scientific reports

Check for updates

OPEN

EDITORIAL

Cancer neuroscience: illuminating the neural dimension of tumor biology

Saurabh Agarwal

The nervous system plays a dynamic and active role in cancer progression, influencing tumor growth, invasion, metastasis, and response to therapy. Neural components within the tumor microenvironment communicate with cancer cells through neurotransmitters, neurotrophic factors, and electrical signaling, whereas tumors reciprocally remodel surrounding neural circuits. This Scientific Reports Collection on Cancer Neuroscience highlights recent advances uncovering these complex interactions across molecular, cellular, and systems levels. The featured studies investigate mitochondrial and metabolic modulation in glioblastoma, neural regulatory pathways driving tumor invasiveness, and functional neuroimaging correlates of cognitive outcomes in glioma survivors. Together, these publications illustrate how integrating neuroscience with oncology offers new mechanistic insight and therapeutic opportunities. By illuminating the neural dimension of tumor biology, this Collection aims to inspire interdisciplinary approaches to decipher and therapeutically target the bidirectional crosstalk between the nervous system and cancer.

The nervous system is increasingly recognized as a critical component of cancer biology rather than a passive bystander. The Cancer Neuroscience Collection in Scientific Reports was designed to highlight the emerging convergence between neuroscience and oncology, two disciplines that have, until recently, evolved largely in parallel. The studies assembled here explore how neural elements shape tumor initiation, progression, and therapeutic response, as well as how tumors reciprocally influence neural health and function. Collectively, these contributions provide a foundation for understanding the evolving landscape of this multidisciplinary field and for defining the future challenges and opportunities.

Cancer cells interact continuously with their surrounding microenvironment, which includes vascular, immune, and stromal components. The addition of the nervous system introduces a new layer of biological and therapeutic complexity. Peripheral and central nerves can modulate tumor behavior through neurotransmitters, neurotrophic factors, and synaptic-like signaling, whereas tumors can promote axonogenesis and neural remodeling to create a microenvironment conducive to growth and metastasis. This reciprocal communication, now broadly referred to as cancer neuroscience, has become an area of increasing interest. Mechanistic studies have shown that neuronal activity can drive proliferation and invasion through noradrenergic, cholinergic, and glutamatergic pathways, whereas immune-neural signaling loops modulate inflammation and immune evasion[1]. Neural influences are now recognized across diverse malignancies, including glioma, pancreatic, prostate, and breast cancers[2]. Together, these findings position the nervous system as both a driver and a promising therapeutic target in oncology.

Collection overview

The studies published in this Collection collectively illustrate the expanding scope of cancer neuroscience, where neural systems, tumor metabolism, and molecular signaling intersect to influence cancer behavior and therapeutic outcomes.

Diagnostic and molecular insights

Lebrun et al. evaluated DNA methylation-based classification in adult and pediatric CNS tumors, revealing its superior diagnostic precision and particular value in complex pediatric cases[3]. Their findings reinforce the importance of integrating molecular neuropathology and machine-learning classifiers in refining tumor diagnosis and therapeutic planning.

Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, New York, NY 11439, USA. email: agarwals@stjohns.edu

Löding et al. advanced the concept of liquid biopsy for brain tumors, showing that distinct metabolic profiles precede glioma diagnosis by years. Longitudinal plasma metabolomics revealed early increases in TCA cycle intermediates (fumarate, malate, and pyruvate) and amino acid catabolites, detectable up to eight years before diagnosis[4]. These results highlight the potential of metabolic biomarkers for early detection and disease monitoring in glioma.

DNA methylation, metabolomic, and neuroimaging approaches can refine diagnostic precision and patient stratification in brain cancer to improve patient outcomes. These works highlight a growing shift toward systems-level biomarkers that integrate molecular, metabolic, and connectomic data to detect and monitor neural–tumor interplay.

Tumor-neural crosstalk and mechanistic pathways

Marshall et al. demonstrated that cell-penetrating peptide-mediated mitochondrial transplantation amplifies radiation-induced reactive oxygen species in glioblastoma (GBM) models, enhancing cytotoxicity and potentially overcoming radio-resistance through metabolic augmentation[5]. This innovative approach exemplifies how manipulating mitochondrial dynamics can enhance the efficacy of radiotherapy in tumors that are resistant to treatment.

Wu et al. identified *SLCO4A1-AS1*, a super-enhancer-driven long noncoding RNA, as a biomarker and potential therapeutic target in GBM. Elevated expression correlated with the mesenchymal and classical subtypes, linking enhancer regulation, transcriptional plasticity, and tumor aggressiveness. Functionally, its knockdown suppressed proliferation and invasiveness, underscoring the therapeutic potential of targeting lncRNA-super-enhancer networks in neuro-oncology[6].

In pediatric cancer, Sönmez et al. uncovered that MAP4 kinase-mediated repression of the neural adhesion molecule CLSTN1 (calsyntenin-1) promotes medulloblastoma invasiveness[7]. Their work connects MAP4K signaling and neuronal adhesion to tumor-microenvironment interactions, revealing how neural molecular machinery is hijacked to enable tumor spread.

These studies highlight converging molecular phenomena that define cancer neuroscience and demonstrate how neurotransmitter signaling, cell adhesion molecules, and mitochondrial processes collectively shape proliferation, invasion, and radioresistance.

Translational and therapeutic innovation

De Roeck et al. investigated functional connectome alterations in glioma survivors, demonstrating that the disruption of bilateral putamen hubs correlates with diminished cognitive performance and attention, suggesting persistent network-level consequences of tumor growth and treatment[8]. This study bridges the fields of neuroimaging and cognitive neuroscience, emphasizing the need to assess neural network integrity as both a clinical endpoint and a therapeutic target.

Taken together, the studies in this Collection reveal how cancer neuroscience spans molecular, metabolic, and systems-level phenomena, from mitochondrial energetics and enhancer regulation to neural adhesion and network reorganization. They define a transdisciplinary landscape where understanding neural-tumor communication is central to developing next-generation diagnostics and therapeutics. Despite these advances, critical gaps remain in modeling the dynamic neural-tumor interface and translating mechanistic findings into clinical interventions. Future efforts must integrate multi-omics, functional neuroimaging, and in vivo neural-tumor models to unravel the causal mechanisms underlying this complex biological interplay.

Future perspectives

Translational innovation and therapeutics safety

Cancer neuroscience is entering an era of integration and mechanistic exploration, which requires defining how neural activity influences tumor growth, immune modulation, and metastasis[9]. Repurposing neuroactive drugs such as β-adrenergic antagonists or muscarinic inhibitors may dampen pro-tumorigenic neural signaling, whereas non-invasive neuromodulation could one day reshape the tumor microenvironment. However, rigorous preclinical validation and safety profiling remain essential to ensure specificity and avoid neurotoxicity[10]. Importantly, cancer neuroscience research now extends beyond central nervous system tumors to include peripheral malignancies, where sympathetic and parasympathetic fibers regulate tumorigenic signaling[1,2]. Exploring these networks, particularly their interaction with immune and stromal components, represents a major opportunity for discovery.

Mult-omics and neural biomarker integration

Neural biomarkers derived from multimodal imaging, electrophysiology, and circulating neurotrophic factors are critical for advancing personalized cancer neuroscience. These tools enable precise patient stratification and real-time monitoring of neural-tumor communication, fostering more efficient and tailored therapeutic strategies[11]. Next-generation technologies, such as spatial transcriptomics and connectomics, are poised to map the molecular architecture of tumor innervation. Longitudinal imaging and single-cell analyses will reveal how neural circuits remodel in response to therapy[12,13], linking molecular perturbations to network-level outcomes.

Next-generation tools and neuroengineering models

The integration of emerging technologies, such as artificial intelligence and CRISPR-based gene editing, is transforming experimental capabilities. AI facilitates the integration of complex datasets from imaging, spatial transcriptomics, and electrophysiology to decode neural-tumor interactions and identify predictive biomarkers. CRISPR enables the precise manipulation of genes in neural and tumor cells, unraveling causal pathways and validating therapeutic targets, particularly in CNS cancers such as gliomas. Combining these approaches with

spatial profiling will enhance our understanding of the neuron-glia-cancer interplay and neuroimmune crosstalk, which is crucial for developing personalized interventions[14]. Advances in microfluidic brain-on-chip systems and bioengineered innervated organoids now allow high-fidelity modeling of bidirectional tumor-neuron communication, incorporating electrical activity and synaptic feedback. When combined with AI analytics and CRISPR perturbations, these systems can provide dynamic testbeds for therapeutics, bridging bench-to-bedside translation with predictive modeling[15].

Infrastructure and collaboration

To catalyze progress, the field requires the development of shared infrastructure such as standardized co-culture models, interoperable data repositories, and multidisciplinary training programs. Collaborative frameworks that integrate neuroscience, oncology, and immunology are crucial for addressing neurobiological complexity and accelerating the discovery and translation of new insights (Fig. 1).

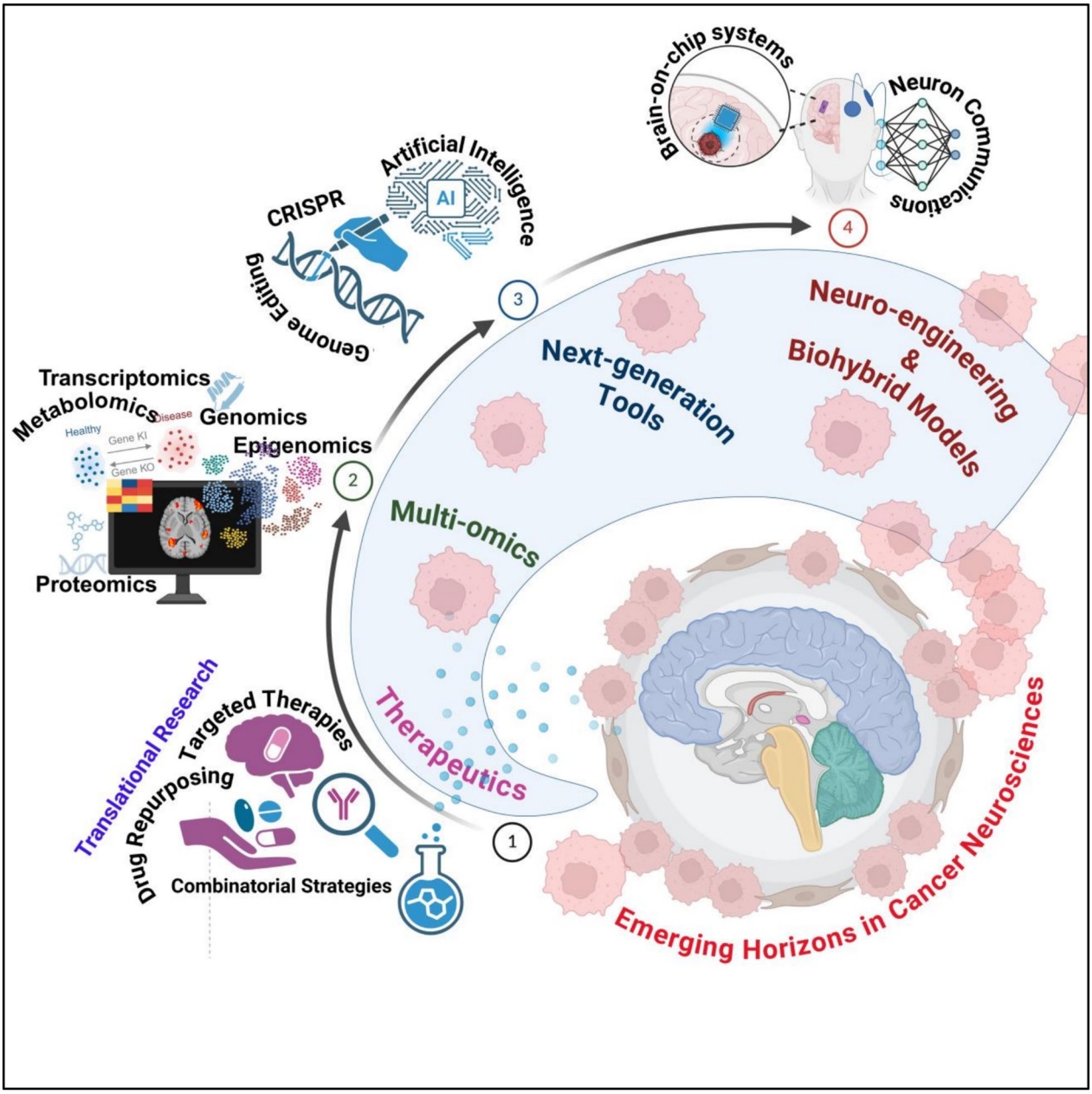

Fig. 1. Emerging horizons in cancer neurosciences.

Conclusions

In summary, the Cancer Neuroscience Collection captures a rapidly evolving research landscape. By illustrating how neural circuits, metabolic pathways, regulatory networks, and patient-level functional outcomes intersect, these studies define the neural dimension of cancer biology. They advocate for an integrated research paradigm, in which understanding and ultimately modulating neural-tumor interactions become central to the development of next-generation therapies. The nervous system remains an untapped frontier in oncology, and advancing cancer neuroscience will require the same qualities that have fueled its emergence thus far: curiosity, collaboration, and rigor.

Published online: 24 December 2025

References

1. Pu, T. et al. Neuro-immune crosstalk in cancer: mechanisms and therapeutic implications. *Signal Transduct. Target Ther.* **10**(1), 176 (2025).
2. Huang, Q. et al. Neuroscience of cancer: unraveling the complex interplay between the nervous system, the tumor and the tumor immune microenvironment. *Mol. Cancer* **24**(1), 24 (2025).
3. Lebrun, L. et al. Diagnostic impact of DNA methylation classification in adult and pediatric CNS tumors. *Sci. Rep.* **15**(1), 2857 (2025).
4. Loding, S. et al. Blood based metabolic markers of glioma from pre-diagnosis to surgery. *Sci. Rep.* **14**(1), 20680 (2024).
5. Marshall, K. L. et al. Enhancing radiation-induced reactive oxygen species generation through mitochondrial transplantation in human glioblastoma. *Sci. Rep.* **15**(1), 7618 (2025).
6. Wu, Y. et al. Super-enhancer-driven SLCO4A1-AS1 is a new biomarker and a promising therapeutic target in glioblastoma. *Sci. Rep.* **15**(1), 954 (2025).
7. Sonmez, E. et al. MAP4 kinase-regulated reduced CLSTN1 expression in medulloblastoma is associated with increased invasiveness. *Sci. Rep.* **15**(1), 946 (2025).
8. De Roeck, L. et al. Brain network topology and its cognitive impact in adult glioma survivors. *Sci. Rep.* **14**(1), 12782 (2024).
9. Huang, S. et al. Cancer-nervous system crosstalk: from biological mechanism to therapeutic opportunities. *Mol. Cancer* **24**(1), 133 (2025).
10. Winkler, F. et al. Cancer neuroscience: State of the field, emerging directions. *Cell* **186**(8), 1689–1707 (2023).
11. Liu, J. et al. Advances in multimodal imaging techniques for evaluating and predicting the efficacy of immunotherapy for NSCLC. *Cancer Manag. Res.* **17**, 1073–1086 (2025).
12. Serban, M., Toader, C. & Covache-Busuioc, R. A. Brain tumors, AI and psychiatry: predicting tumor-associated psychiatric syndromes with machine learning and biomarkers. *Int. J. Mol. Sci.* **26**(17) (2025).
13. Yang, Y. et al. Spatial transcriptomics analysis identifies therapeutic targets in diffuse high-grade gliomas. *Front. Mol. Neurosci.* **17**, 1466302 (2024).
14. Bhat, A. A. et al. Integration of CRISPR/Cas9 with artificial intelligence for improved cancer therapeutics. *J. Transl. Med.* **20**(1), 534 (2022).
15. Ishahak, M. et al. Genetically engineered brain organoids recapitulate spatial and developmental states of glioblastoma progression. *Adv. Sci. (Weinh)* **12**(10), e2410110 (2025).

Declarations

Competing interests

The author declares no competing interests. The author served as Guest Editor for this Scientific Reports Collection.

Correspondence and requests for materials should be addressed to S.A.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2025