EDITORIAL OPEN ACCESS

Editorial: Microglial Signaling Molecules in Brain Tumors: Alchemizing Neuroinflammation into Therapy

Saviya Kashif[1,*], Areeba Patel[1]

[1]College of Molecular Medicine, Ziauddin University, Karachi, Pakistan; [*]saviya.kashif@zu.edu.pk

Brain tumors are among the most challenging diseases of the central nervous system, due not only to the intrinsic aggressiveness of malignant cells, but also to the complex biological environment where these tumors develop [1]. Among the factors that shape this environment, neuroinflammation has been acknowledged as an important determinant of tumor behavior. There is increasing evidence that inflammatory responses in the brain are not merely secondary to tumor growth. Instead, interactions between malignant cells and the immune, stromal, and neural compartments can actively shape tumor progression, invasion, immune evasion, and therapeutic resistance [2, 3].

This shift in perspective raises an important question: should neuroinflammation in brain tumors still be viewed primarily as a pathological response or a possible therapeutic target?

1. From Inflammatory Response to Tumor-Supportive Environment

Glioblastoma (GBM) is the most aggressive primary malignant brain tumor in adults and is characterized by rapid growth and invasiveness, often leading to poor prognosis despite aggressive treatment and a highly complex tumor microenvironment [4]. It contains tumor cells and also endothelial cells, components of the extracellular matrix, resident immune cells, infiltrating immune cells, and many soluble mediators [5]. Tumor-associated macrophages and microglia are especially important components, and inflammatory cells may constitute a large proportion of the tumor mass [5].

Microglia are the resident immune cells of the central nervous system. Under normal conditions, microglia fulfill essential functions in immune surveillance, tissue homeostasis, synaptic regulation, and response to injury. However, in the tumor microenvironment, their behavior is heavily influenced by signals from the malignant cells and the surrounding tissues [6]. Microglia and infiltrating macrophages are not a homogeneous population but show a high degree of functional plasticity and can adopt different states depending on their location, cellular origin, and local molecular signals [7].

Tumor-associated macrophages and microglia increase tumor cell survival, angiogenesis, invasion, immune suppression, and resistance to therapy. Importantly, recent studies have shown these cells are not biologically the same [8].

2. Microglia: From Immune Surveillance to Tumor Adaptation

The relationship between microglia and brain tumors is thus not purely one of immune activation. It is a dynamic interplay in which the tumor cells can modulate the milieu of immune cells to promote their own survival.

In glioblastoma, microglia and macrophages can be activated by cytokines, chemokines, growth factors, and other molecular signals from the tumor. Such interactions may create an immunosuppressive milieu that restricts effective antitumor immunity. At the same time, inflammatory mediators can affect tumor-cell proliferation, migration, angiogenesis and tissue invasion [9, 10].

The spatial organization of these cells provides additional evidence of their functional diversity. Recent studies have shown that immunosuppressive populations of macrophages are enriched in hypoxic and necrotic regions of glioblastoma while microglia are found in abundance at invasive tumor margins, and may have unique inflammatory and interferon-associated signatures [11, 12]. These findings challenge the classical view of fixed phenotypes of tumor-associated macrophages and support a model of continuous and context-dependent cellular states.

But this difference is more than a biological curiosity. These differences have direct therapeutic implications.

3. Why Targeting Neuroinflammation is Not Straightforward

Inflammatory responses in the brain are highly heterogeneous, and immune cells can have tumor-supportive and tumor-restrictive functions depending on their state and location. Thus, eliminating microglia or macrophages alone may also

eliminate potentially beneficial immune functions along with tumor-supportive populations. Moreover, the heterogeneity of glioblastoma itself suggests that the same intervention may have differential effects between tumors or even different regions of the same tumor [13].

This may explain why translation of immune-based approaches into effective therapies for glioblastoma has been considerably more difficult than in several other cancers. Glioblastoma is often described as an immunologically "cold" tumor with a highly immunosuppressive microenvironment, in which effective antitumor immune responses are impaired. Instead of trying to eliminate inflammation, the more promising strategy may be to reprogram the inflammatory microenvironment.

4. From Depletion to Reprogramming

Therapies targeting tumor-associated microglia and macrophages are increasingly considering different approaches, such as inhibition of their recruitment, depletion of specific populations, modulation of their functional state, enhancement of phagocytosis, and disruption of their interactions with tumor cells [9].

Recent advances in single-cell RNA sequencing and spatial transcriptomics have opened an important opportunity to move beyond broad cellular classifications and identify distinct immune-cell populations and functional states within individual tumors [14, 15]. These technologies may enable future therapies to target specific tumor-supportive populations, rather than broadly suppressing the immune response. The transition from depletion to precision reprogramming is especially fascinating.

5. The Therapeutic Opportunity Ahead

The future of neuro-oncology may thus lie in targeting not only malignant cells but also comprehending their sustaining ecosystem. Therapies targeting tumor-associated microglia and macrophages may provide an adjunct to current treatments including surgery, radiotherapy, chemotherapy, and immunotherapy [16-18]. Recent data suggest that modulation of these immune populations can reprogram the tumor microenvironment and potentially enhance responses to standard therapies [19].

However, there are still a number of challenges. Therapeutic development is challenged by the marked heterogeneity of tumor-associated immune cells, the blood–brain barrier, spatial heterogeneity within tumors, treatment-induced changes of the microenvironment, and the difficulty of discriminating beneficial from tumor-supportive inflammation [20]. Crucially, promising results from experimental models must still be translated into safe and effective clinical interventions.

Future research should therefore move toward integrated approaches combining molecular profiling, spatial analysis, functional characterization and patient-specific tumor biology. Researchers should not think of neuroinflammation as a single pathway, but as a dynamic network of interactions between tumor cells, microglia, macrophages, endothelial cells, neurons and other components of the brain microenvironment.

6. Conclusion

Neuroinflammation is recognized to play a role beyond a bystander phenomenon in brain tumors. This is a dynamic component of the tumor microenvironment that may influence tumor progression, immune evasion, invasion, and therapy response. Microglia and tumor-associated macrophages are particularly important players in this network owing to their abundance, plasticity, and capacity to directly interact with malignant cells.

However, the therapeutic challenge is not merely to suppress neuroinflammation. Rather, it is to understand its complexity well enough to direct it.

The findings suggest that next-generation brain tumor therapies may have to shift away from a broad targeting of cancer cells to simultaneous targeting of the cellular ecosystem that allows them to survive. Advances in single-cell and spatial technologies are making the possibility of identifying and therapeutically reprogramming specific inflammatory cell states increasingly feasible. Turning neuroinflammation from a tumor-supporting mechanism to an antitumor opportunity may ultimately represent an important step toward more effective and personalized treatment for patients with brain tumors.

REFERENCES

[1] Cieśluk M, Pogoda K, Piktel E, Wnorowska U, Deptuła P, Bucki R. Mechanical properties of the extracellular environment of human brain cells drive the effectiveness of drugs in fighting central nervous system cancers. Brain Sci. 2022; 12(7): 927. https://doi.org/10.3390/brainsci12070927

[2] Nóbrega AHL, Pimentel RS, Prado AP, Garcia J, Frozza RL, Bernardi A. Neuroinflammation in glioblastoma: the role of the microenvironment in tumour progression. Curr Cancer Drug Targets. 2024; 24(6): 579-94. https://doi.org/10.2174/0115680096265849231031101449
[3] Wu T, Zhang Y, Han J. Targeting the nervous system: mechanistic insights into neuro-tumor communication and therapeutic opportunities. Acta Pharm Sin B. 2026; 16(9): 5592-621. https://doi.org/10.1016/j.apsb.2026.07.011
[4] Pouyan A, Ghorbanlo M, Eslami M, Jahanshahi M, Ziaei E, Salami A, *et al*. Glioblastoma multiforme: insights into pathogenesis, key signaling pathways, and therapeutic strategies. Mol Cancer. 2025; 24(1): 1-51. https://doi.org/10.1186/s12943-025-02267-0
[5] Butler M, Prasad S, Srivastava SK. Targeting glioblastoma tumor microenvironment. In: Birbrair A, Eds. Tumor Microenvironments in Organs. Advances in Experimental Medicine and Biology, vol 1296. Cham: Springer; 2020, p. 1-9. https://doi.org/10.1007/978-3-030-59038-3_1
[6] Qin J, Ma Z, Chen X, Shu S. Microglia activation in central nervous system disorders: a review of recent mechanistic investigations and development efforts. Front Neurol. 2023; 14: 1103416. https://doi.org/10.3389/fneur.2023.1103416
[7] Prinz M, Priller J. Microglia and brain macrophages in the molecular age: from origin to neuropsychiatric disease. Nat Rev Neurosci. 2014; 15(5): 300-12. https://doi.org/10.1038/nrn3722
[8] Andersen RS, Anand A, Harwood DSL, Kristensen BW. Tumor-associated microglia and macrophages in the glioblastoma microenvironment and their implications for therapy. Cancers (Basel). 2021; 13(17): 4255. https://doi.org/10.3390/cancers13174255
[9] Zhao W, Zhang Z, Xie M, Ding F, Zheng X, Sun S, *et al*. Exploring tumor-associated macrophages in glioblastoma: from diversity to therapy. NPJ Precis Oncol. 2025; 9(1): Article number: 126. https://doi.org/10.1038/s41698-025-00920-x
[10] Wang G, Zhong K, Wang Z, Zhang Z, Tang X, Tong A, *et al*. Tumor-associated microglia and macrophages in glioblastoma: from basic insights to therapeutic opportunities. Front Immunol. 2022; 13: 964898. https://doi.org/10.3389/fimmu.2022.964898
[11] Pires-Afonso Y, Niclou SP, Michelucci A. Revealing and harnessing tumour-associated microglia/macrophage heterogeneity in glioblastoma. Int J Mol Sci. 2020; 21(3): 689. https://doi.org/10.3390/ijms21030689
[12] Liu X, Li M, Wei Z, Shang T, Zou W. Border-associated macrophages in CNS health and disease: a comprehensive review of ontogeny, heterogeneity, and functional plasticity at neural interfaces. ASN Neuro. 2026; 18(1): Article: 2687503. https://doi.org/10.1080/17590914.2026.2687503
[13] Wu H, Wang Y, Tian Y, Feng S, Yang X, Yuan X, *et al*. Glycolytic reprogramming in cancer: immune crosstalk, nutrient competition, and supportive care perspectives. Front Immunol. 2026; 17: 1862570. https://doi.org/10.3389/fimmu.2026.1862570
[14] Le J, Dian Y, Zhao D, Guo Z, Luo Z, Chen X, *et al*. Single-cell multi-omics in cancer immunotherapy: from tumor heterogeneity to personalized precision treatment. Mol Cancer. 2025; 24(1): Article number: 221. https://doi.org/10.1186/s12943-025-02426-3
[15] Shi W, Zhang Z, Xu X, Tian Y, Feng L, Huang X, *et al*. Single-cell and spatial transcriptomics integration: new frontiers in tumor microenvironment and cellular communication. Front Immunol. 2025; 16: 1649468. https://doi.org/10.3389/fimmu.2025.1649468
[16] Khafaga DSR, Basem Y, AlAtar HM, Sherif A, Ata A, Sabry F, *et al*. Cancer neuroscience: linking neuronal plasticity with brain tumor growth and resistance. Biology (Basel). 2026; 15(2): 108. https://doi.org/10.3390/biology15020108
[17] Gong Y, Lin W, Fang X, Zhang R, Luo M, Wu H, *et al*. Advances in cellular immune theranostic approaches for glioblastoma: current trends and future directions. Cancer Innov. 2025; 4(4): e70018. https://doi.org/10.1002/cai2.70018
[18] Ardizzone A, Basilotta R, Filippone A, Crupi L, Lanza M, Lombardo SP, *et al*. Recent emerging immunological treatments for primary brain tumors: focus on chemokine-targeting immunotherapies. Cells. 2023; 12(6): 841. https://doi.org/10.3390/cells12060841
[19] Datta M, Coussens LM, Nishikawa H, Hodi FS, Jain RK. Reprogramming the tumor microenvironment to improve immunotherapy: emerging strategies and combination therapies. Am Soc Clin Oncol Educ Book. 2019; (39): 165-74. https://doi.org/10.1200/EDBK_237987
[20] Silver A, Feier D, Ghosh T, Rahman M, Huang J, Sarkisian MR, *et al*. Heterogeneity of glioblastoma stem cells in the context of the immune microenvironment and geospatial organization. Front Oncol. 2022; 12: 1022716. https://doi.org/10.3389/fonc.2022.1022716