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Personal View

Glioblastoma and brain connectivity: the need for a paradigm shift

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Summary

Despite substantial advances in cancer treatment, for patients with glioblastoma prognosis remains bleak. The emerging field of cancer neuroscience reveals intricate functional interplays between glioblastoma and the cellular architecture of the brain, encompassing neurons, glia, and vessels. New findings underscore the role of structural and functional connections within hierarchical networks, known as the connectome. These connections contribute to the location, spread, and recurrence of a glioblastoma, and a patient's overall survival, revealing a complex interplay between the tumour and the CNS. This mounting evidence prompts a paradigm shift, challenging the perception of glioblastomas as mere foreign bodies within the brain. Instead,

these tumours are intricately woven into the structural and functional fabric of the brain. This radical change in thinking holds profound implications for the understanding and treatment of glioblastomas, which could unveil new prognostic factors and surgical strategies and optimise radiotherapy. Additionally, a connectivity approach suggests that non-invasive brain stimulation could disrupt pathological neuron–glioma interactions within specific networks.

Introduction

Glioblastoma has a bleak prognosis, with a median overall survival of approximately 15 months after surgical diagnosis and a 5-year survival rate below 8%.1, 2, 3 Efforts to enhance prognosis are ongoing,[4] but progress to date has led to only marginal improvements in survival.[5] Although substantial improvements in survival rates have been achieved for other cancers,[6] the bleak trajectory of glioblastoma prompts a reconsideration of our approach to this disease. Traditionally, research has concentrated on the tumour itself, investigating molecular profiles, genetic mutations, histology,7, 8 and its microenvironment (including immunological infiltrates and radiomics).9, 10 This approach mirrors that of other cancers like lung, prostate, breast, and stomach tumours. However, a crucial aspect that is often overlooked is the unique organ host of a glioblastoma: the brain.

The novel field of cancer neuroscience11, 12 (panel 1) offers a paradigm shift by transitioning from an exclusive focus on the tumour to exploring the intricate interactions between a glioblastoma and the brain. This perspective spans from the synaptic level, at the microscale, to neural networks and their connectivity properties, at the macroscale. Contrary to viewing changes in synaptic activity and brain connectivity as mere consequences of the presence of a glioblastoma, this approach recognises them as pivotal contributors to carcinogenesis, influencing cancer growth and spread. This fundamental change towards a connectivity-based approach has the potential to revolutionise the understanding and management of glioblastoma, enhance prognosis, refine current treatments such as surgery and radiotherapy, and open avenues for novel treatment strategies.

A qualitative analogy is to envision the brain as a railway system, with the structural pathways representing the tracks and the functional interactions representing the amount of traffic on those tracks. This analogy emphasises communication through nodes and edges; however, studies published within the past 5 years have shown that activity propagates through dynamic waves across the connectome (the comprehensive map of white matter tracts and cortical functional connections).[17] Can understanding the structure and function of the brain shed new light on the pathophysiology of glioblastoma? A positive answer emerges from studies of neurodegenerative diseases and stroke. In several disorders characterised by the accumulation of misfolded proteins, pathology spreads through anatomical pathways and preferentially begins in specific functional networks, indicating a widespread involvement of the connectome.18, 19, 20 Similarly, even small stroke lesions can disrupt structural and functional brain connections widely, and these disruptions strongly correlate with neurological impairment and recovery of function.21, 22 Overall, these findings underscore the broader relevance of the connectome paradigm in understanding the pathophysiology across neurological disorders, possibly including glioblastoma.

Our Personal View aims to highlight key aspects of the relationship between brain connectivity and glioblastoma. We review notions on structural and functional connectivity, emphasising the role of this approach in comprehending pathophysiology. We also examine the clinical implications of this paradigm shift, considering its potential impact on personalised prognosis and the development of innovative treatments. The examination of brain connectivity will centre on the in-vivo characterisation of macroscale structural and functional pathways using MRI techniques, specifically diffusion MRI and functional MRI (fMRI).

Section snippets

Structural connectivity and cancer spreading

Structural connectivity, measured by use of diffusion tensor imaging (tractography), can be assessed before neurosurgery to identify eloquent white matter tracts passing through or around the tumour.[23] This information is uploaded onto intraoperative surgical navigation systems to help the neurosurgeon preserve specific functions linked with those tracts (eg, motor functions linked with corticospinal tract integrity, or linguistic abilities associated with the preservation of the arcuate…

Functional connectivity and carcinogenesis

Most resting-state fMRI studies of patients with brain tumours focus on a single network at a time (eg, language, default mode, or frontoparietal network), and have shown differences with healthy controls and correlations with the impairment of the corresponding functional domain (eg, language or attention).43, 44 To date, only a few studies have applied a whole brain multinetwork approach to studying brain tumours, which has shown that functional networks far away from a glioblastoma lesion…

Potential therapeutic approaches

Surgical approaches try to strike a balance between complete tumour removal and preservation of neurological function, often referred to as maximal safe resection. It has been proposed that, especially in patients with specific molecular profiles, the resection borders should extend beyond the edges of contrast-enhanced tissue.[69] Connectivity measures could offer surgeons reliable prognostic indexes before surgery. Nowadays, connectivity measures such as diffusion tensor imaging are used to…

Conclusions and future directions

A dynamic, bidirectional interplay unfolds between cancer cells and neurons, challenging the notion that glioblastoma merely resides passively in the brain. Instead, the tumour actively engages with both the structural and functional organisation of the brain. Delving into the intricacies of this structural and functional connectivity will unveil a deeper understanding of glioblastoma and enhance prognosis. The reliability of connectivity-derived measures as prognostic factors has been robustly …

Declaration of interests

AS, LP, and MC report a patent pending (102022000015360; PCT IB2023/057357) for the method to compute the tract density index *("Un nuovo indice prognostico di sopravvivenza nel glioblastoma multiforme basato sulle alterazioni delle connessioni della sostanza bianca cerebrale misurato con tecniche di diffusione RM"*). AB declares no competing interests.…

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