ScienceDirect

Cancer Letters

Volume 612, 1 March 2025, 217492

Emerging neuroimmune mechanisms in cancer neuroscience

Yingying Huang [a 1], Xin Zhou [a b 1], Jiaqi Liu [a 1], Ying Cao [a], Wei Fu [a b], Jing Yang [a c]

[a] School of Life Sciences, Peking University Third Hospital Cancer Center, Center for Life Sciences, State Key Laboratory of Membrane Biology, IDG/McGovern Institute for Brain Research, Peking University, Beijing, 100871, China

[b] Department of General Surgery, Peking University Third Hospital, Beijing, 100191, China

[c] Peking Union Medical College Hospital, Beijing, 100730, China

Received 21 December 2024, Revised 11 January 2025, Accepted 20 January 2025, Available online 21 January 2025, Version of Record 24 January 2025.

What do these dates mean?

Check for updates

Show less

Share Cite

https://doi.org/10.1016/j.canlet.2025.217492 ↗

Get rights and content ↗

Highlights

- Cancer neuroscience explores how neural signals influence tumor prognosis.
- Neuroimmune mechanisms represent a key aspect of cancer neuroscience.
- Research promises better therapeutic strategies for cancers and related complications.

Abstract

It has become increasingly recognized that neural signals can profoundly influence the prognosis of various cancer types. In the past years, we have witnessed “cancer neuroscience,” which primarily focuses on the complex crosstalk between tumors and neural signals, emerging as a new, multidisciplinary direction of biomedical science. This review aims to summarize the current knowledge of this research frontier, with an emphasis on the neuroimmune mechanisms enacted through the reciprocal interactions between tumors and the central or peripheral nervous system. In addition, we wish to highlight several key questions of cancer neuroscience and its neuroimmune action that warrant future research and translational efforts, including novel strategies for manipulating neural signals for antitumor immunotherapies, as well as managing cancer-related neurological or psychiatric complications.

Section snippets

A brief overview of neuroimmunology

For laying a foundation of detailed discussions in the context of cancers, we briefly outline the key principles of neuroimmunology, which can be generally categorized into two parts, i.e., neuroimmune mechanisms in the central nervous system or in peripheral organs.

(1) Neuroimmunology of the central nervous system (CNS). Maintenance of the CNS functions and homeostasis is facilitated by several immune barriers, including the blood-brain barrier (BBB), the blood-cerebrospinal fluid (CSF) barrier, …

…

Cancer neuroscience in the CNS

As discussed above, the BBB and other barrier structures effectively separate the CNS from peripheral immune cells and their derived factors. As a result, the immune microenvironment of tumors, either primary or metastatic, residing within the CNS may markedly differ from that of peripheral solid tumors [5,24]. In this section, we will highlight key advances in the knowledge of cancer neuroscience in the CNS, with a focus on gliomas.

Gliomas, which arise from the progenitor cells of astrocytes …

Cancer neuroscience in peripheral solid tumors

In contrast to the scenario of the CNS, cancer neuroscience in peripheral solid tumors involves neural innervations of sensory, sympathetic, or parasympathetic origin [[53], [54], [55]]. For the purpose of this review, we primarily discuss the involvement of the autonomic nervous system, i.e., sympathetic or parasympathetic innervations, that have been a research focus of the field.

We note that the potential neuroimmune function of sensory signals in peripheral cancers is emerging, to which …

Future perspectives

Cancer neuroscience has gained broad attention in recent years, reflecting the shared interests and combined efforts of neuro-oncology, neurobiology, and neuroimmunology. Of particular importance, scientific achievements in this emerging multidisciplinary field have promoted the development of novel diagnostic or therapeutic strategies against tumors within the CNS or in peripheral organs. Despite those exciting advances, cancer neuroscience still remains at its nascent stage, with the ongoing …

CRediT authorship contribution statement

Yingying Huang: Writing – review & editing, Writing – original draft, Investigation. **Xin Zhou:** Writing – review & editing, Writing – original draft, Investigation. **Jiaqi Liu:** Writing – original draft, Investigation. **Ying Cao:** Writing – original draft, Investigation. **Wei Fu:** Writing – review & editing, Writing – original draft. **Jing Yang:** Writing – review & editing, Writing – original draft. …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

Acknowledgments

We apologize for omitting many important references due to space limitations. This work has been funded by the National Key Research and Development Program of China (#2023YFA1801901 to J.Y.), the National Natural Science Foundation of China (#32125017, #32150008, and #82441057to J.Y.; #82273104 to W.F.), the Beijing Nova Program (#20230484485 to X.Z.), and the Beijing Natural Science Foundation (#7232086, #L244055, and #Z240013 to J.Y.). …

Special issue articles Recommended articles

References (125)

C. Swanton
Embracing cancer complexity: hallmarks of systemic disease
Cell (2024)

D. Hanahan *et al.*
Cancer hallmarks intersect with neuroscience in the tumor microenvironment
Cancer Cell (2023)

F. Winkler
Cancer neuroscience: state of the field, emerging directions
Cell (2023)

P.H. Black
Stress and the inflammatory response: a review of neurogenic inflammation
Brain Behav. Immun. (2002)

L. Ampie *et al.*
Immunological defense of CNS barriers against infections
Immunity (2022)

M.V. Russo *et al.*
Immune surveillance of the CNS following infection and injury
Trends Immunol. (2015)

Humsa S. Venkatesh
Neuronal activity promotes glioma growth through neuroligin-3 secretion
Cell (2015)

M. Lad
Glioblastoma induces the recruitment and differentiation of dendritic-like "hybrid" neutrophils from skull bone marrow
Cancer Cell (2024)

R.R. Maas
The local microenvironment drives activation of neutrophils in human brain tumors
Cell (2023)

J. Zhao
Disease-specific suppressive granulocytes participate in glioma progression
Cell Rep. (2024)

D.H. Gutmann *et al.*
Microglia/brain macrophages as central drivers of brain tumor pathobiology
Neuron (2019)

J. Lu
Suppressive immune microenvironment and CART therapy for glioblastoma: future prospects and challenges
Cancer Lett. (2024)

L.J. Weisbrod

Diffuse intrinsic pontine glioma (DIPG): a review of current and emerging treatment strategies
Cancer Lett. (2024)

A.R. Mekapogu
HGF/c-Met pathway inhibition combined with chemotherapy increases cytotoxic T-cell infiltration and inhibits pancreatic tumour growth and metastasis
Cancer Lett. (2023)

L. Wang
Crosstalk between the nervous system and tumor microenvironment: functional aspects and potential therapeutic strategies
Cancer Lett. (2024)

H.D. Reavis *et al.*
Tumor innervation: cancer has some nerve
Trends Cancer (2020)

H.B. Huan
Sympathetic nervous system promotes hepatocarcinogenesis by modulating inflammation through activation of alpha1-adrenergic receptors of Kupffer cells
Brain Behav. Immun. (2017)

M.B. Nilsson
Stress hormones regulate interleukin-6 expression by human ovarian carcinoma cells through a Src-dependent mechanism
J. Biol. Chem. (2007)

E.V. Yang
Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression
Brain Behav. Immun. (2009)

Y. Xia
Catecholamines contribute to the neovascularization of lung cancer via tumor-associated macrophages
Brain Behav. Immun. (2019)

E. de la Torre
Proliferative actions of muscarinic receptors expressed in macrophages derived from normal and tumor bearing mice
Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. (2008)

S.R. Zanetti
Expression and functional role of α7 nicotinic receptor in human cytokine-stimulated natural killer (NK) cells

J. Biol. Chem. (2016)

J.C. Zimring
Regulation of CD8+ cytolytic T lymphocyte differentiation by a cholinergic pathway
J. Neuroimmunol. (2005)

S.L. Prescott *et al.*
Internal senses of the vagus nerve
Neuron (2022)

A. Rutledge
Spinal cord injuries and nerve dependence in prostate cancer
Trends in cancer (2017)

Y. Liu
The intersection of the nervous system and breast cancer
Cancer Lett. (2024)

H.M. Wang
Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy
Ann. Oncol. (2013)

M.S. Oh
The impact of beta blockers on survival outcomes in patients with non-small-cell lung cancer treated with immune checkpoint inhibitors
Clin. Lung Cancer (2021)

D. Hanahan
Hallmarks of cancer: new dimensions
Cancer Discov. (2022)

A.H. Zahalka *et al.*
Nerves in cancer
Nat. Rev. Cancer (2020)

H.H. Young
ON the presence of nerves in tumors and of other structures in them as revealed by a modification of EHRLICH'S method of "vital staining" with methylene blue
J. Exp. Med. (1897)

M. Steinhoff
Modern aspects of cutaneous neurogenic inflammation
Arch. Dermatol. (2003)

J. Kipnis *et al.*
Neuroimmunology in 2017: the central nervous system: privileged by immune

connections
Nat. Rev. Immunol. (2018)

D.F. Finn *et al.*
Twenty-first century mast cell stabilizers
Br. J. Pharmacol. (2013)

L.M. Coussens *et al.*
Inflammation and cancer
Nature (2002)

J. Fares
Molecular principles of metastasis: a hallmark of cancer revisited
Signal Transduct. Targeted Ther. (2020)

H. Zhao
Inflammation and tumor progression: signaling pathways and targeted intervention
Signal Transduct. Targeted Ther. (2021)

D. Wu
The blood–brain barrier: structure, regulation and drug delivery
Signal Transduct. Targeted Ther. (2023)

M. Prinz
Microglia and central nervous system–associated macrophages—from origin to disease modulation
Annu. Rev. Immunol. (2021)

A.S. Papadopoulos *et al.*
Hypothalamic–pituitary–adrenal axis dysfunction in chronic fatigue syndrome
Nat. Rev. Endocrinol. (2012)

E. Carbone
Chromaffin cells of the adrenal medulla: physiology, pharmacology, and disease
Compr. Physiol. (2019)

X. Ding
Panicle-shaped sympathetic architecture in the spleen parenchyma modulates antibacterial innate immunity
Cell Rep. (2019)

Y. Cao *et al.*
Neuroanatomy of lymphoid organs: lessons learned from whole-tissue imaging studies
Eur. J. Immunol. (2023)

S. Moriyama

β(2)-adrenergic receptor-mediated negative regulation of group 2 innate lymphoid cell responses
Science (2018)

T. Liu
Local sympathetic innervations modulate the lung innate immune responses
Sci. Adv. (2020)

R. Mancusi *et al.*
The neuroscience of cancer
Nature (2023)

L.R. Schaff *et al.*
Glioblastoma and other primary brain malignancies in adults: a review
JAMA (2023)

Q.T. Ostrom
The epidemiology of glioma in adults: a "state of the science" review
Neuro Oncol. (2014)

H.S. Venkatesh
Electrical and synaptic integration of glioma into neural circuits
Nature (2019)

V. Venkataramani
Glutamatergic synaptic input to glioma cells drives brain tumour progression
Nature (2019)

There are more references available in the full text version of this article.

Cited by (0)

1 Authors Contributed Equally.

View full text