Tumour Microenvironment in Brain Cancer: A Neural Niche or a Hijacked Memory System?

Hafiz Muhammad Haseeb Khaliq[1,2]

[1]Department of Pathology, University of Health Sciences, Lahore, Pakistan
[2]International Max Planck Research School IMPRS, Berlin, Germany

Primary brain cancers, particularly glioblastoma, remain among the most difficult cancers to treat.[1] Tumour-induced neurogenesis has sparked a conceptual debate: should the glioma tumour microenvironment (TME) be viewed as a neural niche, wherein tumour cells tap into a neural ecosystem and exploit it for expansion, or as a hijacked memory system, wherein tumours control the neural circuitry responsible for neuroplasticity and synaptic integration, driving the system to support tumour growth? The niche model has considerable explanatory power; however, most of the recent literature supports the latter concept, namely that gliomas hijack the systems involved in neural development to gain access to, and integrate into, the brain's circuitry, thereby promoting their growth and spread.[2]

The neural niche model in gliomas can be generally described as the functions of endothelial cells, which transport oxygen and glucose, the provision of growth factors by astrocytes, and the secretion of immunosuppressive cytokines by reprogrammed microglia or macrophages, which lay the foundation of the glioma's functional ecosystem.[3] The niche concept embodies the inactive and compositional state of the TME components, such as cell types, signalling cascades, and stromal interactions that incur malignant sustenance. From anti-angiogenic therapies to approaches that modulate immune functions by targeting tumour-associated macrophages (TAMs) have been the sole strategies for targeting glioblastoma.[4]

The term niche fails to explain these phenomena at the circuit level. Glioma cells have been shown to both respond to and alter physiological neuronal activity through electrophysiological and imaging techniques. This suggests bidirectional communication between the tumour and host neurons. Tumours after the innate functioning of neural circuits actively take advantage of neuronal excitability to create an environment that is conducive to their growth.[5]

Correspondence to: Dr. Hafiz Muhammad Haseeb Khaliq, Department of Pathology, University of Health Sciences, Lahore, Pakistan
E-mail: haseebkhaliq119@gmail.com
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According to these results, brain tumours are no longer seen as passive inhabitants of a niche but rather as active participants in the brain's communication system.

The hijacking theory is strongly supported by the presence of synaptic connections between neurons and glial cells. Functional glutamate receptors of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type are used by glioma cells to directly receive excitatory synaptic signals from neurons.[6] These synapses promote calcium influx and cell depolarisation, which trigger proliferative signalling pathways in tumour cells. Additionally, tumour cells release brain-derived neurotrophic factor (BDNF) and neuroligin-3, which increase neuronal activity and create a feed-forward loop of excitation. Most gliomas can change chloride ion regulation, a feature unusual in mature neurons, thereby transforming gamma- aminobutyric acid (GABA)-ergic signalling into depolarising, tumour-supporting signals.[7] Activity-dependent strengthening, trophic feedback, and circuit remodelling are examples of synaptic plasticity that are altered rather than disrupted by these signalling changes. One important mechanism for tumour cell adaptability is their capacity to take over various neurotransmitter systems. As a result, gliomas promote malignancy by exploiting the cellular machinery underlying memory and learning.[8]

Neuronal coupling is just one aspect. Microglia and infiltrating macrophages, which are essential for synaptic pruning and homeostatic plasticity, are absent in the context of gliomas. Through special circuit remodelling, microglia strengthen patho-logical circuits in areas affected by gliomas.[9] Surprisingly, the same process that creates memory formation also creates a self-reinforcing system for tumour growth by influencing neurons and glial components. Moreover, in this pathological state, increased neuronal excitation and glial pruning translate to tumour persistence. Therefore, rather than being a static supportive niche, the glioma TME resembles a transformed memory network.[10]

Therapeutic measures should stop the flow of malignant information, in addition to focusing on the niche at the cellular level. For instance, targeting AMPA receptor signalling pathways or neuroligin-3 release has yielded encouraging outcomes.[11] Restoring microglial homeostasis through pharmacological or genetic means may also help to normalise anti-tumour immunity while lowering pathological circuit remodelling.[12] This

approach operates on the principle of dynamic modulation, disrupting tumour-built communication channels without compromising the physiological plasticity necessary for cognition. Since tumours have parasitised processes involved in memory development, this approach carries an inherent risk of collateral paralysis of learning, attention, and memory.[13]

As a result, accurate interventions are essential for the success of treatment. In addition to conventional oncological endpoints such as progression-free survival, clinical trial design should incorporate neurocognitive endpoints and biomarkers of circuit function. The goal is to preserve the cognitive capacities that define human identity, not merely prolong life.[14]

Human understanding of brain tumours has evolved, as evidenced by the dual concepts of the neural niche and the hijacked memory model. While the hijacking memory systems explain how gliomas integrate into neural circuits and co-opt the molecular machinery of memory, the niche framework offers insights into the components of the TME that support malignancy. These results imply that brain tumours are parasitic participants within the brain's communication networks rather than merely passive inhabitants. Overall, the most convincing framework for directing clinical innovation and scientific research is provided by the hijacked memory model.

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