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Cancer neuroscience: Mechanistic advances in neural infiltration, circuit remodeling, and tumor microenvironment modulation

Regina Omodolapo Oluwaniyi [1, *], Ann Christopher Francis [2], Iyiola Aanuoluwa Temitayo [3], Chinedu Joseph Eze [4], Hajarah Oyindamola Abdulraheem [5], Obianujunwa Mercy Ubah [6] and Tobiloba Philip Olatokun [7]

[1] *Department of Medical Laboratory Science, Lead City University, Ibadan, Nigeria.*
[2] *Department of Biotechnology, University of Texas Health Sciences Center at Tyler, USA.*
[3] *Department of Biochemistry, Federal University of Technology, Minna, Nigeria.*
[4] *Department of Human Physiology, Federal University Lokoja, Nigeria.*
[5] *Department of College of Medicine, Lagos State University, Ojo, Lagos, Nigeria.*
[6] *Department of Histopathology, National Hospital Abuja, Nigeria.*
[7] *Department of Internal Medicine (Consulting group), Obafemi Awolowo University Health center, Ile-Ife, Osun, Nigeria.*

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Abstract

The intricate interplay between tumors and the nervous system has emerged as a transformative frontier in oncology, redefining our understanding of cancer progression and unveiling novel therapeutic horizons. This review synthesizes cutting-edge advances in cancer neuroscience, illuminating how tumor–neuron interactions drive malignancy across cancers such as glioblastoma, pancreatic ductal adenocarcinoma, prostate, and breast cancer. Tumors actively recruit peripheral and autonomic nerves through neurotrophic signaling, fostering perineural invasion and establishing feedback loops that amplify tumor growth and metastasis. Gliomas, in particular, form synapse-like structures with neurons, harnessing glutamatergic signaling to enhance proliferation and invasion, while neural modulation of the immune microenvironment promotes immunosuppression, shielding tumors from immune surveillance. Neural signaling further sustains cancer stem cell niches, fueling tumor dormancy and recurrence. Innovative therapeutic strategies, including surgical denervation, pharmacological inhibitors like β-blockers and AMPA receptor antagonists, and CRISPR-based gene silencing, show promise in disrupting these neural-driven mechanisms, with combination therapies enhancing the efficacy of immunotherapy and chemotherapy. Advanced tools, such as spatial transcriptomics, single-cell RNA sequencing, optogenetics, and electrophysiology, have unraveled the molecular and functional dynamics of tumor–neuron crosstalk, paving the way for precision oncology. Despite these breakthroughs, challenges like tumor heterogeneity, neurotoxicity, and technological barriers underscore the need for targeted delivery systems and robust clinical trials. By bridging neuroscience and oncology, this review highlights the transformative potential of targeting tumor–neuron interactions to improve patient outcomes, offering a compelling vision for future research and clinical innovation in the fight against neurologically active cancers.

Keywords: Cancer Neuroscience; Tumor–Neuron Interactions; Perineural Invasion; Glutamatergic Signaling; Neural Circuit Remodeling; Immunosuppression; Cancer Stem Cells; Synaptic Therapies

1. Introduction

Cancer neuroscience has emerged as a transformative interdisciplinary field, revealing the intricate interplay between the nervous system and cancer progression. Far from being passive bystanders, neural elements actively influence tumor growth, metastasis, immune evasion, and therapeutic resistance through mechanisms such as tumor-induced

* Corresponding author: Regina Omodolapo Oluwaniyi; Email: reginadolipee2@gmail.com

neurogenesis, synapse-like signaling, and neural circuit remodeling. This review synthesizes recent advances in understanding these tumor–neuron interactions, explores their impact on the tumor microenvironment, and evaluates novel therapeutic strategies targeting neural pathways, emphasizing their potential synergy with conventional treatments. By integrating insights from neuroscience and oncology, we aim to highlight opportunities for innovative therapies and address critical research gaps to improve patient outcomes.

1.1. Overview of Cancer Neuroscience

Cancer neuroscience represents a burgeoning field that investigates the dynamic, bidirectional interactions between the nervous system and malignant tumors, fundamentally reshaping our understanding of cancer biology. According to Monje et al. [1], tumors such as gliomas and pancreatic adenocarcinomas co-opt neural elements to enhance their proliferation, invasion, and immune evasion, challenging the traditional view of tumors as neurologically inert entities [1]. This paradigm shift has revealed that cancer cells not only respond to neural signals but also actively remodel neural circuits, creating a microenvironment conducive to malignancy. For instance, studies have demonstrated that tumors secrete neurotrophic factors like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which promote neural infiltration and support tumor growth [2]. The field's rapid growth is evidenced by a nearly twentyfold increase in publications co-mentioning "cancer" and "neuroscience" from the early 2000s to the 2020s, underscoring its clinical and scientific significance [3].

The scope of cancer neuroscience extends beyond primary brain tumors to include cancers of epithelial origin, such as prostate, pancreatic, and gastric tumors, where neural infiltration is a hallmark of aggressive disease. Findings from Magnon et al. [4] indicate that autonomic nerves, including sympathetic and parasympathetic branches, play distinct roles in tumor initiation and metastasis, respectively. For example, in prostate cancer, sympathetic innervation drives early tumor development, while parasympathetic signaling facilitates metastatic spread [4]. These neural influences are mediated through neurotransmitters like norepinephrine and acetylcholine, which activate oncogenic signaling pathways such as cAMP-PKA and Wnt/β-catenin [5]. Moreover, neural signaling modulates the tumor immune microenvironment, promoting immunosuppression and therapeutic resistance, as shown in studies linking stress-induced adrenergic signaling to reduced T cell activity [6]. This complex interplay positions cancer neuroscience as a critical frontier for understanding tumor biology holistically.

The integration of neuroscience into oncology has also unveiled novel therapeutic opportunities. In a landmark study by Venkataramani et al. [7], glioma cells were shown to form functional glutamatergic synapses with neurons, enabling tumors to hijack neural circuits for proliferation. Such findings have spurred investigations into neural-targeted therapies, including surgical denervation, pharmacological blockade of β-adrenergic receptors, and inhibition of synaptic pathways [8]. These strategies show promise in preclinical models, with β-blockers like propranolol improving survival in breast and prostate cancers by mitigating neural-driven immunosuppression [9]. As cancer neuroscience continues to evolve, it offers a framework to decode the neural circuitry of cancer, paving the way for innovative treatments that could transform clinical management and patient outcomes.

The interdisciplinary nature of cancer neuroscience necessitates collaboration across neurobiology, oncology, and immunology to fully elucidate its mechanisms and therapeutic potential. Recent advances in technologies like spatial transcriptomics enable precise mapping of tumor–neuron interactions, revealing spatial gradients of gene expression that drive malignancy [10]. However, challenges remain, including the need for standardized protocols and ethical considerations in neural-targeted interventions. By synthesizing these insights, this review aims to provide a comprehensive foundation for understanding cancer neuroscience and its implications for personalized oncology.

1.2. Historical Context

Historically, neuroscience and oncology developed as distinct disciplines, creating a research gap that obscured the nervous system's role in cancer biology. Neuroscience focused on the structure and function of the nervous system, while oncology concentrated on carcinogenesis, tumor pathology, and treatment development, rarely considering neural influences beyond chemotherapy-induced neurotoxicity [11]. According to Hanahan and Weinberg [12], early cancer research emphasized cellular and molecular hallmarks like sustained proliferation and angiogenesis, with little attention to neural contributions [12]. This disciplinary divide delayed recognition of phenomena like perineural invasion (PNI), a common feature in pancreatic and head and neck cancers, where tumor cells invade nerve sheaths to facilitate spread [13]. The oversight was particularly pronounced for non-neuronal tumors, as brain tumors were the primary focus of neuro-oncological studies until the early 2010s.

A pivotal shift occurred with studies in the early 2010s that systematically documented neural infiltration in non-neuronal tumors. In a classic study by Magnon et al. [4], sympathetic and parasympathetic innervation was shown to be essential for prostate cancer progression, with surgical denervation reducing tumor incidence in mouse models [4]. This work challenged the assumption that neural elements were merely passive components of the tumor microenvironment and sparked a re-examination of neural roles across cancer types. Similarly, Ayala et al. [14] highlighted PNI as a prognostic factor in prostate cancer, correlating nerve density with higher Gleason scores and worse outcomes. These findings prompted researchers to investigate neural signaling in other cancers, such as pancreatic ductal adenocarcinoma (PDAC), where PNI occurs in 70–100% of cases and contributes to pain and recurrence [15].

The convergence of neuroscience and oncology was further catalyzed by discoveries of synapse-like communication in tumors. Venkataramani et al. [7] provided compelling evidence that glioma cells form functional glutamatergic synapses with neurons, integrating into neural circuits to promote proliferation. This breakthrough expanded the scope of cancer neuroscience, revealing that tumors actively exploit neural mechanisms to enhance malignancy. Concurrently, studies like Cole and Sood [6] linked stress-induced adrenergic signaling to tumor progression, demonstrating that norepinephrine activates β-adrenergic receptors to drive angiogenesis and immune evasion. These insights underscored the need to bridge the historical gap between disciplines, fostering an integrative approach to cancer research.

The historical separation of neuroscience and oncology has thus given way to a unified field that recognizes the nervous system as a dynamic participant in cancer biology. As noted by Sloan et al. [16], neural signaling influences multiple cancer hallmarks, from invasion to immune modulation, necessitating a reevaluation of therapeutic strategies. The growing recognition of these interactions has spurred interdisciplinary collaborations, leveraging tools like electrophysiology and spatial transcriptomics to unravel tumor–neuron dynamics [10]. This historical context highlights the urgency of synthesizing neural mechanisms in cancer to inform novel treatments and improve patient outcomes. To provide a chronological overview of the pivotal discoveries that bridged neuroscience and oncology, Table 1 summarizes key historical milestones in cancer neuroscience, highlighting the evolution from early observations to modern integrative studies.

Table 1 Key Historical Milestones in Cancer Neuroscience

Year	Milestone/Discovery	Key Researchers /Study	Cancer Type(s) Involved	Impact/Significance	Reference
Early 2000s	Recognition of perineural invasion (PNI) as a prognostic factor in non-neuronal tumors	Ayala et al.	Prostate, pancreatic	Established neural infiltration as a marker of aggressive disease, correlating with higher Gleason scores	[14]
2009	Review of PNI literature emphasizing its role in cancer spread	Liebig et al.	Pancreatic, head and neck	Highlighted PNI as a common mechanism for local invasion and metastasis	[13]
2010	Sympathetic nervous system induces metastatic switch in breast cancer	Sloan et al.	Breast	Demonstrated stress-induced adrenergic signaling promotes metastasis via β-adrenergic receptors	[16]
2011	Hallmarks of cancer updated, but neural contributions overlooked	Hanahan & Weinberg	General	Underscored historical gap in recognizing neural roles in cancer hallmarks like invasion and angiogenesis	[12]
2011	β-blockers associated with reduced breast cancer mortality	Barron et al.	Breast	Provided early evidence for neural-targeted therapies improving survival	[9]
2012	Molecular pathways linking β-adrenergic signaling to cancer progression	Cole & Sood	General	Linked stress hormones like norepinephrine to tumor growth and immune evasion	[6]

2013	Autonomic nerve development contributes to prostate cancer progression	Magnon et al.	Prostate	Showed sympathetic nerves drive initiation, parasympathetic drive metastasis; denervation reduces incidence	[4]
2014	Denervation suppresses gastric tumorigenesis	Zhao et al.	Gastric	Vagotomy reduces tumor incidence via disrupted cholinergic signaling	[5]
2014	ProNGF correlates with Gleason score and drives nerve infiltration in prostate cancer	Pundavela et al.	Prostate	Identified neurotrophic factors like proNGF as drivers of axonogenesis	[2]
2015	Neuronal activity promotes glioma growth through neuroligin-3 secretion	Venkatesh et al.	Glioma	Revealed synapse-like communication via synaptic proteins	[18]
2015	Sympathetic nervous system regulation of the tumor microenvironment	Cole et al.	General	Detailed how norepinephrine modulates MDSCs and immunosuppression	[19]
2017	Nerve growth factor promotes gastric tumorigenesis through cholinergic signaling	Hayakawa et al.	Gastric	Linked vagal nerve signaling to Wnt/β-catenin activation	[20]
2018	β2 adrenergic-neurotrophin feedforward loop promotes pancreatic cancer	Renz et al.	Pancreatic	Identified feedback loops involving BDNF and norepinephrine	[24]
2019	Glutamatergic synaptic input drives brain tumor progression	Venkataramani et al.	Glioma	Confirmed functional synapses in gliomas using electrophysiology	[7], [48]
2019	Electrical and synaptic integration of glioma into neural circuits	Venkatesh et al.	Glioma	Showed calcium transients and EPSCs in tumor cells	[50]
2020	Roadmap for the emerging field of cancer neuroscience	Monje et al.	General	Defined the field and called for interdisciplinary research	[1]
2020	Nerves in cancer	Zahalka & Frenette	General	Reviewed autonomic nerves' roles in initiation and metastasis	[8]
2022	Spatial transcriptomics technology in cancer research	Yu et al.	General	Enabled mapping of tumor-neuron interactions spatially	[10]
2023	The neural addiction of cancer	Magnon & Hondermarck	General	Highlighted addictive-like neural dependency in tumors	[3]
2023	Glioma synapses recruit mechanisms of adaptive plasticity	Taylor et al.	Glioma	Demonstrated adaptive synaptic plasticity in tumors	[56]

1.3. Rationale and Scope

The rationale for reviewing neural mechanisms in tumor biology stems from mounting evidence that the nervous system is a critical regulator of cancer progression, influencing hallmarks such as proliferation, invasion, angiogenesis,

and immune evasion. According to Hanahan [17], the nervous system's role in cancer extends beyond structural support, with neural signaling actively shaping the tumor microenvironment to promote malignancy. For instance, studies have shown that tumors induce neurogenesis and axonogenesis, recruiting nerve fibers to create a pro-tumorigenic niche [2]. This neural involvement is not limited to brain tumors; cancers like PDAC, prostate, and gastric tumors exhibit significant neural infiltration, correlating with aggressive phenotypes and poor prognosis [4, 15]. Understanding these mechanisms is essential for identifying novel therapeutic targets to disrupt tumor–neuron crosstalk.

A key driver of this review is the discovery of functional neural–tumor interactions that mirror synaptic communication. In a novel study by Venkatesh et al. [18], glioma cells were found to express synaptic proteins like neuroligin-3, enabling them to form synapse-like junctions with neurons, which drive proliferation through glutamatergic signaling. Similarly, Zhao et al. [5] demonstrated that cholinergic signaling via muscarinic receptors promotes gastric cancer stemness and invasion, highlighting the broad relevance of neural pathways across cancer types. These findings suggest that tumors exploit neural circuits to gain growth advantages, necessitating a comprehensive synthesis of these mechanisms to guide therapeutic development. Moreover, neural signaling modulates immune responses, with stress-induced catecholamines promoting immunosuppression via β-adrenergic receptors, as shown by Cole et al. [19].

The scope of this review encompasses the multifaceted roles of the nervous system in cancer, from structural neural infiltration to functional synapse-like communication and immune modulation. We explore how tumors induce neurogenesis, remodel neural circuits, and exploit neurotransmitters to enhance malignancy, drawing on evidence from glioblastoma, PDAC, and prostate cancer [1, 4, 7]. Additionally, we evaluate therapeutic strategies targeting tumor–neuron interactions, including surgical denervation, β-blockers, and synaptic inhibitors, which show promise in preclinical and clinical settings [8, 9]. The review also addresses emerging tools like spatial transcriptomics for mapping tumor–neuron interactions and ethical challenges in neural-targeted therapies [10]. By integrating these dimensions, we aim to provide a cohesive framework for advancing cancer neuroscience and its translation into personalized oncology.

This review is timely given the rapid expansion of cancer neuroscience and its potential to transform clinical practice. Recent studies, such as those by Hayakawa et al. [20], demonstrate that vagal nerve signaling drives gastric tumorigenesis, with vagotomy reducing tumor incidence, underscoring the therapeutic potential of neural modulation. Similarly, retrospective analyses suggest that β-blocker use improves survival in breast and prostate cancers, highlighting the feasibility of repurposing existing drugs [9]. By synthesizing these advances, this review seeks to bridge neuroscience and oncology, fostering interdisciplinary approaches to decode the neural circuitry of cancer and develop innovative therapies to improve patient outcomes worldwide.

2. Neural Infiltration in the Tumor Microenvironment

The tumor microenvironment (TME) is a dynamic ecosystem where cancer cells interact with stromal, immune, and neural elements to promote tumor progression. Neural infiltration, characterized by tumor-induced neurogenesis and axonogenesis, has emerged as a critical driver of malignancy across various cancers. Tumors actively recruit peripheral and autonomic nerves, leveraging neurotrophic factors and neurotransmitters to create a pro-tumorigenic niche. This section explores the mechanisms of neural infiltration, focusing on tumor-induced nerve growth and the roles of sympathetic and parasympathetic nerves in facilitating tumor growth, metastasis, and immune modulation. Figure 1 illustrates the main steps involved in perineural invasion (PNI), highlighting the dynamic interactions between tumor cells, nerves, and the perineural matrix that facilitate neural infiltration and tumor progression.

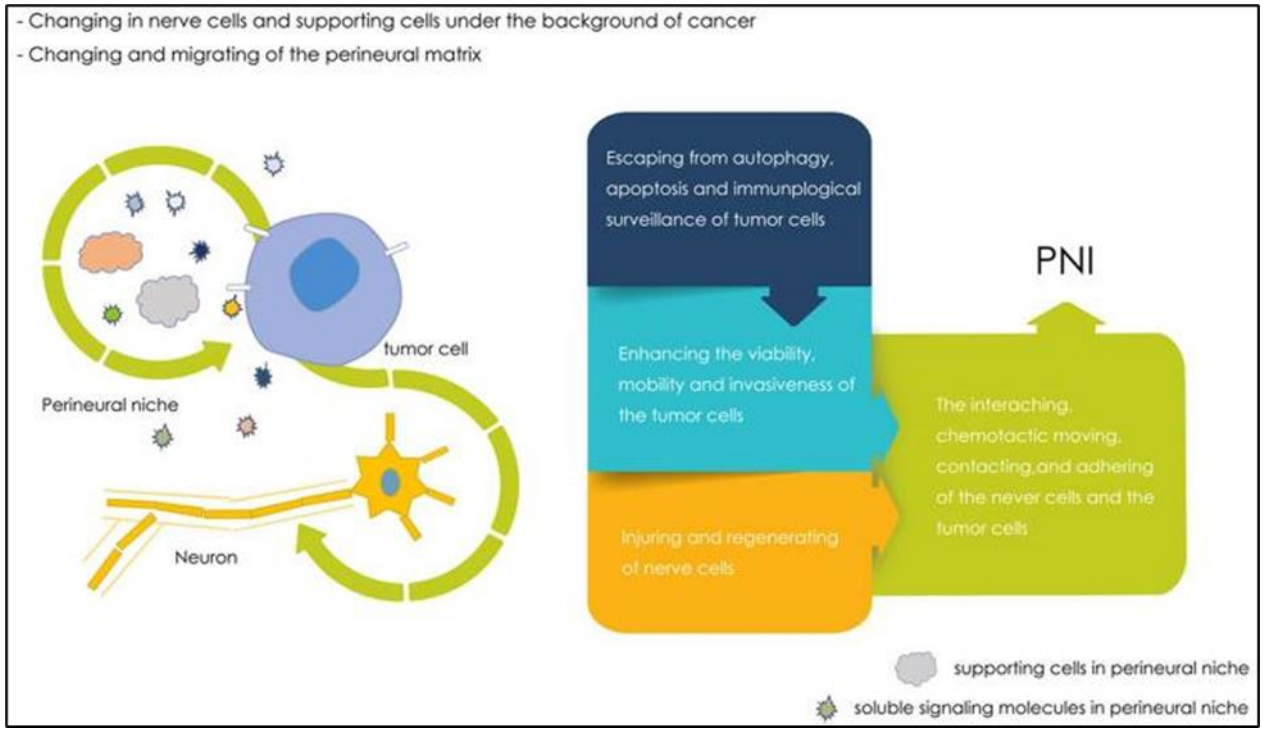

Figure 1 Main Steps in Perineural Invasion (PNI). Reproduced from Chen et al. [15] with permission

2.1. Tumor-Induced Neurogenesis and Axonogenesis

2.1.1. Neurotrophic Factors

Tumor-induced neurogenesis and axonogenesis represent pivotal mechanisms by which cancers recruit neural elements to support their growth and dissemination. According to Demir et al. (2014), tumor cells secrete neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which bind to tropomyosin receptor kinase (Trk) receptors on neurons, stimulating nerve sprouting into the TME [21]. In pancreatic ductal adenocarcinoma (PDAC), for instance, high levels of NGF and BDNF promote axonogenesis, contributing to perineural invasion (PNI) observed in 70–100% of cases [22]. This neural infiltration correlates with increased tumor recurrence and severe pain, highlighting its clinical significance. The binding of NGF to TrkA receptors activates intracellular signaling pathways, including Ras/MAPK and PI3K/Akt, which enhance neuronal survival and outgrowth, creating a feedback loop that sustains tumor aggressiveness [23].

The role of neurotrophic factors extends beyond direct neural stimulation to remodeling the TME. Studies by Renz et al. [24] demonstrate that PDAC cells secrete BDNF, which not only promotes nerve growth but also enhances tumor cell survival by upregulating anti-apoptotic pathways. In head and neck squamous cell carcinoma (HNSCC), neurotrophic factors facilitate PNI, enabling tumor cells to invade nerve sheaths and spread locally, a process associated with poor prognosis [25]. The overexpression of TrkB receptors in HNSCC further amplifies BDNF-mediated signaling, driving tumor invasion and metastasis [26]. These findings underscore the paracrine signaling loop between tumor cells and neurons, where neurotrophins create a microenvironment conducive to both neural infiltration and tumor progression. The pro-survival signaling pathways activated by mature neurotrophins (mNT) binding to Trk receptors are detailed in Figure 2, illustrating downstream cascades like RAS-MAPK and PI3K/AKT that drive tumor cell proliferation and invasion in cancers such as PDAC

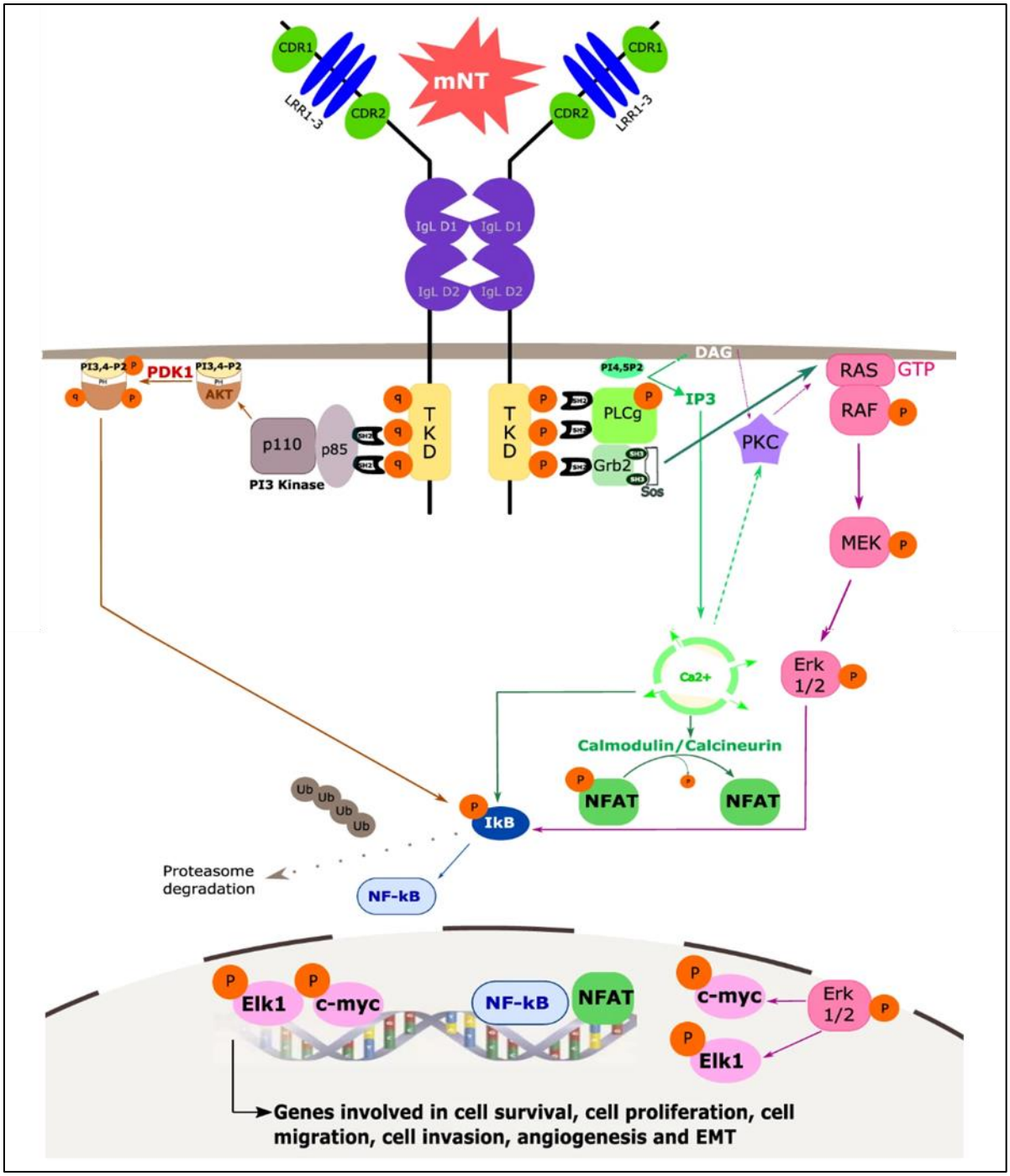

Figure 2 mNT/Trk Pro-Survival Signaling Pathways. Reproduced from Blondy et al. [26] with permission under a Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/

Moreover, neurotrophic factors contribute to therapy resistance by fostering a protective neural niche. Research by Peng et al. [27] indicates that NGF secretion in PDAC enhances resistance to gemcitabine by activating PI3K/Akt signaling, which promotes tumor cell survival under chemotherapeutic stress. Similarly, in prostate cancer, NGF-driven neural infiltration correlates with higher Gleason scores, suggesting a link between nerve density and aggressive disease phenotypes [28]. The therapeutic implications are significant, as targeting neurotrophic signaling with Trk inhibitors, such as entrectinib, has shown promise in preclinical models by reducing tumor innervation and growth [29]. These insights highlight the critical role of neurotrophic factors in orchestrating tumor–neuron interactions and their potential as therapeutic targets. To comprehensively outline the neurotrophic factors involved in tumor-induced neurogenesis and axonogenesis, Table 2 details their sources, receptors, signaling pathways, associated cancers, and therapeutic implications, drawing from key studies.

Table 2 Neurotrophic Factors and Their Roles in Tumor-Neuron Interactions

Neurotrophic Factor	Source (Tumor/Other)	Receptor(s)	Key Signaling Pathways	Associated Cancers	Role in Tumor Progression	Potential Therapeutic Target	Reference
Nerve Growth Factor (NGF)	Tumor cells, CSCs	TrkA, p75NTR	Ras/MAPK, PI3K/Akt	Prostate, PDAC, breast	Promotes axonogenesis, PNI, tumor survival, therapy resistance	Trk inhibitors (e.g., entrectinib)	[2], [14], [23], [27]
Brain-Derived Neurotrophic Factor (BDNF)	Tumor cells, Schwann cells	TrkB	PI3K/Akt, MAPK	PDAC, HNSCC, glioma	Enhances nerve sprouting, anti-apoptotic effects, CSC maintenance	TrkB antagonists	[21], [24], [26]
ProNGF (precursor to NGF)	Tumor cells	p75NTR, sortilin	JNK, NF-κB	Prostate	Drives nerve infiltration, correlates with Gleason score	p75NTR blockers	[2]
Glial Cell Line-Derived Neurotrophic Factor (GDNF)	Tumor stroma	RET, GFRα1	MAPK, PI3K	Pancreatic, breast	Supports neural niche, promotes invasion	RET inhibitors	[21]
Neurotrophin-3 (NT-3)	CSCs	TrkC	PI3K/Akt	Glioma, prostate	Maintains CSC stemness, enhances motility	TrkC inhibitors	[30], [32]
Neurotrophin-4/5 (NT-4/5)	Tumor cells	TrkB	MAPK	HNSCC, gastric	Facilitates PNI, upregulates MMPs	TrkB blockade	[25]
Galanin	Tumor cells	GALR1-3	cAMP inhibition	HNSCC	Modulates neural niche, favors PNI	Galanin antagonists	[25]
Neuroligin-3 (NLGN3)	Glioma cells, neurons	Neurexins	Synaptic adhesion	Glioma	Forms synapse-like junctions, drives proliferation	CRISPR silencing, antibodies	[18], [49], [52]
Artemin	Tumor stroma	RET/GFRα3	MAPK	Pancreatic	Promotes hypersensitivity, neural remodeling	Artemin blockers	[21]
Persephin	CSCs	RET/GFRα4	PI3K	Breast	Supports tumor dormancy	RET inhibitors	[23]

2.1.2. Role of Cancer Stem Cells (CSCs)

Cancer stem cells (CSCs), a subset of tumor cells with self-renewal and tumor-initiating capabilities, play a significant role in promoting neural infiltration within the TME. According to Ebben et al. [30], CSCs in glioblastoma secrete NGF and BDNF, which stimulate axonogenesis and create a neural-rich microenvironment that supports CSC maintenance [30]. This bidirectional interaction enhances tumor innervation while reinforcing the CSC niche, contributing to therapeutic resistance. For example, in PDAC, CSCs express stem cell markers like CD133 and secrete neurotrophins that promote nerve sprouting, correlating with increased PNI and worse clinical outcomes [31].

The molecular mechanisms underlying CSC-driven neural infiltration involve complex signaling networks. Findings from Di Donato et al. [32] indicate that CSCs in prostate cancer upregulate NGF expression, which activates TrkA receptors on neurons, triggering MAPK signaling and nerve outgrowth [32]. This neural remodeling supports CSC survival by providing trophic signals that maintain stemness, as evidenced by increased expression of pluripotency markers like Sox2 and Nanog [33]. Additionally, CSCs can modulate the extracellular matrix (ECM) through neurotrophin-induced protease activity, facilitating nerve infiltration and tumor invasion [34]. In HNSCC, CSC-driven neural infiltration is linked to local recurrence, with neurotrophins enhancing CSC motility and invasiveness [25].

The interplay between CSCs and neural elements also influences tumor dormancy and recurrence. Research by Wang et al. [22] suggests that neural infiltration creates a niche that sustains quiescent CSCs, which can later reactivate to drive tumor relapse [22]. In prostate cancer, CSC-mediated nerve growth is associated with androgen-independent tumor progression, a hallmark of therapy resistance [28]. These findings highlight the role of CSCs in orchestrating a neural-rich TME that supports both tumor progression and resistance to conventional therapies. Targeting CSC-neuron interactions, such as through neurotrophin antagonists, could disrupt this niche and improve therapeutic outcomes [29].

The clinical relevance of CSC-driven neural infiltration is underscored by its prognostic implications. In a comprehensive study by Stopczynski et al. [35], increased nerve density in PDAC was linked to CSC activity, correlating with higher rates of PNI and reduced overall survival. Similarly, in glioblastoma, CSC-mediated neurotrophin secretion enhances tumor aggressiveness by promoting neural circuit integration [30]. These insights suggest that therapeutic strategies targeting CSC-neuron crosstalk could mitigate tumor progression and recurrence, offering a novel avenue for intervention in neural-dependent cancers.

2.2. Recruitment of Peripheral and Autonomic Nerves

2.2.1. Sympathetic and Parasympathetic Contributions

The recruitment of peripheral and autonomic nerves into the TME is a highly coordinated process that significantly enhances tumor progression. In a seminal study by Magnon et al. [4], sympathetic nerves, which release norepinephrine, were shown to promote early tumor development in prostate cancer, while parasympathetic nerves, releasing acetylcholine, facilitated metastatic spread [4]. Surgical ablation of sympathetic nerves reduced tumor incidence in mouse models, whereas parasympathetic denervation impaired metastasis, highlighting distinct roles for autonomic innervation [4]. This dual contribution is observed across multiple cancers, including gastric and pancreatic tumors, where nerve density correlates with aggressive phenotypes [36].

Sympathetic innervation exerts its pro-tumorigenic effects through adrenergic signaling. According to Cole et al. [19], norepinephrine activates β2-adrenergic receptors (β2-AR) on tumor cells, triggering cAMP-PKA signaling that enhances proliferation and angiogenesis [19]. In breast cancer, sympathetic nerve infiltration increases vascular endothelial growth factor (VEGF) expression, promoting tumor vascularization and growth [37]. Similarly, in gastric cancer, sympathetic signaling upregulates matrix metalloproteinases (MMPs), facilitating tumor invasion [38]. These findings suggest that sympathetic nerves create a permissive microenvironment for tumor progression by modulating both tumor and stromal cell behavior.

Parasympathetic innervation, in contrast, often drives later stages of cancer progression. Research by Zhao et al. [5] demonstrates that acetylcholine, released by parasympathetic nerves, activates muscarinic M3 receptors in gastric cancer, promoting Wnt/β-catenin signaling and stemness [5]. In PDAC, parasympathetic nerve infiltration is associated with PNI and increased metastatic potential, as cholinergic signaling enhances tumor cell motility [39]. The interplay between sympathetic and parasympathetic nerves thus forms a dynamic neural network that supports multiple facets of tumor biology, from initiation to dissemination.

The therapeutic potential of targeting autonomic innervation is significant. Studies by Saloman et al. [40] show that denervation strategies, such as vagotomy in gastric cancer, reduce tumor growth by disrupting cholinergic signaling. Similarly, β-blockers, which antagonize β2-AR, have been shown to improve survival in prostate and breast cancer patients by mitigating sympathetic-driven tumor progression [9]. These findings underscore the critical role of autonomic nerves in the TME and highlight the need for targeted therapies to disrupt neural-tumor interactions.

2.2.2. Adrenergic and Cholinergic Signaling

Adrenergic signaling, mediated by norepinephrine and β-adrenergic receptors, is a key driver of tumor progression within the TME. Findings from Thaker et al. [41] indicate that β2-AR activation in ovarian cancer enhances VEGF

production, promoting angiogenesis and tumor growth. This signaling pathway also inhibits apoptosis and modulates immune responses by increasing myeloid-derived suppressor cell (MDSC) activity, which suppresses T cell function [19]. In prostate cancer, adrenergic signaling correlates with higher tumor grades, as norepinephrine-driven cAMP-PKA activation enhances tumor cell proliferation and ECM remodeling [42].

Cholinergic signaling, mediated by acetylcholine and muscarinic receptors, plays a complementary role in tumor progression. In a pivotal study by Felton et al. [43], muscarinic M3 receptor activation in colon cancer was shown to promote cell proliferation and invasion via EGFR and Wnt/β-catenin pathways [43]. In gastric cancer, cholinergic signaling enhances cancer stem cell activity, contributing to tumor recurrence [5]. Additionally, acetylcholine modulates the TME by promoting stromal cell activation and ECM remodeling, facilitating tumor dissemination [44]. These effects highlight the synergistic roles of adrenergic and cholinergic signaling in creating a tumor-supportive neural niche.

The clinical relevance of these signaling pathways is evident in retrospective studies showing improved outcomes with neural-targeted therapies. According to Powe et al. [45], β-blocker use in breast cancer patients is associated with reduced metastasis and improved survival, likely due to inhibition of adrenergic signaling. Similarly, muscarinic receptor antagonists show promise in preclinical models of gastric and pancreatic cancers by reducing tumor growth and invasion [40]. These findings suggest that targeting adrenergic and cholinergic pathways could disrupt neural-driven tumor progression, offering a complementary approach to conventional therapies. The complexity of neural signaling in the TME underscores the need for precise therapeutic strategies. Research by Armaiz-Pena et al. [46] highlights that chronic stress, which elevates norepinephrine levels, exacerbates tumor progression through β-adrenergic signaling, emphasizing the role of patient stress management in cancer care. Combining neural modulators with existing therapies, such as immunotherapy, could enhance efficacy by mitigating neural-driven immunosuppression [47]. These insights position adrenergic and cholinergic signaling as critical therapeutic targets in cancer neuroscience. For a detailed comparison of neurotransmitters involved in autonomic nerve recruitment and their impacts on tumor biology, Table 3 lists key neurotransmitters, receptors, pathways, effects on the TME, associated cancers, and therapeutic interventions.

Table 3 Neurotransmitters and Signaling Pathways in Tumor Progression

Neurotransmitter	Receptor(s)	Signaling Pathways	Effects on TME	Associated Cancers	Therapeutic Interventions	Reference
Norepinephrine	β2-AR, β3-AR	cAMP-PKA, MAPK	Increases VEGF, MMPs, MDSC recruitment, angiogenesis	Breast, prostate, ovarian	β-blockers (e.g., propranolol)	[19], [37], [41], [42]
Acetylcholine	Muscarinic M3	Wnt/β-catenin, EGFR	Promotes stemness, invasion, ECM remodeling	Gastric, PDAC, colon	Muscarinic antagonists, vagotomy	[5], [39], [43], [44]
Glutamate	AMPA, NMDA	Calcium influx, MAPK, PI3K/Akt	Enhances proliferation, synaptic integration, excitability	Glioma, brain metastases	AMPA/NMDA antagonists (e.g., perampanel, memantine)	[48], [49], [52], [53]
Dopamine	DRD2, DRD4	PI3K/Akt, STAT3	Maintains CSC stemness, inhibits autophagy	Glioblastoma, prostate	Dopamine receptor antagonists	[87], [88], [89]
GABA	GABAA, GABAB	Chloride influx, cAMP inhibition	Suppresses proliferation in some contexts, but promotes invasion	Colon, breast	GABA modulators	[57]
Epinephrine	β-AR	cAMP-PKA	Similar to norepinephrine:	Ovarian, breast	β-blockers	[41], [46]

			angiogenesis, immune evasion			
Serotonin	5-HT receptors	MAPK, PI3K	Promotes migration, stemness	Breast, prostate	Serotonin antagonists	[65]
Histamine	H1-H4	cAMP, PLC	Modulates immune response, angiogenesis	Gastric, pancreatic	Histamine blockers	[38]
Neuropeptide Y	Y1-Y5	cAMP inhibition	Enhances angiogenesis, neural remodeling	Prostate, breast	NPY antagonists	[8]
Substance P	NK1	MAPK, NF-κB	Promotes inflammation, PNI	PDAC, HNSCC	NK1 antagonists	[25]

3. Synapse-Like Communication in Tumors

The discovery of synapse-like communication between neurons and cancer cells has revolutionized our understanding of tumor biology, revealing a sophisticated mechanism by which tumors integrate into neural circuits. Initially identified in gliomas, these synapse-like structures enable bidirectional signaling, allowing cancer cells to exploit neuronal activity for proliferation, invasion, and therapy resistance. This section explores the functional synapses formed by tumor cells, focusing on glutamatergic signaling and electrophysiological responses, and examines how cancer cells mimic neuronal properties through ion channels and adhesion molecules, highlighting their role in tumor progression. As shown in Figure 3, cancer cells co-opt neuronal signaling pathways, including autocrine and paracrine neurotrophin and neurotransmitter circuits, to promote hallmark capabilities like immune evasion and metastasis.

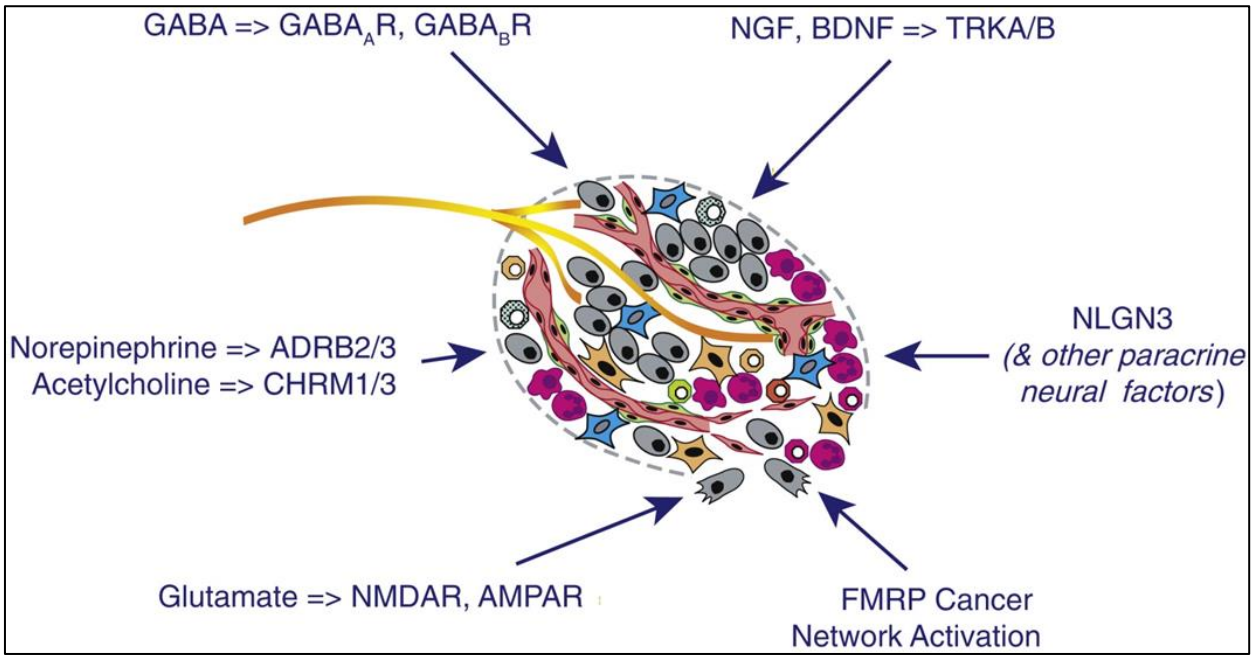

Figure 3 Neuronal Regulatory Pathways Co-opted in Cancer Cells. Reproduced from Hanahan, & Monje [44] with permission

3.1. Functional Synapses in Gliomas

3.1.1. Glutamatergic Signaling

The identification of functional synapses between neurons and glioma cells marks a paradigm shift in cancer neuroscience, demonstrating that tumors can actively participate in neural communication. In a groundbreaking study by Venkataramani et al. [48], glioma cells were shown to form glutamatergic synapses with neurons, enabling direct excitatory signaling that drives tumor proliferation. These synapses involve vesicular glutamate transporters (VGLUTs) in presynaptic neurons releasing glutamate, which binds to AMPA and NMDA receptors on glioma cells, triggering calcium influx and activating oncogenic pathways like MAPK and PI3K/Akt [49]. This synaptic integration allows gliomas to hijack neural circuits, enhancing their growth and invasiveness within the brain's neuroectodermal environment.

Glutamatergic signaling in gliomas is not merely a passive response but a dynamic process that amplifies malignancy. According to Guichet et al. [49], neuronal activity increases glioma growth by enhancing glutamate-mediated stimulation, with transcriptomic analyses revealing the expression of synaptic proteins like synaptophysin and postsynaptic density protein 95 (PSD95) in tumor cells. This molecular mimicry enables gliomas to integrate into existing neural networks, receiving excitatory inputs that promote cell cycle progression [50]. In high-grade glioblastomas, glutamatergic synapses are particularly prevalent, correlating with aggressive phenotypes and poor prognosis [51]. Figure 4 presents electrophysiological traces and quantifications showing how BDNF–TrkB signaling enhances glutamatergic currents in glioma cells, underscoring the role of synaptic plasticity in tumor proliferation. These findings highlight the critical role of synaptic communication in driving glioma progression. The therapeutic implications of targeting glutamatergic signaling are significant. Research by Venkatesh et al. [52] demonstrates that pharmacological blockade of AMPA receptors with drugs like perampanel, an FDA-approved anti-epileptic, reduces glioma cell excitability and tumor growth in preclinical models. Similarly, NMDA receptor antagonists, such as memantine, suppress activity-regulated genes in gliomas, delaying tumor progression [53]. These interventions show promise in synergizing with standard therapies like temozolomide, suggesting a translational path for disrupting tumor–neuron synapses [54]. However, challenges remain, including minimizing neurotoxicity due to the essential role of glutamate receptors in normal brain function, necessitating precise drug delivery strategies.

The broader relevance of glutamatergic signaling extends to other cancers with neural interactions. For instance, brain metastases from breast and lung cancers exhibit similar synaptic integration, as shown by Zeng et al. [55], suggesting that this mechanism is not exclusive to primary brain tumors. These findings underscore the need for further research to elucidate the molecular underpinnings of synaptic communication across cancer types, potentially revealing novel therapeutic targets to interrupt tumor–neuron crosstalk.

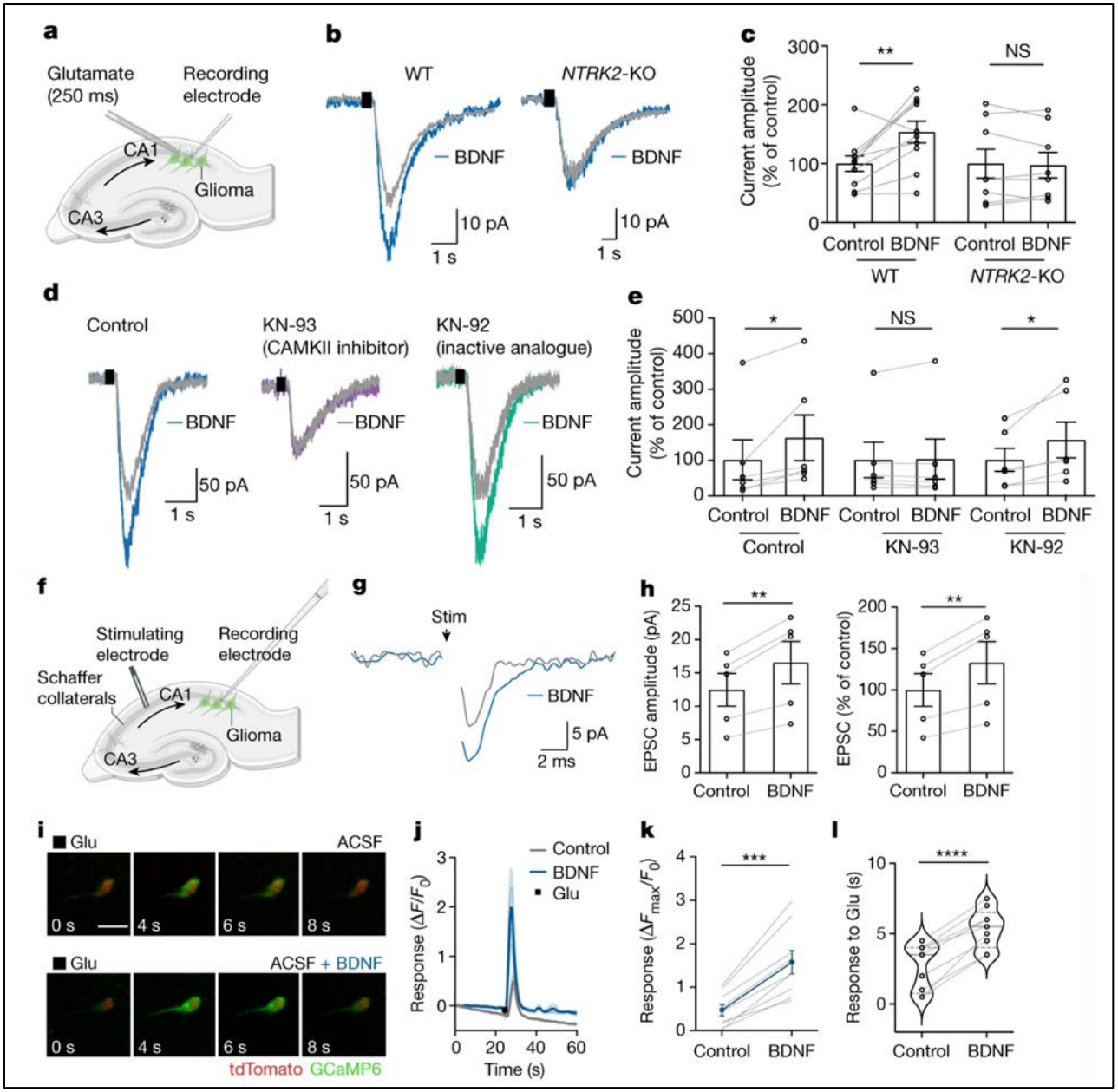

Figure 4 BDNF–TrkB Signaling Enhances Glutamatergic Currents in Glioma Cells

(a) Experimental setup for electrophysiological recordings in GFP+ SU-DIPG-VI glioma xenografts in hippocampal CA1, with local glutamate puff application. (b) Representative electrophysiological traces showing glutamate-evoked inward currents (black rectangle) in SU-DIPG-VI glioma cells before (grey) and after (blue) 30-minute BDNF perfusion in wild-type and NTRK2-knockout (NTRK2-KO) glioma models. (c) Quantification of glutamate-evoked current amplitude from panel b (n = 10 cells from 6 wild-type mice; n = 8 cells from 6 NTRK2-KO mice). (d) Representative traces of glutamate-evoked currents (black rectangle) in SU-DIPG-VI xenografts before (grey) and after (blue, purple, green) 30-minute BDNF perfusion. Left: control. Middle: with 2-hour pre-incubation of CAMKII inhibitor KN-93. Right: with 2-hour pre-incubation of KN-92 (inactive analogue of KN-93). (e) Quantification of current amplitude from panel d (n = 6 cells per group from 5 control mice, 3 KN-93-treated mice, and 3 KN-92-treated mice). (f) Experimental setup as in panel a, using Schaffer collateral afferent stimulation to evoke responses. (g) Representative averaged voltage-clamp traces of excitatory postsynaptic currents (EPSCs) in glioma cells triggered by axonal stimulation (black arrow) before (grey) and after (blue) BDNF application. (h) Quantification of EPSC amplitude from panel g (n = 5 out of 43 glioma cells showing EPSCs, from 4 mice). (i) Two-photon in situ imaging (8-second time series) of glioma cell calcium transients evoked by local glutamate puff before (top) and after (bottom) 30-minute BDNF perfusion (100 ng ml^{-1}). Green indicates GCaMP6s fluorescence in glioma cells; red indicates tdTomato nuclear tag. Scale bar: 10 μm. (j) GCaMP6s fluorescence intensity traces of SU-DIPG-XIII-FL glioma cells in response to glutamate puff, with or without BDNF. Light

grey: individual vehicle-treated cell traces; dark grey: average vehicle-treated trace. Light blue: individual BDNF-treated cell traces; dark blue: average BDNF-treated trace (n = 4 cells per group). (k) Quantification of calcium transient responses in SU-DIPG-XIII-FL GCaMP6s cells to glutamate puff with or without BDNF (n = 9 cells from 3 mice). (l) Duration of calcium transients in SU-DIPG-XIII-FL GCaMP6s cells in response to glutamate puff before and after BDNF exposure (n = 9 cells from 3 mice). Data are presented as mean ± s.e.m. Statistical analysis performed using two-tailed paired Student's t-test for panels c, e, h, k, and l. Reproduced from Taylor et al. [56] with permission, under a Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.

3.1.2. Electrophysiological Responses

The ability of cancer cells to exhibit electrophysiological responses akin to neurons represents a striking adaptation that enhances their integration into neural circuits. In a pivotal study by Venkataramani et al. [48], patch-clamp electrophysiology revealed spontaneous and evoked excitatory postsynaptic currents (EPSCs) in glioma cells co-cultured with neurons, confirming functional synaptic inputs mediated by AMPA receptors. These EPSCs were abolished by AMPA receptor antagonists, validating the role of glutamatergic signaling in tumor excitability [56]. This electrophysiological activity enables glioma cells to respond to neuronal cues, promoting synchronized migration and invasion across brain tissue.

Advanced imaging techniques have further elucidated these electrophysiological responses. Research by Venkatesh et al. [52] utilized genetically encoded calcium indicators like GCaMP6s to visualize real-time calcium oscillations in glioma cells in response to neuronal stimulation, mirroring neuronal calcium transients. These oscillations drive downstream signaling cascades that enhance tumor cell proliferation and motility [57]. In vivo studies in mouse models confirm that glioma cells receive and respond to neuronal inputs, and disrupting these signals reduces tumor growth and invasiveness [58]. This dynamic interaction positions gliomas as active participants in neural networks, challenging traditional views of tumor physiology.

The electrophysiological properties of tumor cells also contribute to therapy resistance. According to Pan et al. [59], glioma cells' ability to synchronize with neural activity via EPSCs creates a protective microenvironment that shields them from chemotherapeutic agents. This synchronization may underlie the resilience of glioblastoma to standard treatments, as neural inputs sustain tumor cell survival under stress [60]. Targeting these electrophysiological responses, such as through AMPA receptor blockade, offers a novel strategy to sensitize tumors to therapy, as demonstrated in preclinical studies combining perampanel with radiation [54]. The discovery of electrophysiological responses in tumors extends beyond gliomas to other neurotropic cancers. For example, studies by Jung et al. [61] suggest that breast cancer brain metastases exhibit similar excitatory responses, integrating into neural circuits to enhance metastatic growth. These findings highlight the widespread relevance of electrophysiological tumor–neuron interactions and underscore the need for targeted therapies to disrupt these synaptic connections, potentially improving outcomes in neurologically active cancers. To encapsulate the functional aspects of synapse-like communication, Table 4 outlines key synaptic structures, proteins, electrophysiological responses, associated cancers, and therapeutic targets identified in recent studies.

Table 4 Synapse-Like Structures and Electrophysiological Features in Tumors

Synaptic Structure/Feature	Key Proteins Involved	Electrophysiological Response	Associated Cancers	Role in Progression	Therapeutic Target	Reference
Glutamatergic synapses	VGLUT, AMPA/NMDA receptors, PSD95	EPSCs, calcium transients	Glioma, brain metastases	Drives proliferation, invasion	AMPA antagonists (perampanel)	[48], [49], [52]
Synapse-like junctions	Neuroligin-3, neurexins	Synchronized oscillations	Glioma	Enhances neural integration	CRISPR silencing of NLGN3	[18], [72]
Voltage-gated Na+ channels	Nav1.5, Nav1.7	Depolarization, action potentials	Breast, prostate	Acidifies ECM, promotes invasion	Nav blockers	[62], [63], [70]

Voltage-gated K+ channels	Kv10.1 (Eag1), Kv11.1 (hERG)	Membrane potential stabilization	Ovarian, cervical, breast	Cell cycle progression, apoptosis resistance	Kv inhibitors	[65], [66], [67]
Voltage-gated Ca2+ channels	CaV3.2 (T-type)	Calcium influx	Pancreatic, glioma	Activates MAPK/PI3K, proliferation	Ca2+ channel blockers	[68], [69]
Adhesion-based synapses	N-cadherins, protocadherins	Adhesion-mediated signaling	PDAC, prostate, HNSCC	Facilitates PNI, motility	N-cadherin inhibitors	[73], [74], [76]
Contactin-mediated junctions	Contactins	Axon guidance	Pancreatic	Promotes innervation, metastasis	Contactin antibodies	[77]
Gap junctions	Connexins	Electrical coupling	Glioma	Synchronizes tumor cells with neurons	Connexin inhibitors	[51]
Exosomal synapses	miR-21, miR-124	Indirect signaling	PDAC, glioma	Remodels neural circuits remotely	Exosome inhibitors (GW4869)	[80], [82]
Neuro-immune synapses	PD-L1 on nerves	T cell exhaustion	Prostate, breast	Immunosuppression	PD-1 inhibitors + denervation	[94], [96]

3.2. Neuronal Mimicry by Cancer Cells

3.2.1. Voltage-Gated Ion Channels

Cancer cells' ability to mimic neuronal properties, particularly through the expression of voltage-gated ion channels (VGICs), enables them to modulate their microenvironment and enhance tumor progression. According to Brackenbury [62], voltage-gated sodium channels (Nav1.5 and Nav1.7) are upregulated in breast and prostate cancers, facilitating sodium influx that activates the Na+/H+ exchanger, acidifying the extracellular environment. This acidification promotes extracellular matrix (ECM) degradation via proteases like cathepsins and matrix metalloproteinases (MMPs), enhancing tumor invasion and metastasis [63]. Inhibition of Nav1.5 with selective blockers reduces invasiveness in preclinical models, underscoring its therapeutic potential [64].

Voltage-gated potassium channels (VGKCs) also play a critical role in tumor biology. Research by Pardo and Stühmer [65] demonstrates that Kv10.1 (Eag1) is overexpressed in ovarian and cervical cancers, where it regulates membrane potential and promotes cell cycle progression. Pharmacological inhibition of Kv10.1 induces apoptosis and reduces tumor growth, suggesting its role as an oncogenic driver [66]. Similarly, Kv11.1 (hERG) channels stabilize membrane potential in breast cancer cells, enhancing resistance to chemotherapy [67]. These channels represent a form of "onco-channelopathy," where neuronal-like electrical activity drives malignancy.

Voltage-gated calcium channels (VGCCs) further contribute to tumor progression by mediating calcium influx, a critical regulator of proliferation and migration. In a comprehensive study by Monteith et al. [68], CaV3.2 T-type calcium channels were shown to be upregulated in pancreatic cancer, activating MAPK and PI3K/Akt pathways to promote tumor growth and survival. Calcium channel blockers reduce proliferation in preclinical models, offering a repurposing opportunity for existing drugs [69]. The ectopic expression of VGICs across cancers highlights their role in neuronal mimicry, providing novel therapeutic targets to disrupt tumor–neuron interactions.

The clinical relevance of VGICs is underscored by their association with aggressive disease phenotypes. For instance, Nav1.7 expression in prostate cancer correlates with advanced tumor stages and poorer prognosis [70]. These findings suggest that targeting VGICs could mitigate tumor invasiveness and enhance therapeutic efficacy, particularly in cancers with high neural infiltration. Ongoing research aims to develop specific inhibitors to balance efficacy and minimize off-target effects in normal excitable tissues [71].

3.2.2. Synaptic Adhesion Molecules

Cancer cells' expression of synaptic adhesion molecules (SAMs) facilitates their physical and functional integration into neural circuits, enhancing tumor–neuron crosstalk. In a landmark study by Guichet et al. [49], neuroligin-3 (NLGN3) was identified as a key SAM in glioma cells, binding to neurexins on neurons to form synapse-like junctions that promote tumor proliferation. Genetic disruption of NLGN3 significantly impairs glioma growth in preclinical models, highlighting its role as a therapeutic target [72]. These junctions enable bidirectional signaling, allowing tumors to receive neural inputs while modulating neuronal activity. N-cadherins, another class of SAMs, mediate tumor–neuron adhesion in cancers like breast and prostate. According to Wheelock et al. [73], N-cadherin overexpression enhances perineural invasion (PNI) by facilitating tumor cell adhesion to nerve sheaths, promoting motility and resistance to apoptosis. In pancreatic cancer, N-cadherins contribute to PNI, correlating with local recurrence and poor prognosis [74]. These adhesion molecules initiate intracellular signaling cascades that enhance cytoskeletal remodeling and tumor invasiveness, amplifying malignancy [75].

Additional SAMs, such as protocadherins and contactins, further mediate tumor–neuron interactions. Research by Chen et al. [76] shows that protocadherins modulate invasive behavior in pancreatic cancer, while contactins contribute to axon guidance and tumor innervation [77]. Super-resolution microscopy has visualized these synapse-like structures at tumor–neuron interfaces, confirming their ultrastructural basis [49]. These findings highlight the sophisticated molecular mimicry by cancer cells, enabling them to co-opt neural networks for growth advantages.

The therapeutic potential of targeting SAMs is significant. Studies by Mandal et al. [78] suggest that antibodies or small molecules disrupting NLGN3-neurexin interactions can inhibit tumor innervation and progression. Similarly, N-cadherin inhibitors show promise in reducing PNI in preclinical models of prostate cancer [79]. These strategies offer a novel approach to disrupting tumor–neuron crosstalk, potentially enhancing the efficacy of existing therapies and improving outcomes in neurotropic cancers.

4. Neural Circuit Remodeling in Tumor Progression

Neural circuit remodeling in the tumor microenvironment (TME) represents a dynamic process where tumors and neurons engage in bidirectional communication to enhance malignancy. Tumors not only recruit nerves but also rewire neural circuits through trophic signaling and exosomal interactions, creating feedback loops that sustain tumor growth, invasion, and stemness. This section explores how these neural circuits are remodeled, focusing on feedback loops between tumors and neurons, and their impact on cancer stem cells (CSCs) and tumor dormancy, which drive progression and recurrence in cancers like glioblastoma, pancreatic ductal adenocarcinoma (PDAC), and prostate cancer.

4.1. Feedback Loops in Tumor–Neuron Crosstalk

4.1.1. Bidirectional Signaling

Neural circuit remodeling is driven by bidirectional signaling, where tumors and neurons exchange molecular cues to create a pro-tumorigenic microenvironment. In a seminal study by Magnon et al. [4], prostate cancer cells were shown to secrete nerve growth factor (NGF), promoting sympathetic and parasympathetic nerve infiltration, while neurons release norepinephrine and acetylcholine, activating oncogenic pathways like cAMP-PKA and Wnt/β-catenin in tumor cells. This reciprocal signaling enhances tumor proliferation and metastasis, with sympathetic nerves driving early tumor growth and parasympathetic nerves facilitating dissemination. In glioblastoma, neuronal activity amplifies tumor growth by releasing glutamate, which stimulates AMPA receptors on tumor cells, further reinforcing neural circuit integration [48].

The molecular mechanisms of bidirectional signaling involve complex neurotrophic and neurotransmitter pathways. According to Hayakawa et al. [20], gastric cancer cells induce vagal nerve infiltration through NGF secretion, while cholinergic signaling via muscarinic M3 receptors activates Wnt/β-catenin, promoting tumor cell stemness and invasion. Similarly, in PDAC, tumor-derived neurotrophins like BDNF enhance nerve sprouting, which in turn releases norepinephrine to activate β2-adrenergic receptors (β2-AR), driving tumor cell proliferation and angiogenesis [24]. These feedback loops create a self-sustaining cycle where neural activity fuels tumor progression, and tumor signals recruit additional innervation.

The clinical implications of bidirectional signaling are profound, as disrupting these feedback loops offers therapeutic potential. Research by Zahalka et al. [42] demonstrates that β-adrenergic blockade with propranolol inhibits prostate cancer growth by reducing norepinephrine-driven signaling, suggesting a role for neural modulators in cancer therapy.

Similarly, vagotomy in gastric cancer models disrupts cholinergic signaling, reducing tumor incidence and progression [5]. These findings highlight the importance of targeting bidirectional signaling to interrupt neural circuit remodeling and mitigate tumor aggressiveness.

The complexity of these interactions necessitates advanced tools to map and disrupt tumor–neuron crosstalk. Spatial transcriptomics, as noted by Ravi and Monje [10], reveals spatially distinct patterns of neurotrophin and neurotransmitter receptor expression, offering insights into the molecular architecture of neural circuits in the TME. Future therapies targeting these signaling pathways could enhance the efficacy of existing treatments, such as chemotherapy and immunotherapy, by breaking the neural feedback loops that sustain malignancy [80].

4.1.2. Exosomal Communication

Exosomal communication represents a novel mechanism by which tumors and neurons remodel neural circuits, facilitating long-range signaling within the TME. According to Yang et al. [80], tumor-derived exosomes containing microRNAs (e.g., miR-21, miR-124) modulate neuronal gene expression, promoting neurite outgrowth and nerve infiltration in PDAC. Conversely, neuronal exosomes transfer neurotrophic factors and miRNAs, such as miR-124-3p, to tumor cells, suppressing proliferation in some contexts while enhancing CSC maintenance in others [81]. This bidirectional exosomal exchange creates a dynamic communication network that supports tumor progression.

The content of tumor-derived exosomes is critical to their pro-tumorigenic effects. Research by Abels et al. [82] shows that glioblastoma-derived exosomes enriched with miR-21 promote neuronal remodeling by upregulating synaptic proteins like neuroligin-3 in neurons, enhancing tumor–neuron synaptic connectivity. In prostate cancer, exosomes containing neurotrophins like BDNF stimulate nerve sprouting, correlating with increased perineural invasion (PNI) and metastasis [83]. These exosomes also carry proteases that degrade the ECM, facilitating neural infiltration and tumor spread [84]. Neuronal exosomes, in turn, influence tumor behavior by modulating the TME. Findings from Ge et al. [81] indicate that neuronal exosomes in glioma models transfer miR-124-3p, which downregulates tumor suppressor genes, promoting CSC survival and therapy resistance. In PDAC, neuronal exosomes enhance tumor cell motility by delivering neurotrophic factors, creating a neural niche that supports tumor dissemination [80]. These findings underscore the role of exosomes as mediators of neural circuit remodeling, amplifying tumor–neuron interactions across distances.

Therapeutically, targeting exosomal communication offers a novel strategy to disrupt neural circuit remodeling. Studies by Kamerkar et al. [85] suggest that engineered exosomes can deliver siRNAs to silence oncogenic miRNAs in tumor cells, reducing neural infiltration and tumor growth in preclinical models. Similarly, inhibiting exosome release with drugs like GW4869 impairs tumor–neuron crosstalk, offering a potential adjuvant therapy [86]. These approaches highlight the promise of targeting exosomal pathways to break the neural feedback loops driving tumor progression.

4.2. Impact on Cancer Stem Cells and Dormancy

4.2.1. Nerve-Driven Stemness

Neural circuit remodeling significantly influences cancer stem cells (CSCs), which are critical for tumor initiation, recurrence, and therapy resistance. According to Ebben et al. [30], neural signaling via β-adrenergic and dopaminergic pathways maintains CSC stemness in glioblastoma by activating STAT3 and Wnt/β-catenin signaling. Norepinephrine, released by sympathetic nerves, upregulates pluripotency markers like Sox2 and Oct4 in CSCs, enhancing their self-renewal capacity [87]. In prostate cancer, adrenergic signaling via β2-AR promotes CSC survival, correlating with androgen-independent tumor progression [42]. The molecular mechanisms of nerve-driven stemness involve neurotransmitter-mediated signaling cascades. Research by Jeon et al. [88] demonstrates that glioblastoma CSCs express dopamine receptors (DRD2), which, upon activation by neuronal dopamine, trigger PI3K/Akt signaling, promoting stemness and resistance to temozolomide. Similarly, in PDAC, cholinergic signaling via muscarinic receptors enhances CSC viability by activating Notch signaling, contributing to tumor recurrence [39]. These neural signals create a supportive niche that sustains CSC populations, driving long-term tumor progression.

Therapeutic strategies targeting nerve-driven stemness show promise in preclinical models. Studies by Renz et al. [24] indicate that β-blockers like propranolol reduce CSC proliferation in PDAC by inhibiting adrenergic signaling, sensitizing tumors to chemotherapy. Similarly, dopamine receptor antagonists impair CSC maintenance in glioblastoma, offering a novel approach to prevent recurrence [89]. These findings highlight the potential of neural-targeted therapies to disrupt the CSC niche and improve clinical outcomes. The clinical relevance of nerve-driven stemness is evident in its association with poor prognosis. In a comprehensive study by Goffart et al. [90], high expression of neural signaling markers like β2-AR and DRD2 in glioblastoma correlated with reduced overall survival, underscoring the prognostic

significance of CSC–neuron interactions. Targeting these neural pathways could mitigate CSC-driven tumor progression, offering a complementary strategy to conventional therapies.

4.2.2. Niche Remodeling

Neural circuit remodeling creates a specialized niche that supports CSC dormancy and tumor recurrence, particularly in cancers with high neural infiltration. According to Bapat et al. [22], Schwann cells and neurotrophins in the PDAC TME form a neural niche that maintains quiescent CSCs, enabling them to evade therapy and reactivate later. In prostate cancer, nerve-derived neurotrophins like NGF create a protective niche that supports CSC dormancy, contributing to metastatic relapse [28]. This niche remodeling enhances tumor resilience and complicates treatment.

The role of Schwann cells in niche remodeling is particularly significant. Research by Bunimovich et al. [91] shows that Schwann cells in the TME secrete neurotrophic factors and ECM components, creating a supportive environment for CSC survival. In glioblastoma, Schwann cell-derived signals enhance CSC resistance to radiation by upregulating DNA repair pathways [92]. These findings suggest that neural niche remodeling is a critical mechanism for maintaining tumor heterogeneity and driving recurrence. Therapeutic disruption of the neural niche offers a promising approach to prevent tumor relapse. Studies by Demir et al. [21] demonstrate that targeting neurotrophic signaling with Trk inhibitors reduces CSC niche formation in PDAC, decreasing tumor recurrence rates in preclinical models. Similarly, denervation strategies, such as vagotomy, disrupt the neural niche in gastric cancer, impairing CSC survival [5]. These interventions highlight the potential of targeting niche remodeling to eliminate dormant CSCs and improve long-term outcomes.

The clinical challenge lies in identifying biomarkers of neural niche activity to guide therapy. According to Saloman et al. [40], increased nerve density and neurotrophin expression in PDAC correlate with CSC activity and worse prognosis, suggesting their use as prognostic indicators. Advanced imaging and transcriptomic tools could further map the neural niche, enabling personalized strategies to target CSC-driven recurrence [10]. These insights underscore the critical role of neural circuit remodeling in sustaining tumor progression and the need for innovative therapies to disrupt these interactions.

5. Neural Modulation of the Tumor Immune Microenvironment

The nervous system profoundly influences the tumor immune microenvironment (TME), modulating immune responses to promote tumor progression and therapy resistance. Neural signaling, particularly through sympathetic and stress-related pathways, shapes immune cell behavior, fostering immunosuppression that enables tumors to evade immune surveillance. This section explores how neural signals regulate immune cells and how stress-induced mechanisms exacerbate immunosuppression, highlighting their impact on tumor progression and therapeutic opportunities in cancers such as prostate, breast, and pancreatic ductal adenocarcinoma (PDAC).

5.1. Neural Regulation of Immune Cells

5.1.1. Sympathetic Tone and MDSCs

Sympathetic neural signaling significantly alters the tumor immune microenvironment by promoting immunosuppressive cell populations, notably myeloid-derived suppressor cells (MDSCs). According to Cole et al. [19], norepinephrine released by sympathetic nerves activates β2-adrenergic receptors (β2-AR) on MDSCs, enhancing their proliferation and immunosuppressive functions in the TME. In breast cancer models, this adrenergic signaling increases MDSC accumulation, suppressing CD8+ T cell activity and promoting tumor growth [37]. This neural-driven immunosuppression creates a barrier to effective immune responses, facilitating tumor progression and metastasis. The molecular mechanisms underlying sympathetic regulation of MDSCs involve cytokine and chemokine signaling. Research by Caller et al. [93] demonstrates that norepinephrine upregulates interleukin-6 (IL-6) and CCL2 in the TME, recruiting MDSCs and polarizing macrophages toward an M2-like immunosuppressive phenotype. In prostate cancer, β2-AR activation on MDSCs enhances arginase-1 and iNOS expression, depleting arginine and inhibiting T cell proliferation [42]. These findings highlight the role of sympathetic signaling in creating an immune-evasive TME, contributing to aggressive disease phenotypes.

Therapeutic strategies targeting sympathetic tone show promise in reversing immunosuppression. In a pivotal study by Bucsek et al. [47], β-blockers like propranolol were shown to reduce MDSC accumulation and restore CD8+ T cell function in breast cancer models, enhancing the efficacy of immune checkpoint inhibitors. Similarly, sympathetic denervation in prostate cancer models decreases MDSC infiltration, improving immune surveillance [94]. These interventions suggest that modulating sympathetic signaling could enhance immunotherapy outcomes by alleviating

neural-driven immunosuppression. The clinical relevance of sympathetic regulation of MDSCs is underscored by its association with poor prognosis. According to Qiao et al. [95], elevated β2-AR expression in the TME correlates with increased MDSC activity and reduced overall survival in pancreatic cancer patients. These insights emphasize the need to integrate neural-targeted therapies with immunotherapies to overcome immunosuppressive barriers and improve patient outcomes in neurologically active cancers.

5.1.2. Neuro-Immune Synapses

Neural elements within the TME form synapse-like interactions with immune cells, further modulating immune responses to favor tumor progression. Research by Zhang et al. [94] reveals that nerve fibers in prostate cancer express programmed death-ligand 1 (PD-L1), which interacts with PD-1 on T cells, promoting T cell exhaustion and reducing effector function. These neuro-immune synapses enable tumors to exploit neural signaling to suppress immune surveillance, enhancing their ability to evade cytotoxic T cell responses [19]. This mechanism is particularly pronounced in cancers with high neural infiltration, such as PDAC and prostate cancer. The formation of neuro-immune synapses involves complex molecular interactions. According to Gysler et al. [96], sympathetic nerve-derived norepinephrine enhances PD-L1 expression on tumor-associated macrophages via β2-AR signaling, further amplifying immunosuppression. In breast cancer, nerve fibers facilitate the recruitment of regulatory T cells (Tregs) through CCL2 secretion, creating an immune-tolerant TME [37]. These synapse-like interactions create a localized immunosuppressive niche, shielding tumors from immune attack and promoting progression.

Disrupting neuro-immune synapses offers a novel therapeutic avenue. Studies by Zhang et al. [94] demonstrate that sympathetic denervation reduces PD-L1 expression in the TME, enhancing the efficacy of PD-1 inhibitors in prostate cancer models. Similarly, pharmacological inhibition of β2-AR signaling with propranolol decreases Treg accumulation, restoring anti-tumor immunity [47]. These findings suggest that targeting neuro-immune interactions could synergize with checkpoint inhibitors, overcoming immune evasion in neurologically active tumors. The prognostic significance of neuro-immune synapses is evident in clinical studies. Research by Ino et al. [97] shows that high nerve density and PD-L1 expression in PDAC correlate with reduced T cell infiltration and worse survival, highlighting the role of neural signaling in immune modulation. Advanced imaging techniques, such as spatial transcriptomics, could further map these neuro-immune interactions, guiding the development of targeted therapies to disrupt immunosuppressive synapses [10].

5.2. Stress and Immunosuppression

5.2.1. Cortisol and Norepinephrine Effects

Chronic stress exacerbates tumor progression by amplifying neural-driven immunosuppression through cortisol and norepinephrine signaling. According to Chen et al. [98], stress-induced cortisol release from the hypothalamic-pituitary-adrenal (HPA) axis inhibits CD8+ T cell infiltration and activation in the TME, promoting tumor immune evasion in breast cancer models. Concurrently, norepinephrine from sympathetic nerves enhances VEGF and IL-6 production, fostering angiogenesis and immunosuppression [19]. These stress-related signals create a tumor-supportive microenvironment, particularly in cancers like breast and ovarian cancer with high neural infiltration.

The molecular pathways linking stress to immunosuppression involve both glucocorticoid and adrenergic signaling. Research by Thaker et al. [41] demonstrates that norepinephrine activates β2-AR on ovarian cancer cells, upregulating VEGF and MMPs, which recruit immunosuppressive MDSCs and promote tumor vascularization. Similarly, cortisol signaling through glucocorticoid receptors (GR) suppresses interferon-gamma production, impairing T cell effector functions [99]. In PDAC, stress-induced signaling enhances CSC survival, contributing to therapy resistance and recurrence [24].

The clinical impact of stress-induced immunosuppression is significant, as chronic stress is associated with worse outcomes in cancer patients. Studies by Lutgendorf et al. [100] show that elevated cortisol levels in ovarian cancer patients correlate with reduced T cell infiltration and shorter progression-free survival. Similarly, norepinephrine-driven immunosuppression in prostate cancer is linked to increased metastatic potential [42]. These findings underscore the need to address stress-related neural signaling as part of comprehensive cancer care.

5.2.2. Therapeutic Implications

Targeting stress-induced neural signaling offers a promising strategy to reverse immunosuppression and enhance anti-tumor immunity. In a landmark study by Bucsek et al. [47], β-blockers like propranolol were shown to mitigate norepinephrine-driven immunosuppression in breast cancer, increasing CD8+ T cell infiltration and enhancing PD-1 inhibitor efficacy. Similarly, glucocorticoid receptor antagonists, such as mifepristone, restore T cell function in preclinical models, suggesting a role in combination therapies [99]. These interventions highlight the potential of neural modulators to improve immunotherapy outcomes.

Non-pharmacological approaches, such as stress management, also show promise in mitigating neural-driven immunosuppression. Research by Antoni et al. [101] demonstrates that cognitive-behavioral stress management reduces cortisol levels in breast cancer patients, correlating with improved immune function and survival. In prostate cancer, stress reduction strategies decrease norepinephrine levels, enhancing T cell responses [100]. These findings suggest that integrating stress management with neural-targeted therapies could optimize anti-tumor immunity.

The combination of neural modulators with immunotherapy is a key area of ongoing research. According to Qiao et al. [95], β-blockers enhance the efficacy of checkpoint inhibitors in pancreatic cancer by reducing MDSC and Treg activity, improving tumor clearance. Clinical trials, such as those exploring propranolol with anti-PD-1 therapies (e.g., NCT03384836), are evaluating these synergistic effects [102]. These studies highlight the translational potential of targeting stress-induced neural signaling to overcome immunosuppression. The challenge lies in optimizing these therapies to minimize off-target effects. Research by Armaiz-Pena et al. [46] emphasizes the need for precise dosing and timing of β-blockers to avoid disrupting normal immune function. Advanced technologies, such as single-cell RNA sequencing, could identify specific immune cell populations affected by neural signaling, guiding personalized therapeutic strategies [10]. These insights position neural modulation as a critical component of next-generation cancer therapies, with the potential to transform treatment outcomes in neurologically active cancers.

6. Therapeutic Targeting of Tumor–Neuron Interactions

The discovery of tumor–neuron interactions has opened novel therapeutic avenues to disrupt neural-driven cancer progression. Strategies targeting neural infiltration, synaptic communication, and their immunomodulatory effects show promise in preclinical and clinical settings, particularly for cancers like glioblastoma, pancreatic ductal adenocarcinoma (PDAC), and prostate cancer. This section explores denervation and neural blockade, synaptic pathway inhibition, and combination therapies with immunotherapy and chemotherapy, highlighting their potential to improve outcomes while addressing challenges like tumor heterogeneity and neurotoxicity.

6.1. Denervation and Neural Blockade

6.1.1. Surgical Denervation

Surgical denervation, aimed at disrupting neural innervation within the tumor microenvironment (TME), has emerged as a promising strategy to inhibit tumor progression. In a landmark study by Magnon et al. [4], surgical ablation of sympathetic nerves in prostate cancer mouse models significantly reduced tumor incidence, while parasympathetic denervation impaired metastasis, demonstrating distinct roles of autonomic nerves in cancer progression. Similarly, vagotomy in gastric cancer models suppresses tumor growth by disrupting cholinergic signaling via muscarinic M3 receptors, which drive Wnt/β-catenin-mediated proliferation [5]. These findings highlight the potential of surgical denervation to interrupt tumor–neuron crosstalk and mitigate malignancy.

The efficacy of surgical denervation is particularly evident in cancers with high perineural invasion (PNI). Research by Saloman et al. [40] shows that ablation of sensory neurons in PDAC models slows tumor initiation and progression by reducing neurotrophin-driven neural infiltration. In head and neck squamous cell carcinoma (HNSCC), denervation reduces PNI-associated recurrence, as nerve infiltration correlates with aggressive phenotypes [25]. However, surgical denervation poses challenges, including invasive procedures and potential side effects like sensory or autonomic dysfunction, necessitating careful patient selection and precise surgical techniques. Clinical translation of surgical denervation remains limited but promising. According to Zhao et al. [5], vagotomy in gastric cancer patients undergoing resection is associated with improved survival, suggesting a role for neural modulation in clinical settings. Preclinical studies in PDAC also demonstrate that combining denervation with chemotherapy enhances tumor control by reducing neural-driven therapy resistance [24]. These findings underscore the need for clinical trials to evaluate the feasibility and efficacy of surgical denervation as an adjuvant therapy in neurologically active cancers.

6.1.2. Pharmacological Inhibitors

Pharmacological inhibition of neural signaling offers a less invasive alternative to surgical denervation, targeting neurotransmitter and neurotrophic pathways to disrupt tumor–neuron interactions. In a pivotal study by Barron et al. [9], β-blockers like propranolol were shown to reduce metastasis and improve survival in breast and prostate cancer patients by inhibiting norepinephrine-driven β2-adrenergic receptor (β2-AR) signaling. This blockade suppresses angiogenesis, tumor cell proliferation, and immunosuppression, highlighting its multifaceted anti-tumor effects [47]. Similarly, Trk inhibitors, such as entrectinib, impair tumor innervation by targeting neurotrophin receptors, reducing nerve density and tumor growth in NTRK-fusion cancers [29].

The molecular specificity of pharmacological inhibitors enhances their therapeutic potential. Research by Renz et al. [24] demonstrates that β-blockers in PDAC models inhibit CSC survival and sensitize tumors to gemcitabine, suggesting synergy with chemotherapy. In prostate cancer, muscarinic receptor antagonists reduce cholinergic-driven invasion, offering a complementary approach to denervation [39]. These inhibitors are particularly appealing due to their established safety profiles in other conditions, such as hypertension and epilepsy, facilitating rapid clinical translation. Challenges in pharmacological inhibition include off-target effects and tumor heterogeneity. According to Zahalka et al. [42], β2-AR signaling varies across tumor types, requiring personalized dosing strategies to maximize efficacy while minimizing systemic effects. Additionally, resistance to Trk inhibitors can emerge due to mutations in neurotrophin receptors, necessitating combination therapies to overcome adaptive mechanisms [29]. Ongoing clinical trials, such as those evaluating propranolol in breast cancer (e.g., NCT02596867), are assessing these inhibitors' efficacy in disrupting neural-driven tumor progression.

The clinical relevance of pharmacological inhibitors is supported by retrospective analyses. Studies by Powe et al. [45] show that breast cancer patients on β-blockers have lower recurrence rates, suggesting a protective effect against neural-driven metastasis. These findings position pharmacological inhibitors as a feasible strategy to target tumor–neuron interactions, with the potential to enhance standard therapies and improve outcomes in cancers with significant neural involvement.

6.2. Targeting Synaptic Pathways

6.2.1. AMPA/NMDA Antagonists

Targeting synaptic pathways, particularly glutamatergic signaling, offers a novel approach to disrupt tumor–neuron communication in gliomas and other neurotropic cancers. In a groundbreaking study by Venkataramani et al. [48], AMPA receptor antagonists, such as perampanel, were shown to reduce glioma cell excitability and tumor growth by blocking glutamatergic synapses formed with neurons. Similarly, NMDA receptor antagonists like memantine suppress activity-regulated genes, delaying tumor progression in preclinical models [52]. These drugs, already approved for epilepsy and Alzheimer's disease, offer a repurposing opportunity for cancer therapy.

The molecular mechanisms of synaptic inhibition involve disrupting calcium-dependent signaling cascades. According to Guichet et al. [49], AMPA receptor activation in glioma cells triggers calcium influx, activating MAPK and PI3K/Akt pathways that promote proliferation and invasion. Blocking these receptors reduces tumor cell responsiveness to neuronal glutamate, impairing synaptic integration and growth [54]. In glioblastoma, combining AMPA/NMDA antagonists with temozolomide enhances tumor control, suggesting synergistic effects with standard therapies [52].

Challenges in targeting synaptic pathways include minimizing neurotoxicity, as glutamate receptors are critical for normal brain function. Research by Ligon et al. [54] emphasizes the need for tumor-specific delivery systems, such as nanoparticle-based drug carriers, to enhance selectivity and reduce side effects. Additionally, tumor heterogeneity in receptor expression requires personalized approaches to optimize therapeutic outcomes [10]. These challenges highlight the importance of developing targeted delivery methods to translate synaptic inhibitors into clinical practice.

The broader applicability of synaptic inhibitors extends to brain metastases. Studies by Zeng et al. [55] show that breast and lung cancer metastases form glutamatergic synapses with neurons, suggesting that AMPA/NMDA antagonists could have utility beyond primary brain tumors. Clinical trials evaluating perampanel in glioblastoma (e.g., NCT03636958) are underway, providing critical data on efficacy and safety [103]. These findings underscore the potential of synaptic inhibitors to disrupt neural-driven tumor progression across multiple cancer types.

6.2.2. CRISPR-Based Gene Silencing

CRISPR-based gene silencing offers a precise approach to disrupt synaptic pathways by targeting genes critical for tumor–neuron communication. In a novel study by Venkatesh et al. [52], CRISPR-mediated silencing of neuroligin-3 (NLGN3) in glioma cells disrupted synapse-like junctions with neurons, significantly reducing tumor growth in mouse models. Similarly, silencing synaptic vesicle genes like SYN1 impairs glutamate release by tumor cells, weakening their integration into neural circuits [49]. These targeted interventions highlight the potential of gene editing to interrupt tumor–neuron crosstalk.

The specificity of CRISPR technology allows for the selective targeting of tumor-specific synaptic components. Research by Mandal et al. [78] demonstrates that CRISPR knockout of PSD95, a postsynaptic scaffolding protein, reduces glioma cell responsiveness to neuronal inputs, inhibiting proliferation and invasion. This approach minimizes off-target effects compared to pharmacological inhibitors, as it targets tumor-specific gene expression [10]. In preclinical models, CRISPR-based silencing of synaptic genes synergizes with radiation therapy, enhancing tumor control [54]. Challenges in CRISPR-based therapies include delivery barriers and potential immunogenicity. According to Kamerkar et al. [85], viral or nanoparticle-based delivery systems are needed to ensure efficient CRISPR targeting in vivo, particularly in the brain, where the blood–brain barrier poses a significant obstacle. Additionally, off-target editing risks require rigorous validation to ensure safety [104]. Despite these challenges, CRISPR-based approaches offer a promising avenue for precision oncology, particularly for gliomas with high synaptic activity.

The translational potential of CRISPR-based silencing is supported by early-phase studies. Research by Li et al. [105] highlights the feasibility of CRISPR-based therapies in glioblastoma, with ongoing trials exploring ex vivo gene editing for personalized treatment. These advances suggest that CRISPR-mediated disruption of synaptic pathways could become a cornerstone of neural-targeted cancer therapies, offering a highly specific approach to mitigate tumor progression.

6.3. Combination Therapies

6.3.1. Synergy with Immunotherapy/Chemotherapy

Combining neural-targeted therapies with immunotherapy and chemotherapy offers a synergistic approach to overcome tumor resistance and enhance anti-tumor efficacy. According to Bucsek et al. [47], β-blockers like propranolol enhance the efficacy of PD-1 inhibitors in breast cancer models by reducing MDSC and Treg activity, restoring CD8+ T cell function. In PDAC, combining β-blockers with gemcitabine improves tumor control by inhibiting neural-driven CSC survival, as shown by Renz et al. [24]. These synergistic effects highlight the potential of neural modulators to augment standard therapies.

Synaptic inhibitors also show promise in combination therapies. Research by Ligon et al. [54] demonstrates that AMPA receptor antagonists like perampanel enhance temozolomide efficacy in glioblastoma by reducing neural-driven proliferation, leading to prolonged survival in preclinical models. Similarly, Trk inhibitors like entrectinib synergize with chemotherapy in NTRK-fusion cancers by impairing neurotrophin-driven tumor innervation [29]. These combinations leverage the complementary mechanisms of neural and conventional therapies to target multiple aspects of tumor biology. The molecular basis of these synergies involves disrupting neural-driven resistance mechanisms. According to Cole et al. [19], neural signaling upregulates anti-apoptotic pathways and immunosuppression, which can be counteracted by combining neural inhibitors with immune checkpoint blockers. In prostate cancer, β-blockers reduce PD-L1 expression in the TME, enhancing immunotherapy responses [94]. These findings suggest that neural-targeted therapies can sensitize tumors to standard treatments, improving clinical outcomes.

6.3.2. Clinical Challenges

Despite their promise, combination therapies face significant clinical challenges, including tumor heterogeneity, optimal drug timing, and neurotoxicity. Research by Zahalka et al. [42] highlights that β2-AR expression varies across tumor types and stages, necessitating personalized treatment strategies to maximize efficacy. Similarly, the timing of neural inhibitors relative to chemotherapy or immunotherapy is critical, as asynchronous administration may reduce synergy [47]. Developing biomarkers to guide patient selection and treatment schedules is essential for clinical translation. Neurotoxicity remains a major concern, particularly for synaptic inhibitors. According to Ligon et al. [54], AMPA/NMDA antagonists can impair normal brain function, causing cognitive side effects that limit their use in glioblastoma patients. Targeted delivery systems, such as nanoparticles or convection-enhanced delivery, could mitigate these risks by concentrating drugs within the tumor [85]. Additionally, CRISPR-based therapies require precise delivery to avoid systemic toxicity, as noted by Li et al. [105].

Clinical trials are addressing these challenges to advance combination therapies. Studies like NCT03384836, which evaluate propranolol with anti-PD-1 therapies in solid tumors, provide critical data on safety and efficacy [102]. Similarly, trials of perampanel in glioblastoma (e.g., NCT03636958) are exploring optimal dosing to balance efficacy and neurotoxicity [103]. These efforts underscore the need for rigorous clinical evaluation to translate neural-targeted combination therapies into standard care, offering hope for improved outcomes in neurologically active cancers. To highlight the diversity of therapeutic approaches and their preclinical/clinical evidence, Table 5 compiles key strategies for targeting tumor-neuron interactions, including mechanisms, cancers, outcomes, and challenges.

Table 5 Therapeutic Strategies Targeting Tumor-Neuron Interactions

Strategy	**Mechanism**	**Target(s)**	**Associated Cancers**	**Preclinical/Clinical Evidence**	**Challenges**	**Reference**
Surgical Denervation	Ablation of sympathetic/parasympathetic nerves	Autonomic nerves	Prostate, gastric, PDAC	Reduces tumor incidence/metastasis in models; improved survival post-vagotomy	Invasive, side effects like autonomic dysfunction	[4], [5], [40]
β-Blockers	Block β-adrenergic signaling	β2-AR	Breast, prostate, ovarian	Improves survival, reduces metastasis; synergizes with immunotherapy	Off-target effects, dosing variability	[9], [45], [47]
Trk Inhibitors	Inhibit neurotrophin receptors	TrkA/B/C	PDAC, NTRK-fusion cancers	Reduces innervation and growth	Resistance via mutations	[29]
AMPA/NMDA Antagonists	Block glutamatergic signaling	AMPA/NMDA receptors	Glioma	Reduces proliferation; Phase II trials ongoing	Neurotoxicity	[52], [53], [103]
Muscarinic Antagonists	Inhibit cholinergic signaling	M3 receptors	Gastric, PDAC	Suppresses stemness, invasion	Limited specificity	[39], [43]
CRISPR Gene Silencing	Knockout synaptic genes	NLGN3, PSD95	Glioma	Impairs synaptic integration, reduces growth	Delivery barriers, off-target edits	[52], [72], [104]
Vagotomy	Disrupt vagal nerve signaling	Parasympathetic nerves	Gastric, PDAC	Reduces tumorigenesis	Surgical risks	[5], [20]
Dopamine Receptor Antagonists	Block DRD2/DRD4	Dopamine receptors	Glioblastoma	Impairs CSC survival	CNS side effects	[88], [89]
Exosome Inhibitors	Block exosome release	GW4869 targets	PDAC, glioma	Disrupts remote communication	Systemic toxicity	[86]
Combination: β-Blockers + Immunotherapy	Reduce immunosuppression + checkpoint blockade	β2-AR + PD-1	Breast, prostate	Enhances T cell function; Phase I trials	Timing and heterogeneity	[47], [102]
N-Cadherin Inhibitors	Disrupt adhesion	N-cadherins	PDAC, prostate	Reduces PNI	Specificity	[79]

Voltage-Gated Channel Blockers	Inhibit ion channels	Nav, Kv, CaV	Breast, ovarian, pancreatic	Reduces invasion, proliferation	Off-target on normal tissues	[64], [66], [69]

7. Emerging Tools and Technologies in Cancer Neuroscience

The rapid advancement of cancer neuroscience relies on cutting-edge tools and technologies that enable precise mapping and manipulation of tumor–neuron interactions. These innovations, ranging from spatial transcriptomics to optogenetics, provide unprecedented insights into the molecular and functional dynamics of neural-driven tumor progression. This section explores key technologies, focusing on their applications in studying tumor–neuron crosstalk and their potential to guide the development of novel therapies for cancers like glioblastoma, pancreatic ductal adenocarcinoma (PDAC), and prostate cancer.

7.1. Spatial Transcriptomics and Single-Cell RNA Sequencing

Introduction: Spatial transcriptomics and single-cell RNA sequencing (scRNA-seq) have revolutionized our understanding of the tumor microenvironment (TME) by mapping gene expression with high spatial and cellular resolution. These technologies reveal the molecular underpinnings of tumor–neuron interactions, identifying key pathways and cell types involved in neural-driven malignancy. Their application in cancer neuroscience is critical for developing targeted therapies and personalized treatment strategies.

7.1.1. Spatial Transcriptomics

Spatial transcriptomics enables the visualization of gene expression patterns within the TME, preserving spatial context to reveal how tumor–neuron interactions drive malignancy. In a landmark study by Yu et al. [10], spatial transcriptomics identified gradients of neurotrophin and neurotransmitter receptor expression in glioblastoma, highlighting regions of active tumor–neuron crosstalk that correlate with tumor aggressiveness. This approach has mapped nerve infiltration patterns in PDAC, showing elevated NGF and BDNF expression in areas of perineural invasion (PNI), which drives recurrence and pain [21]. Such insights are critical for identifying therapeutic targets within the neural niche.

The technology's high-resolution mapping capabilities reveal cellular heterogeneity in the TME. According to Monje et al. [1], spatial transcriptomics has identified distinct neuronal and glial populations interacting with glioma cells, elucidating synapse-like communication mediated by neuroligin-3 and AMPA receptors [49]. In prostate cancer, spatial analyses have revealed sympathetic nerve-driven expression of β2-adrenergic receptors (β2-AR), which promote immunosuppression and metastasis [42]. These findings provide a molecular blueprint for targeting neural-driven pathways in specific tumor regions. Therapeutic development benefits significantly from spatial transcriptomics. Research by Ståhl et al. [106] demonstrates its use in identifying spatially restricted drug targets, such as Trk receptors in PDAC, enabling the design of localized therapies like nanoparticle-delivered Trk inhibitors [29, 2015]. However, challenges include the high cost and computational complexity of analyzing large datasets, requiring standardized protocols for clinical translation. Future advancements in spatial transcriptomics could enhance its accessibility, paving the way for precision oncology in neurologically active cancers.

The clinical relevance of spatial transcriptomics lies in its prognostic and diagnostic potential. Studies by Berglund et al. [107] show that spatially mapped gene signatures in breast cancer correlate with neural infiltration and worse survival, suggesting their use as biomarkers. Integrating spatial transcriptomics with other omics technologies could further refine our understanding of tumor–neuron interactions, guiding personalized therapies to disrupt neural-driven malignancy [10].

7.1.2. Single-Cell RNA Sequencing

Single-cell RNA sequencing (scRNA-seq) complements spatial transcriptomics by providing cellular-level resolution of gene expression, uncovering the diversity of cell types involved in tumor–neuron crosstalk. According to Tirosh et al. [108], scRNA-seq in glioblastoma revealed distinct cancer stem cell (CSC) populations expressing synaptic genes like NLGN3, which drive synapse-like interactions with neurons [49]. In PDAC, scRNA-seq identified immune cell subsets modulated by sympathetic nerve signaling, such as MDSCs expressing β2-AR, which promote immunosuppression [93].

The technology's ability to dissect cellular heterogeneity has profound implications for understanding neural-driven tumor progression. Research by Neftel et al. [109] used scRNA-seq to characterize neuronal subtypes in the glioblastoma TME, revealing their role in secreting neurotrophins that sustain CSC stemness [30]. In prostate cancer, scRNA-seq has identified tumor cell subsets responsive to norepinephrine, driving metastasis via cAMP-PKA signaling [42]. These findings highlight the utility of scRNA-seq in identifying specific cellular targets for therapy.

Therapeutic applications of scRNA-seq include guiding precision medicine strategies. Studies by Patel et al. [110] demonstrate that scRNA-seq can identify resistance mechanisms in glioblastoma, such as upregulation of synaptic genes post-therapy, informing the use of AMPA receptor antagonists like perampanel [52]. Challenges include the need for high-quality tissue samples and integration with spatial data to contextualize findings [10]. Advances in computational tools are addressing these issues, enhancing scRNA-seq's translational potential.

The prognostic power of scRNA-seq is evident in its ability to identify actionable biomarkers. In a comprehensive study by Darmanis et al. [111], scRNA-seq revealed neural-immune interactions in glioblastoma, with high PD-L1 expression on nerve-associated macrophages correlating with poor prognosis [94]. These insights underscore scRNA-seq's role in developing targeted therapies and diagnostics, positioning it as a cornerstone of cancer neuroscience research.

7.2. Optogenetics and Electrophysiology

Optogenetics and electrophysiology provide functional insights into tumor–neuron interactions by manipulating and recording neural activity in real time. These tools have elucidated how neuronal signaling drives tumor progression, offering platforms to test therapeutic interventions. Their application in cancer neuroscience is transforming our ability to study and target neural circuits in cancers like glioblastoma and brain metastases.

7.2.1. Optogenetics

Optogenetics enables precise manipulation of neuronal activity using light-sensitive proteins, offering insights into how neural signaling influences tumor behavior. In a pivotal study by Venkatesh et al. [50], optogenetic stimulation of neurons in glioblastoma models increased tumor proliferation via glutamatergic synapses, confirming the role of neuronal activity in driving malignancy [48]. Conversely, optogenetic silencing of neurons reduced tumor growth, highlighting the potential of neural modulation as a therapeutic strategy. The technology's precision allows for targeted interrogation of specific neural circuits. Research by Pan et al. [112] used optogenetics to modulate sympathetic nerve activity in prostate cancer models, demonstrating that norepinephrine release enhances tumor cell invasion via β2-AR signaling [42]. In PDAC, optogenetic inhibition of vagal nerve activity suppressed tumor growth by reducing cholinergic signaling, mirroring the effects of vagotomy [5]. These findings provide a mechanistic basis for developing neural-targeted therapies.

Challenges in optogenetics include its invasive nature and limited clinical applicability. According to Boyden [113], delivering light-sensitive proteins to human tumors requires advanced vectors, such as viral or nanoparticle-based systems, which face regulatory hurdles [85]. Additionally, the complexity of tumor-associated neural circuits demands precise targeting to avoid off-target effects. Despite these challenges, optogenetics remains a powerful tool for preclinical research, guiding the development of neural modulators. The translational potential of optogenetics lies in its ability to inform therapeutic strategies. Studies by Mandal et al. [78] suggest that optogenetic insights could guide the use of pharmacological inhibitors, such as β-blockers or AMPA antagonists, to mimic neural silencing effects [47]. Future advancements in non-invasive optogenetic techniques could enhance its clinical relevance, offering new ways to disrupt tumor–neuron interactions.

7.2.2. Electrophysiology

Electrophysiology, particularly patch-clamp and calcium imaging, provides real-time insights into the functional dynamics of tumor–neuron interactions. In a seminal study by Venkataramani et al. [48], patch-clamp recordings revealed excitatory postsynaptic currents (EPSCs) in glioma cells, confirming their integration into neural circuits via AMPA receptors. Calcium imaging further demonstrated synchronized calcium transients between glioma cells and neurons, driving tumor proliferation [52]. These techniques are critical for understanding the electrophysiological basis of tumor malignancy. In cancers with neural infiltration, electrophysiology has elucidated neurotransmitter-driven signaling. Research by Jung et al. [57] used calcium imaging to show that breast cancer brain metastases exhibit neuronal-like responses to glutamate, promoting metastatic growth [55]. In PDAC, electrophysiological recordings have

identified cholinergic signaling in tumor cells, correlating with increased motility and PNI [39]. These findings highlight electrophysiology's role in mapping functional tumor–neuron interactions.

Therapeutic development benefits from electrophysiological insights. Studies by Gibson et al. [59] demonstrate that blocking AMPA receptor-mediated EPSCs with perampanel reduces tumor growth in glioblastoma models, validating electrophysiological targets [54]. However, the invasive nature of electrophysiological techniques limits their clinical use, requiring integration with non-invasive imaging modalities like MRI [10]. Advances in high-throughput electrophysiology could overcome these barriers, enhancing its translational potential.

The prognostic utility of electrophysiology lies in its ability to identify neural-driven tumor subtypes. According to Venkatesh et al. [50], electrophysiological signatures in glioblastoma, such as high EPSC frequency, correlate with aggressive phenotypes and poor survival. These signatures could guide patient stratification for neural-targeted therapies, such as synaptic inhibitors, improving outcomes in neurologically active cancers [103].

8. Conclusion

The emerging field of cancer neuroscience has unveiled the profound role of tumor–neuron interactions in driving malignancy, reshaping our understanding of cancer biology and opening novel therapeutic avenues. This review has explored the intricate mechanisms by which tumors co-opt neural circuits, from tumor-induced neurogenesis and synaptic communication to neural modulation of the immune microenvironment and cancer stem cell (CSC) niches. These interactions, observed across cancers such as glioblastoma, pancreatic ductal adenocarcinoma (PDAC), prostate, and breast cancer, highlight the nervous system as a critical regulator of tumor progression, metastasis, and therapy resistance.

Tumors actively recruit peripheral and autonomic nerves through neurotrophic factors like NGF and BDNF, fostering perineural invasion and creating feedback loops that sustain tumor growth. In gliomas, synapse-like structures enable tumor cells to integrate into neural circuits, leveraging glutamatergic signaling to enhance proliferation and invasion. Neural signaling, particularly through sympathetic and stress-related pathways, further modulates the tumor immune microenvironment, promoting immunosuppression via MDSCs and Tregs, which hinders effective anti-tumor immunity. These neural-driven mechanisms also sustain CSC populations, contributing to tumor dormancy and recurrence, particularly in cancers with high neural infiltration. Therapeutic strategies targeting these interactions show significant promise. Surgical denervation and pharmacological inhibitors, such as β-blockers and AMPA receptor antagonists, disrupt neural-driven tumor progression, while CRISPR-based gene silencing offers precision targeting of synaptic pathways. Combining these neural-targeted approaches with immunotherapy and chemotherapy enhances efficacy by overcoming resistance mechanisms, as seen in preclinical models of glioblastoma and PDAC. Emerging tools like spatial transcriptomics, single-cell RNA sequencing, optogenetics, and electrophysiology provide unprecedented insights into the molecular and functional dynamics of tumor–neuron crosstalk, guiding the development of personalized therapies.

Despite these advances, challenges remain in translating cancer neuroscience findings into clinical practice. Tumor heterogeneity, off-target effects of neural inhibitors, and the complexity of neural-immune interactions necessitate precise biomarkers and delivery systems to optimize therapeutic outcomes. The high cost and computational demands of advanced technologies also pose barriers to widespread adoption. Future research should focus on developing non-invasive neural modulators, integrating multi-omics data to map tumor–neuron interactions, and conducting clinical trials to validate combination therapies. Addressing these challenges will be critical to harnessing the full potential of cancer neuroscience.

Looking ahead, the interplay between tumors and the nervous system represents a paradigm shift in oncology, offering new perspectives on tumor biology and treatment. By targeting neural-driven mechanisms, we can disrupt the supportive niches that sustain malignancy, paving the way for innovative therapies that improve survival and quality of life for patients with neurologically active cancers. As research progresses, cancer neuroscience holds the promise of transforming cancer care, bridging basic science and clinical application to address some of the most pressing challenges in oncology.

Compliance with ethical standards

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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.

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