephalography (MEG), transcriptomic, and metabolic studies to highlight many of the changes that occur in the host brain. For the construction of this review, an electronic search was conducted using studies that fit the following inclusion criteria: (1) The study focused on glioblastomas, (2) the study looked at brain circuitry, cognitive function, or neuronal activity, and (3) the full text of the study was within the two reviewers' institutional databases. Studies that did not meet these criteria were excluded from this review.

Introduction

It is well established that the brain is one of the most complex, functionally diverse yet precise organs in the human body (2, 22, 27, 39). It is composed of billions of neurons that collectively coordinate sensory perception, emotional responses, higher-order cognition, and motor movements. This system is often referred to as brain circuitry. While neurons are traditionally recognized as the main communicators in the brain's function, they are far from acting alone. Glial cells, which include astrocytes, oligodendrocytes, and microglia, make up a large portion of the brain's cellular composition. Neurons and glial cells exist in approximately a 1:1 ratio in the brain (3, 40, 41).

Glial cells are now known to play a central role in regulating and supporting neural activity. They are involved in maintaining homeostasis, supporting neuron metabolism, defending against immune threats, and remodeling synapses (3, 11, 16, 24). Recent evidence has revealed that glial cells also play an increasingly important role as modulators of the central nervous system; they are no longer thought of as just passive support cells (16, 41). Because they are crucial to the functions carried out by the brain, when these cells become dysregulated, they can give rise to pathologies like gliomas.

Glioblastoma is the most common and severe type of glioma. Glioblastoma is a poorly understood tumor, and its etiology remains unclear (6, 20, 36). However, several risk factors like exposure to radiation, genetic mutations, age, and certain inherited diseases like Li-Fraumeni syndrome and neurofibromatosis have been identified as causes (20, 35, 42).

Some early studies, including Feigin and colleagues, introduced the term "gliosarcoma" to describe brain tumors consisting of glial cells and connective tissues, highlighting its unique cellular makeup (5). A few decades later, Jellinger et al. (1978) classified a broader category of malignant glial tumors as glioblastoma multiforme, based on their diverse morphology and dedifferentiation of astrocyte cells (1). Today, we simply refer to these tumors as glioblastomas, and they remain the most aggressive primary brain tumors in adults (5, 12, 20, 22, 50). Despite advances in surgeries, radiation, and chemotherapy, glioblastomas remain incurable and are associated with rapid progression, treatment resistance, and poor prognosis (20, 22, 36).

However, more recent studies challenge the traditional view of glioblastomas being simply a mass of proliferating cells. Evidence shows that glioblastoma tumors can make themselves at home, becoming an integral part of the brain as they grow and rewire the brain's circuitry to their advantage. This review aims to explore and bring together studies on how

glioblastomas interact with and affect the brain circuitry.

Methods

To construct a comprehensive overview of the relationship between glioblastoma and the brain circuitry, we started our search on Google Scholar. We focused on finding foundational studies on normal brain circuitry, glial cells, and how they interact to solidify our understanding. Following this, we conducted a systematic search on key literature addressing the relationship between glioblastomas and brain circuitry using the PubMed database, covering articles published from 1954 to 2024. We intentionally included old studies to understand the historical development of glioblastoma research and how scientific understanding has evolved. Articles were selected based on relevance to our main topic and on citation numbers. We also used a snowballing method by reviewing the references of our primary articles to expand our literature pool. Inclusion criteria were: 1) Studies focusing on glioblastoma; 2) Inclusion of brain circuitry, cognitive function, neuronal activity; and 3) Availability of full text within our institution's database. Articles without full text availability within the institutional database were excluded from the study. Our exclusion criteria also included studies that were purely molecular without neural context.

Results

Glioblastoma and Brain Circuitry: Integration, Rewiring, and Disruption

Many are beginning to recognize that glioblastomas are not only a mass of rapidly proliferating cells in the brain but also a tumor capable of integrating into neuronal networks and altering their function.

One interesting study by Venkataramani et al. demonstrates that glioma cells can form active synaptic connections with neurons (32). In this study, they used mice with human glioma cells implanted in their brain. Using a calcium imaging technique and a patch-clamp recording, they observed that the glioma cells were expressing AMPA-type glutamate receptors normally found on neurons receiving post-synaptic currents. The calcium imaging showed that those receptors were responding in real time to neuronal firing. Venkataramani and colleagues were able to show that glioma cells exhibited calcium movement activity in coordination with normal brain neurons. In addition to the expression of AMPA type glutamate receptors, another group, Venkatesh and colleagues, argue that active neurons release neuroligin-3, a synaptic factor that is co-opted by glioma cells to stimulate growth (33, 43).

In parallel to the studies conducted by Venkatesh and colleagues, Tetzlaff et al. used rabies virus-based retrograde tracing, a method that labels cells directly connected via synapses, to find that glioma cells received input from normal neurons across multiple brain regions, and that these connections can vary from patient to patient (29). They claim that inhibiting this synaptic input offers strong therapeutic potential. These findings suggest that glioma tumors do not simply exist passively in the brain, but interact with the neurons to benefit their own survival. Krishna et al. proved this in a study where they showed that high neuronal activity near the tumor promoted tumor growth. They, along with several other groups, observed that tumor cells release proteins like thrombospondin-1 (TSP-1), which stimulate the formation of new excitatory synapses (15, 44, 45, 46). This creates a positive feedback loop: active neurons drive tumor progression, and the tumor modifies the microenvironment to increase neuronal activity.

At first glance, the ability of glioma cells to form connections with neurons may seem unsurprising, as healthy astrocytes do form connections with neurons (16). However, these connections are modulatory and involve astrocytes regulating neurotransmitter concentrations, buffering ions, and releasing gliotransmitters around neuronal synapses to influence neuronal activity, without forming a direct synapse (16). In contrast, glioma cells form true functional excitatory synapses, synapses where activating neurotransmitters are exchanged, with neurons. Neurons transmit glutamatergic signals across those synapses, which activate AMPA receptors on glioma cells, allowing the tumor to detect and respond to neuronal activity (32, 33). These functional synapses allow the tumor to integrate into neuronal circuits and exploit them to promote tumor growth (11, 51).

In addition to forming abnormal connections with neurons, the tumor rewires and damages brain circuitry to its advantage. In a study utilizing functional magnetic resonance imaging (fMRI) on patients performing language tasks, conducted by Krishna et

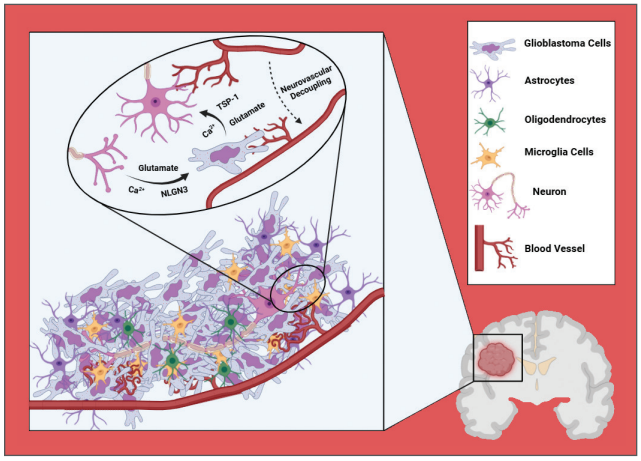

Figure 1. Schematic representation of a zoomed-in view of the glioblastoma tumor microenvironment and glioblastoma cell and neuron interactions. The glioblastoma microenvironment is a complex association of several different glial cells (astrocytes, oligodendrocytes, and microglia), blood vessels, neurons, and glioblastoma cells. Neurons and glioblastoma cells interact in several ways in the tumor microenvironment to alter neuron networks and circuitry.

al., it was observed that in glioma-infiltrated cortical regions, there was still neuronal activity, but this activity was disorganized and spread across the tumor-infiltrated regions. They claimed that this functional rewiring correlates with a decrease in survival rate for patients (15).

Similarly, Bosma et al. used magnetoencephalography (MEG), a neuroimaging technique measuring magnetic fields produced by neuronal activity, and graph theory, a mathematical method modeling pairwise relationships between different groups, to compare cognitive ability between patients with low-grade gliomas and healthy individuals. They found that glioma patients had low clustering on the graph, longer communication paths, and less efficient network structure, especially in theta and beta frequency bands, which are crucial for memory and attention (4). Changes in brain organization caused by these gliomas were linked to worse performance on tasks involving processing speed, attention, and memory.

All these studies show that glioblastomas, even low-grade gliomas, can reorganize the brain network to facilitate their own growth, at the detriment of patients' cognitive ability and survival.

Neurovascular Decoupling in Glioblastomas: Functional Disruption Beyond the Neuron

In a healthy brain, neuronal activity drives local increases in blood flow, a relationship called neurovascular coupling (15, 47). However, glioblastomas disrupt this mechanism. The tumor remodels surrounding vasculature and decouples neuronal activity from vascular response, leading to functionally active regions appearing silent on fMRI.

Holodny et al. conducted a functional brain study on patients with glioblastomas near their motor and sensory cortices using blood oxygenation level-dependent (BOLD) fMRI (BOLD detects changes in the ratio of oxygenated to deoxygenated hemoglobin in brain tissue) (17). Surprisingly, these patients showed low or absent activity in those areas, even though later surgical mapping proved that those brain areas were normal. Researchers hypothesize that the tumors might have affected the local vasculature, hence the perceived lack of activity from BOLD fMRI measurements (8).

This raises a concern: functional brain imaging may fail to accurately represent viable tissues in the periphery of the tumor. If normal brain tissues appear inactive due to disrupted vascular responses, that might lead to misclassifying them as non-functional, potentially affecting surgical decisions and treatment plans (7).

A study by Hou et al. reinforced the idea of this decoupling mechanism by examining how gliomas reduced the association between blood vessels and neurons. The study showed that, compared to healthy controls, patients with glioblastomas had reduced activation volume even when the tumor invasion in that specific brain region was minimal. They concluded that this reduction was not due to structural damage but to an insufficient vascular response (10).

This study provides support for the original hypothesis by Holodny et al. that glioblastomas affect blood vessel activity and structure in the periphery of the tumor.

Neuronal Hyperexcitability and Circuit Misfiring in Glioblastoma

Beyond structural invasion and vascular damage, glioblastomas also alter the electrical function of the brain. One of the most consistent findings in glioblastoma studies is that the glioma-infiltrated tissue becomes hyperexcitable (13, 14, 18, 19, 26). These changes can often lead to seizures and impaired cognition. There are several neurological symptoms commonly present in glioma patients, resulting from functional alterations in areas of the cortex that have been infiltrated. The most common neurological

symptom patients present with is seizures; over 80% of low-grade glioma patients and 50%–60% of high-grade glioma patients suffer from seizures. These can contribute significantly to the deterioration of cognitive function (13, 26).

To investigate how glioblastomas affect neuronal signaling over time, Meyer et al. used 2 glioma mouse models: one slow-growing and the other fast-growing. They monitored neuronal activity using *in vivo* calcium imaging and glutamate sensors, 2 techniques that allow for real-time data collection. Their results showed that the fast-growing glioblastomas produce spontaneous and unregulated neuronal activity through the accumulation of glutamate. They also found that the irregular activity of the neurons is not just confined to the margin of the tumor. It can extend even into the opposite hemisphere (18). Observations by Köhling et al. observations support Meyer and colleagues' findings. In their study, they performed a human glioma xenograft into mice and discovered that not only does the tumor generate seizure activities in its proximity, but the seizure activity propagates to healthy tissues as well (14).

Studies like Montgomery et al. used a wide-field calcium imaging system in a mouse model expressing GCaMP (a genetically encoded calcium indicator) to track neural dynamics across the cortex as tumors grew. Initially, activity patterns across the brain were bilaterally synchronized. However, as the tumor infiltrated into deeper regions of the brain, this synchrony became weak. Neural signals near the tumor zone were firing at fast and irregular intervals. Additionally, regions that previously showed coherent fluctuations in calcium signals lost that coordination, particularly in motor and association cortices. One notable finding is that these bursts emerged before the onset of seizures, suggesting that hyperexcitability is not just a late-stage symptom but a fundamental feature of glioma progression (19).

This overactivity of the neurons can place new demands on energy usage in the brain. The next section will better explore how glioblastomas manipulate the neuronal metabolism to enhance their growth.

Metabolic Adaptations That Support Circuit Hijacking

Like most cancer cells, glioblastomas need energy to survive and thrive. To understand the metabolic adaptations necessary for this, Garofano et al. performed an in-depth transcriptomic analysis (a study of multiple genes at once to observe which ones are actively transcribed) on glioblastoma samples and discovered that these tumors could be divided into metabolic subtypes based on their gene expression profiles. One of the major subtypes showed high expression of genes associated with mitochondrial metabolism, indicating a reliance on oxidative phosphorylation rather than glycolysis for energy production (6). The mitochondrial subtype was also associated with greater tumor aggressiveness and resistance to conventional therapies. While Garofano et al. showed that some glioblastomas rely on mitochondria for energy, Guo et al. (2024) found that under hypoxic conditions, glioma cells rely on glycolysis for energy, which leads to glucose and energy depletion in the brain and causes the release of glutamate in the extracellular environment. The excess glutamate then acts on surrounding neurons, triggering hyperexcitability (7, 48, 49).

Building on metabolic changes induced by glioblastoma, Winkler et al. showed that glioblastoma cells can take advantage of the brain's activity by altering their own metabolic demands. In areas with high levels of neuronal firing, glioblastoma cells rely less on glucose, using alternative energy sources such as lactate and glutamate, which are typically produced by active neurons. This metabolic flexibility enables the tumor cells to survive and thrive in neural circuits, allowing them to integrate more tightly into the surrounding brain tissue (37). Winkler and colleagues also emphasized that this adaptation is not merely a survival mechanism. It is a way for the tumor to embed itself deeper into the functional circuits of the brain, disrupting normal neural signaling and making the tumor more resistant to treatment. This is supported by Numan et al., where they showed that gliomas preferentially grow in regions with high neuronal activity. Using brain scans from over 400 glioma patients and magnetoencephalography data from healthy people, they found that gliomas most often occurred in areas with high broadband power and elevated spiking activity. This selectivity is related to symptom severity and lower functional performance (21).

Together, these studies suggest that glioblastomas leverage neuronal activities and metabolism under both oxygen-rich and oxygen-poor conditions to take advantage of the high neuronal firing of their environment.

Discussion

This review has examined how glioblastomas invade and reshape components of the brain circuitry. From forming excitatory synapses to mimicking neurons' behavior, glioblastoma can rearrange the brain network in many dynamic ways. One common theme that emerged across many of the studies in this review is the impact glioblastomas can have on cognition. For example, Krishna et al. and Montgomery et al. found a decrease in high-order function in glioma-infiltrated regions of the brain; however, the exact mechanism remains unclear (15, 19).

One limitation that many of the studies looked at in this review suffer from is that almost all their data comes from rodent models, which might not capture the full complexity of the human brain network. This review also does not cover how different treatments can change the interactions between glioma cells and neuronal networks.

Glioblastomas, being a rapid and aggressive form of cancer, are often caught late in their development; as a result, many of the interactions we have discussed here have already taken root before treatment is administered (15, 19, 36). However, it is worth mentioning that standard therapies like resection, radiation, and chemotherapy can affect these interactions in a variety of ways. Unfortunately, though these treatments remain palliative, with median survival barely exceeding one year (28, 48, 50).

Furthermore, this review does not investigate the role of genetics in glioblastoma invasion; however, without a doubt, this plays a vital role. Studies like Yu et al. demonstrated that PIK3CA variants of glioblastoma, when compared to other variants, can initiate hyperexcitability and remodel synaptic environment during glioma genesis. Also, this review does not explore how different subtypes of glioblastoma differ in their invasion and neuronal remodeling capabilities. The 4 subtypes of glioblastoma, neural progenitor-like (NPC), oligodendrocyte progenitor-like (OPC), astrocyte progenitor-like (AC), and mesenchymal-like (MES) are each associated with different genetic alterations to CDK4, EGFR, PDGFRA, and NF1, respectively (1, 9, 20, 25, 30, 31, 34). Glioblastomas can arise from any 4 of those progenitors depending on cues from their environment. A better understanding of the role of genetics in glioblastoma would be beneficial in future treatment development.

Conclusion

This review brings into focus the multifaceted ways in which glioblastomas can interact with and manipulate brain circuitry. They build connections, hijack neuronal signals, and disrupt the communication between blood vessels and neurons. As many studies have revealed, this integration is a strategy to promote the survival of the tumor. Consequently, this integration blurs the line between brain and tumor, complicating both diagnosis and, more importantly, treatment (23). We believe that future research should be dedicated to methods of normalizing neuronal networks and vasculature in glioblastoma-infiltrated brains, to improve patient survival and slow cognitive decline. By understanding the interactions between glioblastomas and the brain, we not only gain insights into how we might better treat this disease but also uncover a deeper knowledge of how brain circuitry is organized and how tumors can adapt to a wide variety of microenvironments.

Disclosures

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References

1. Aldape K, Zadeh G, Mansouri S, Reifenberger G, von Deimling A. Glioblastoma: pathology, molecular mechanisms and markers. *Acta Neuropathol*. 2015;129(6):829–848.
2. Bassett DS, Gazzaniga MS. Understanding complexity in the human brain. *Trends Cogn Sci*. 2011;15(5):200–209.
3. Von Bartheld CS, Bahney J, Herculano-Houzel S. The search for true numbers of neurons and glial cells in the human brain: A review of 150 years of cell counting. *J Comp Neurol*. 2016;524(18):3865–3895.
4. Bosma I, Reijneveld JC, Klein M, et al. Disturbed functional brain networks and neurocognitive function in low-grade glioma patients: a graph theoretical analysis of resting-state MEG. *Nonlinear Biomed Phys*. 2009;3(1):9.

5. Feigin IH, Gross SW. Sarcoma arising in glioblastoma of the brain. *Am J Pathol*. 1954;30(5):1023–1039.
6. Garofano L, Migliozzi S, Oh YT, et al. Pathway-based classification of glioblastoma uncovers a mitochondrial subtype with therapeutic vulnerabilities. *Nat Cancer*. 2021;2(2):141–156.
7. Guo X, Qiu W, Li B, Qi Y, Wang S, Zhao R, et al. Hypoxia-induced neuronal activity in glioma patients polarizes microglia by potentiating RNA m6A demethylation. *Clin Cancer Res*. 2024;30(6):1160–1176.
8. Holodny AJ, Schulder M, Liu WC, Maldjian JA, Kalnin AJ. Decreased BOLD functional MR activation of the motor and sensory cortices adjacent to a glioblastoma multiforme: implications for image-guided neurosurgery. *AJNR Am J Neuroradiol*. 1999;20(4):609–12.
9. Hoogstrate Y, Draaisma K, Ghisai SA, et al. Transcriptome analysis reveals tumor microenvironment changes in glioblastoma. *Cancer Cell*. 2023;41(5):678–692.e7.
10. Hou BL, et al. Effect of brain tumor neovasculature on BOLD fMRI activation volume in the primary motor cortex. *AJNR Am J Neuroradiol*. 2006;15;32(2):489-97.
11. Hua T, Shi H, Zhu M, Chen C, Su Y. Glioma-neuronal interactions in tumor progression: Mechanism, therapeutic strategies and perspectives. *Int J Oncol*. 2022;61(6):139.
12. Jellinger K. Glioblastoma multiforme: morphology and biology. *Acta Neuropathol*. 1978;41(2):119–126.
13. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. *Ann Neurol*. 2003; 54:514–520.
14. Köhling R, Senner V, Paulus W, Speckmann EJ. Epileptiform activity preferentially arises outside tumor invasion zone in glioma xenotransplants. *Neurobiol Dis*. 2006;22(1):64–75.
15. Krishna S, Keough M, Chaudhury A, et al. Glioblastoma remodeling of human neural circuits decreases survival. *Nature*. 2023;617(7961):589–97.
16. Linné ML, Aćimović J, Saudargiene A, Manninen T. Neuron–glia interactions and brain circuits. In: Sloot PMA, Hoekstra AG, Panja D, editors. *Computational Modeling of Biological Systems*. Springer; 2022. p. 77–94.
17. Logothetis NK, Wandell BA. Interpreting the BOLD signal. *Annu Rev Physiol*. 2004:66:735-69.
18. Meyer J, Yu K, Luna-Figueroa E, et al. Glioblastoma disrupts cortical network activity at multiple spatial and temporal scales. *Nat Commun*. 2024;15:Article 3742.
19. Montgomery MK, Kim SH, Zhao H, et al. Glioma-induced alterations in neuronal activity and neurovascular coupling during disease progression. *Cell Rep*. 2020;31(1):107500.
20. Neftel C, Laffy J, Filbin MG, et al. An integrative model of cellular states, plasticity, and genetics for glioblastoma. *Cell*. 2019;178(4):835–849.e21.
21. Numan T, Breed LC, Maciel B, et al. Regional healthy brain activity, glioma occurrence and symptomatology. *Brain*. 2022;145(11):3654–65.
22. Osoba D, Aaronson NK, Muller M, et al. Effect of neurological dysfunction on health-related quality of life in patients with high-grade glioma. *J Neurooncol*. 1997;34(3):263–278.
23. Osswald M, Jung E, Sahm F, et al. Brain tumor cells interconnect to a functional and resistant network. *Nature*. 2015;528(7580):93–98.
24. Park HJ, Friston KJ. Structural and functional brain networks: from connections to cognition. *Science*. 2013 Nov 1;342(6158):1238411.
25. Patel AP, Tirosh I, Trombetta JJ, et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. *Science*. 2014;344(6190):1396–1401.
26. Rudà R, Trevisan E, Soffietti R. Epilepsy and brain tumors. *Curr Opin Oncol*. 2010;22:611–620.
27. Sultana OF, Bandaru M, Islam MA, et al. Unraveling the complexity of human brain: Structure, function in healthy and disease states. *Ageing Res Rev*. 2024; 100(102414).
28. Taphoorn MJ, Stupp R, Coens C, Osoba D, Kortmann R, van den Bent MJ, et al. Health-related quality of life in patients with glioblastoma: a randomised controlled trial. *Lancet Oncol*. 2005;6(12):937-44.

29. Tetzlaff CL, et al. Characterizing and targeting glioblastoma neuron-tumor networks with retrograde tracing. *Cell*. 2024.
30. Tirosh I, Venteicher AS, Hebert C, et al. Single-cell RNA-seq supports a developmental hierarchy in human oligodendroglioma. *Nature*. 2016;539(7628):309–313.
31. Varn FS, Johnson KC, Martinek J, et al. Glioma progression is shaped by genetic evolution and microenvironment interactions. *Cell*. 2022;185(13):2184–2199.e16.
32. Venkataramani V, et al. Glioblastoma hijacks neuronal mechanisms for brain invasion. *Cell*. 2024.
33. Venkatesh HS, Johung T, Caretti V, et al. Neuronal activity promotes glioma growth through neuroligin-3 secretion. *Cell*. 2015;515(7525):533–537.
34. Verhaak RGW, Hoadley KA, Purdom E, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*. 2010;17(1):98–110.
35. Weller M, Wick W, Aldape K, et al. Glioma. *Nat Rev Dis Primers*. 2015;1:15017.
36. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol*. 2021;18:170–186.
37. Winkler F, Venkatesh HS, Amit M, et al. Cancer neuroscience: State of the field, emerging directions. *Cell*. 2023;186(8):1689–1707.
38. Yu K, Lin CCJ, Hatcher A, et al. PIK3CA variants selectively initiate brain hyperactivity during glioma genesis. *Nature*. 2020;585(7824):256–260
39. Lou L. Architectures of neuronal circuits. *Science*. 2021;373(6559).
40. Garcia-Cabezas MA, John YJ, Barbas H, et al. Distinction of Neurons, Glia and Endothelial Cells in the Cerebral Cortex: An Algorithm Based on Cytological Features. *Frontiers*. 2016;10.
41. Allen NJ and Lyons DA. Glia as architects of central nervous system formation and function. *Science*. 2018;362(6411):181-185.
42. Yoshikawa MH, Rabelo NN, Telles JPM, et al. Modifiable risk factors for glioblastoma: a systematic review and meta-analysis. *Neurosurg Rev*. 2023;46(143).
43. Venkatesh HS, Tam LT, Woo PJ, et al. Targeting neuronal activity-regulated neuroligin-3 dependency in high-grade glioma. *Nature*. 2017; 549:533–537.
44. Daubon T, Léon C, Clarke K, et al. Deciphering the complex role of thrombospondin-1 in glioblastoma development. *Nat Commun*. 2019;10:1146.
45. Qi C, Lei L, Hu J, Wang G, et al. Thrombospondin-1 is a prognostic biomarker and is correlated with tumor immune microenvironment in glioblastoma. *Oncol Lett* 2021;21:22.
46. Tanase C, Enciu AM, Codrici E, et al. Fatty Acids, CD36, Thrombospondin-1, and CD47 in Glioblastoma: Together and/or Separately? *Int. J. Mol. Sci*. 2022;23(2):604
47. Phillips AA, Chan FHN, et al. Neurovascular coupling in humans: Physiology, methodological advances and clinical implications. *Journal of Cerebral Blood Flow & Metabolism*. 2015;36(4):647-664.
48. Lange F, Hörnschemeyer MF, and Kirschstein T. Glutamatergic Mechanisms in Glioblastoma and Tumor-Associated Epilepsy. *Cells*. 2021;10(5),1226.
49. Biegański M and Szeliga M. Disrupted glutamate homeostasis as a target for glioma therapy. *Pharmacol*. 2024;76:1305–1317.
50. Tykocki T and Eltayeb M. Ten-year survival in glioblastoma. A systematic review. 2018;54:7-13.
51. Venkataramani V, Tanev DI, Strahle C, et al. Glutamatergic synaptic input to glioma cells drives brain tumour progression. *Nature* 2019:573:532–538.