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Altering Neuronal Communication for Cancer Therapy: Mechanisms, Therapeutic Targets and Emerging Strategies

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Abstract : *Background: Cancer is increasingly understood as a disease shaped not only by malignant cells and their surrounding stroma, but also by signals from the nervous system. Neurons can communicate with tumour cells through neurotransmitters, neuropeptides, electrical activity, synaptic contacts and activity-dependent secreted factors. These interactions may support tumour growth, invasion, angiogenesis, immune modulation and treatment resistance. Objective: This review examines how altered neuronal communication contributes to cancer development and evaluates the rationale, evidence and limitations of therapies designed to interrupt tumour–nerve signalling. Methods: A narrative review was prepared from the fifteen references supplied for the assignment, supplemented by established concepts in cancer neuroscience. The literature was organized around central nervous system tumours, peripheral solid tumours, signalling mechanisms and therapeutic opportunities. Results: Experimental studies demonstrate that neuronal activity can promote glioma growth through neuroligin-3, while glioma cells can integrate into neuronal circuits and receive synaptic input. In peripheral cancers, sympathetic and parasympathetic nerves may influence tumour initiation, progression, dissemination and the tumour microenvironment. Candidate interventions include modulation of neurotransmitter receptors, inhibition of activity-regulated factors, nerve-directed approaches and combination strategies with established anticancer treatments. Conclusion: Neuronal communication is a biologically important and potentially actionable component of the tumour ecosystem. However, most therapeutic evidence remains preclinical or early translational. Selective targeting, tumour-specific biomarkers, careful assessment of neurological and cardiovascular effects, and clinical validation are essential before these approaches can become routine cancer treatments*

Keywords: Cancer neuroscience; neuronal communication; tumour–nerve interaction; neurotransmitters; neuroligin-3; glioma; synaptic signalling; neuropeptides; cancer therapy; tumour microenvironment

I. INTRODUCTION

Cancer has traditionally been studied through the interaction of malignant cells with genetic alterations, blood vessels, immune cells and connective tissue. This framework has expanded considerably with the recognition that the nervous system is an active component of the tumour microenvironment. Nerves are present in many organs, release biologically potent signalling molecules and respond dynamically to local tissue conditions. Tumours can grow near existing nerves, recruit or remodel nerve fibres, and release factors that alter neural activity. Conversely, neural signals can change the behaviour of malignant cells and non-malignant cells surrounding them. The field examining these bidirectional relationships is commonly described as cancer neuroscience [1,2].

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Neuronal communication is the transfer of information between neurons and between neurons and other cell types. It occurs through electrical impulses, chemical neurotransmission, neuropeptide release, direct synaptic contacts and paracrine signalling. In a healthy tissue, these processes regulate functions such as movement, sensation, secretion, organ activity and tissue homeostasis. In cancer, the same pathways may be co-opted to support proliferation, survival, migration, invasion, angiogenesis, immune suppression and metastatic spread. The outcome depends on tumour type, anatomical site, nerve subtype, receptor expression and the state of the surrounding microenvironment [1,2].

A major conceptual advance has come from studies of glioma. High-grade gliomas arise in the brain, where malignant cells exist within a highly active neuronal environment. Neuronal activity can release soluble factors, including neuroligin-3 (NLGN3), that stimulate glioma growth. In addition, glioma cells can form functional connections with neurons and receive excitatory synaptic input. These findings suggest that some brain tumours do not simply occupy neural tissue; they can become functionally integrated into neural circuits [3–6].

Neural influences are not limited to brain tumours. Peripheral nerves are found in many organs in which cancers arise, including the prostate, breast, pancreas, stomach and other tissues. Experimental work has implicated sympathetic and parasympathetic signalling in tumour initiation, progression, angiogenesis and dissemination. For example, autonomic nerve development has been linked with prostate cancer progression, while sympathetic signalling has been associated with metastatic changes in breast cancer models [8–10]. These observations have encouraged investigation of nerve density, neural activity and neurotransmitter receptor pathways as potential biomarkers and therapeutic targets.

The phrase ‘altering neuronal communication for cancer therapy’ refers to modifying a disease-associated neural signal rather than indiscriminately suppressing the nervous system. Possible strategies include blocking a tumour-promoting receptor, reducing release of a growth-supporting neural factor, interrupting a pathological synaptic connection, modulating nerve activity, or preventing tumour-induced nerve recruitment. The therapeutic objective is to disrupt signals that benefit the tumour while preserving essential neurological, autonomic and sensory functions.

This review brings together the mechanistic and translational themes represented in the selected literature. It first outlines the main modes of tumour–nerve communication, then considers evidence from brain and peripheral cancers, followed by potential therapeutic approaches, safety considerations and future research needs. Because the evidence base includes mechanistic experiments, animal models and perspective articles, conclusions are framed according to the maturity of the evidence and should not be interpreted as proof of clinical efficacy.

II. MATERIALS AND METHODS

This article was developed as a narrative review using the fifteen references supplied by the requester as its core source list. The selected papers cover cancer neuroscience, neural regulation of cancer, synaptic communication in brain tumours, neuronal activity-regulated NLGN3 signalling, glioma integration into neural circuits, sympathetic and autonomic signalling in peripheral cancers, and emerging therapeutic directions. The papers were grouped thematically rather than subjected to quantitative meta-analysis.

The review focused on five domains: (i) neuronal and tumour-cell communication mechanisms; (ii) neural effects in central nervous system tumours; (iii) autonomic and peripheral nerve effects in extracranial cancers; (iv) therapeutic opportunities and combination strategies; and (v) safety and translational limitations. No pooled effect estimates were calculated. This is a narrative synthesis, not a systematic review; therefore, it does not claim exhaustive database coverage, formal risk-of-bias assessment or PRISMA-compliant study selection.

The references supplied include abbreviated author lists and some bibliographic details that should be checked against the publisher record before submission. In particular, entries supplied with ‘et al.’ are retained in abbreviated form in the working bibliography; a journal submission may require the complete author list. The final reference list is numbered in Vancouver style to align with the previously stated journal-format preference.

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III. BIOLOGICAL BASIS OF NEURONAL COMMUNICATION IN CANCER

3.1 The tumour–nerve microenvironment

The tumour microenvironment is a complex ecosystem containing malignant cells, fibroblasts, endothelial cells, immune cells, extracellular matrix, blood vessels and peripheral or central nerve fibres. Neural elements may be present before tumour formation or may increase as a tumour develops. Tumour cells can release neurotrophic factors and chemotactic signals that encourage nerve growth, while nerve terminals can release neurotransmitters and neuropeptides that act on tumour and stromal cells. This creates a reciprocal signalling loop in which nerves influence cancer biology and cancer alters the local nervous system [1,2,11].

The density and type of nerve fibres vary by organ and tumour. Sympathetic fibres commonly release noradrenaline, parasympathetic fibres use acetylcholine, and sensory fibres may release neuropeptides such as substance P and calcitonin gene-related peptide. These molecules can act on receptors expressed by cancer cells, vascular cells, immune cells and fibroblasts. The same transmitter may have different effects in different tissues because receptor subtype, intracellular signalling and cell context determine the biological response.

3.2 Electrical activity and chemical synaptic signalling

Neurons communicate electrically through action potentials and chemically through transmitter release at synapses. When an action potential reaches a nerve terminal, calcium-dependent vesicle fusion releases neurotransmitters into a synaptic cleft. Transmitters bind to ionotropic receptors, which directly regulate ion channels, or metabotropic receptors, which activate intracellular signalling cascades. These mechanisms can alter membrane potential, calcium concentration, cyclic nucleotide pathways, kinase activity and gene expression.

Cancer cells may respond to these signals even when they are not conventional neurons. Expression of neurotransmitter receptors, ion channels and synaptic proteins can allow malignant cells to detect neuronal activity. In glioma, glutamatergic synaptic input can depolarize tumour cells and promote calcium-dependent signalling. This provides a direct route by which electrical activity in surrounding neural circuits can influence tumour-cell behaviour [3,4].

3.3 Neurotransmitters and neuropeptides

Glutamate is the principal excitatory neurotransmitter in the central nervous system. In the tumour context, glutamate can participate in excitatory signalling between neurons and glioma cells. Gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in much of the adult brain, may also influence tumour cells depending on receptor expression and cellular state. Acetylcholine, noradrenaline, dopamine, serotonin and several neuropeptides have been investigated in peripheral and central malignancies. Their effects are not uniform: a pathway may promote growth in one tumour type and have a different or even opposing effect in another.

Neuropeptides can act over distances greater than the narrow synaptic cleft and may influence vascular tone, inflammation, immune-cell recruitment and stromal activity. Consequently, the neural contribution to cancer is not restricted to direct neuron-to-tumour synapses. Diffuse paracrine signalling and systemic autonomic effects may also shape tumour progression [1,2,11].

3.4 Neurotrophic factors and nerve recruitment

Neurotrophic factors support neuronal survival, differentiation and growth. Tumours can exploit related growth-factor systems to promote innervation, while nerves can release mediators that support tumour-cell survival and tissue remodelling. Nerve recruitment, sometimes described as tumour-associated neurogenesis or axonogenesis, may increase the availability of local neural signals. The relationship is reciprocal: cancer-associated inflammation, tissue damage and tumour-derived mediators may alter nerve structure and function, while neural activity can influence tumour-associated stroma.

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3.5 Synaptic proteins and activity-dependent factors

Synaptic adhesion proteins and activity-regulated secreted factors are particularly relevant in brain tumours. Neuroligin-3 is a synaptic protein whose release can be stimulated by neuronal activity. Experimental studies have shown that neuronal activity promotes glioma growth through NLGN3, identifying an activity-dependent signal that links normal neural function to malignant-cell proliferation [5]. Subsequent work investigated the therapeutic potential of targeting this dependency in high-grade glioma [6]. These studies helped establish neural activity as a potential therapeutic axis in brain cancer.

Communication mode	Principal components	Potential cancer-related effect
Electrical / synaptic	Action potentials, glutamate receptors, ion channels, synaptic proteins	Tumour-cell depolarization, calcium signalling and growth-related activity
Neurotransmitter-mediated	Glutamate, noradrenaline, acetylcholine, serotonin and dopamine	Altered proliferation, survival, migration or stromal signalling, depending on receptor context
Neuropeptide-mediated	Substance P, CGRP and other neuropeptides	Inflammation, vascular responses, immune modulation and tumour–stroma communication
Neurotrophic / axonal	Neurotrophic factors and axon-guidance pathways	Nerve recruitment, survival of neural fibres and remodelling of the tumour niche
Activity-dependent secreted factors	Neuroligin-3 and related mediators	Coupling of neural activity to tumour growth and cellular plasticity

IV. NEURONAL COMMUNICATION IN BRAIN TUMOURS

4.1 Neuronal activity as a growth-supporting signal

The brain is an electrically active organ, and glioma cells develop within this dynamic environment. Work by Venkatesh and colleagues showed that neuronal activity can promote glioma growth through secretion of NLGN3 [5]. The importance of this finding lies in its demonstration that activity in non-malignant neurons can generate a signal that directly supports malignant-cell expansion. It also suggests that tumour growth may be influenced by the functional state of nearby neural circuits, not solely by tumour-intrinsic mutations.

NLGN3 is released in an activity-dependent manner and can activate growth-associated pathways in glioma cells. This creates a mechanistic link between neuronal firing and tumour proliferation. The pathway is of interest because it may provide a relatively defined molecular target: rather than suppressing all neuronal activity, an intervention could potentially inhibit the tumour's response to a specific activity-regulated factor. However, NLGN3 biology is complex and its physiological roles in synaptic function must be considered when designing therapeutic interventions.

4.2 Functional integration of glioma into neural circuits

A further advance was the demonstration that glioma cells can form functional synaptic connections with neurons. Venkatesh and colleagues reported electrical and synaptic integration of glioma into neural circuits [4]. This observation challenges the older view of glioma cells as passive neighbours of neurons. Instead, tumour cells can receive neuronal input and use neural signals to influence their own activity and growth.

Synaptic integration may contribute to tumour progression through repeated activity-dependent stimulation. It may also help explain the invasive behaviour of some glioma cells, since neural networks provide extensive anatomical pathways through brain tissue. The discovery of functional neuron–glioma connections raises several questions: whether synapses are present in all glioma subtypes, whether their abundance predicts outcome, how they change during treatment, and whether disrupting them can be achieved without unacceptable effects on normal brain function.

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4.3 Glutamatergic signalling and excitability

Glutamatergic signalling is central to excitatory neurotransmission and is an important area of investigation in glioma. Tumour-cell receptors and ion channels can translate extracellular glutamate into changes in membrane potential and intracellular calcium. These signals may affect proliferation, migration and interactions with surrounding neurons. Excessive glutamate signalling can also disturb neuronal function and contribute to excitotoxic stress in adjacent tissue. Thus, glutamate-related pathways may influence both tumour biology and neurological symptoms.

A therapeutic strategy aimed at glutamatergic communication must distinguish tumour-promoting signalling from normal neurotransmission. Broad inhibition of glutamate receptors could impair cognition, movement or other neurological functions. More selective approaches may focus on tumour-enriched receptor subtypes, tumour-specific channel dependencies, synaptic adhesion molecules or downstream pathways that are disproportionately active in malignant cells.

4.4 Implications for glioma treatment

The standard management of high-grade glioma commonly involves combinations of surgery, radiotherapy and systemic anticancer therapy, selected according to tumour type, molecular features and patient condition. Neural signalling research does not replace these approaches. Rather, it offers a potential complementary strategy: identify a neural pathway that sustains tumour growth and inhibit it alongside established treatment. The NLGN3 dependency work is an example of translating a mechanistic discovery into a therapeutic hypothesis [6].

Potential benefits of neural-targeted treatment include limiting activity-dependent growth signals, reducing tumour–neuron communication and possibly influencing invasion or treatment resistance. Important uncertainties remain regarding drug delivery into the brain, blood–brain barrier penetration, tumour heterogeneity, adaptive pathway bypass and the effects of long-term neural modulation. Clinical benefit must be demonstrated in appropriately designed trials rather than inferred from preclinical findings.

V. NEURONAL COMMUNICATION IN PERIPHERAL CANCERS

5.1 Autonomic nervous system and tumour progression

The autonomic nervous system regulates involuntary organ functions and includes sympathetic and parasympathetic branches. These branches can influence tissue physiology through neurotransmitter release, changes in blood flow, glandular secretion, smooth-muscle activity and immune regulation. Tumours arising in autonomically innervated organs may therefore be exposed to neural signals that alter the local environment. Cancer neuroscience research suggests that autonomic signalling can affect tumour growth and metastatic behaviour, although the direction and magnitude of effects vary across tumour types [1,2,11].

5.2 Sympathetic signalling in breast cancer models

Sloan and colleagues reported that the sympathetic nervous system can induce a metastatic switch in a primary breast cancer model [8]. This work contributed to the idea that stress-related neural signalling may influence cancer progression through pathways that extend beyond the malignant cell itself. Sympathetic neurotransmitters can act on adrenergic receptors and alter signalling in tumour cells and components of the microenvironment. The findings are important mechanistically, but animal-model observations should not be translated into claims that everyday psychological stress directly causes metastasis in people.

5.3 Chronic stress, angiogenesis and ovarian carcinoma models

Thaker and colleagues demonstrated in a mouse model of ovarian carcinoma that chronic stress promoted tumour growth and angiogenesis [9]. The study connected stress-associated neuroendocrine and adrenergic signalling with vascular changes in the tumour environment. Angiogenesis is essential for the supply of oxygen and nutrients to expanding tumours, and neural or stress-related pathways may influence pro-angiogenic mediators. These findings

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support investigation of stress-responsive pathways as biological modifiers, but they do not establish stress reduction as a substitute for cancer treatment.

5.4 Autonomic nerve development in prostate cancer

Magnon and colleagues reported that autonomic nerve development contributes to prostate cancer progression [10]. Their work helped establish that nerve fibres can be active participants in tumour development rather than incidental structures. The study also highlighted the importance of distinguishing nerve subtypes and their respective signalling functions. It has encouraged investigation of nerve density, neural growth factors and autonomic pathways as possible biomarkers or therapeutic targets in prostate cancer.

5.5 Beyond breast, ovarian and prostate cancer

The broader cancer neuroscience literature considers neural influences across multiple organ systems and tumour types [1,2,7,11,12]. Peripheral nerve signalling may influence tumour-cell behaviour directly, but it may also act indirectly through immune cells, fibroblasts, endothelial cells and tissue-resident stem or progenitor cells. As a result, the same neural intervention could have several biological consequences. Future studies need to map which nerve subtypes and receptors are relevant in each cancer rather than assuming that a single neural pathway is universally tumour-promoting.

Cancer context	Neural theme reported in the selected literature	Potential therapeutic relevance
Glioma / high-grade brain tumours	Neuronal activity, NLGN3 release and functional synaptic integration [4–6]	Interrupt activity-dependent tumour growth or tumour–neuron synaptic signalling
Breast cancer models	Sympathetic signalling associated with a metastatic switch [8]	Investigate adrenergic signalling and neural regulation of metastatic traits
Ovarian carcinoma model	Chronic stress-associated signalling linked to tumour growth and angiogenesis [9]	Study stress-responsive pathways and tumour vascular biology
Prostate cancer	Autonomic nerve development associated with progression [10]	Investigate nerve subtype-specific pathways and tumour innervation
Other solid tumours	Broader tumour–nerve crosstalk and neural regulation [1,2,7,11,12]	Develop tumour-specific maps of neural pathways and biomarkers

VI. THERAPEUTIC STRATEGIES TO ALTER NEURONAL COMMUNICATION

6.1 Blocking tumour response to neurotransmitters

One therapeutic concept is to prevent cancer cells from responding to a tumour-promoting neurotransmitter. This may involve receptor antagonism, selective modulation of receptor signalling or inhibition of downstream effectors. The approach is attractive because it targets the receiving side of the communication pathway and may avoid complete suppression of nerve activity. However, receptor expression can differ between patients and tumour regions, and the same receptor may be expressed in normal tissues. Biomarker-guided selection and careful pharmacological characterization are therefore essential.

6.2 Modulating activity-dependent growth factors

The NLGN3 pathway provides a clear example of an activity-dependent factor that may be targeted in glioma [5,6]. Therapeutic strategies could aim to reduce release of the factor, neutralize it extracellularly, block its receptor or inhibit downstream signalling within tumour cells. Each option has different pharmacological requirements. An extracellular

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neutralizing approach may need adequate penetration into the brain and tumour interstitial space, while receptor or downstream inhibitors must achieve sufficient selectivity to avoid widespread effects on normal synaptic biology.

6.3 Disrupting pathological synaptic communication

The discovery of neuron-to-glioma synapses creates a rationale for studying synaptic proteins, adhesion molecules, ion channels and excitatory receptors as treatment targets [4]. A successful intervention would ideally weaken the tumour's access to growth-promoting neural input while preserving normal neuronal communication. This is challenging because many synaptic proteins are essential to normal brain function. Tumour-selective expression patterns, local delivery and molecularly targeted agents may help improve the therapeutic window.

6.4 Modulating autonomic signalling

In peripheral cancers, autonomic signalling may be modified by targeting receptors or downstream pathways associated with sympathetic or parasympathetic activity. Preclinical studies have provided a rationale for investigating adrenergic and cholinergic pathways in selected tumour contexts [8–10]. However, systemic modulation of autonomic function can affect heart rate, blood pressure, gastrointestinal motility and other essential physiological processes. Clinical studies must therefore establish both anticancer benefit and acceptable systemic safety.

6.5 Targeting nerve recruitment and tumour innervation

If tumour progression depends partly on increased innervation, another approach is to interfere with signals that attract, sustain or remodel nerve fibres in the tumour. Candidate mechanisms include neurotrophic factors, axon-guidance molecules and tumour-derived mediators that promote neurite growth. Such strategies may reduce the local supply of neural signals. They also carry risks because nerve growth and repair are necessary for normal tissue maintenance, sensation and recovery after injury.

6.6 Combination with established cancer treatments

Neural pathway modulation is more likely to be developed as a component of multimodal therapy than as a stand-alone treatment. A neural-targeted agent could potentially be combined with surgery, radiotherapy, chemotherapy, targeted therapy or immunotherapy, depending on the cancer type. Combination studies should determine whether neural modulation improves tumour control, reduces recurrence or sensitizes malignant cells to existing treatments. They must also test whether treatment-related inflammation, tissue injury or changes in neural activity alter the relevant pathway.

6.7 Potential treatment framework

Strategy	Target level	Rationale	Key limitation
Neurotransmitter receptor modulation	Tumour-cell or stromal receptor	Reduce response to a tumour-promoting transmitter	Receptor heterogeneity and effects in normal organs
Activity-dependent factor inhibition	Secreted mediator such as NLGN3	Interrupt neuron-activity-to-tumour-growth signalling	Brain delivery and physiological functions of the target
Synaptic pathway disruption	Synaptic adhesion proteins, ion channels or receptors	Reduce functional neural input to malignant cells	Risk of disrupting normal neural circuits
Autonomic pathway modulation	Adrenergic or cholinergic signalling	Alter neural regulation of tumour and stroma	Cardiovascular and autonomic adverse effects
Anti-innervation approaches	Neurotrophic and axon-guidance signals	Limit tumour-associated nerve recruitment	Potential interference with normal nerve repair
Combination treatment	Neural pathway plus	Address multiple tumour-	Drug interactions and

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	standard therapy	supporting mechanisms	difficulty attributing benefit

VII. ROLE OF NEURONAL COMMUNICATION IN THE TUMOUR MICROENVIRONMENT

7.1 Angiogenesis and vascular regulation

Tumour growth requires an adequate blood supply. Neural signals can influence vascular tone and may affect endothelial-cell behaviour and angiogenic mediator production. The ovarian carcinoma model reported by Thaker and colleagues linked chronic stress-associated signalling with enhanced angiogenesis and tumour growth [9]. This suggests that neural and neuroendocrine pathways may contribute to vascular remodelling in selected contexts. However, the relative importance of direct neural effects, endocrine responses and immune-mediated mechanisms needs further clarification.

7.2 Immune regulation

Neural signalling can influence immune-cell trafficking, cytokine release and inflammatory tone. Tumour-associated nerves may therefore alter antitumour immunity indirectly, by changing the behaviour of macrophages, lymphocytes, dendritic cells or other immune populations. The interaction is likely bidirectional: immune-derived mediators can also affect nerve activity and neural structure. This raises the possibility that neural pathway modulation could influence responses to immunotherapy, but this remains an active research question rather than an established clinical strategy.

7.3 Fibroblasts and extracellular matrix

Cancer-associated fibroblasts contribute to extracellular matrix deposition, tissue stiffness, growth-factor release and immune regulation. Neural transmitters and neuropeptides may affect fibroblast activation and matrix remodelling. Conversely, fibroblasts can release factors that influence nerve growth. Such interactions may shape tumour invasion and the physical architecture of the microenvironment. A complete understanding of tumour–nerve crosstalk therefore requires analysis of the entire tissue ecosystem rather than isolated tumour cells.

7.4 Metastasis and invasion

Metastasis involves local invasion, entry into vessels, survival in circulation, exit into distant tissues and colonization. Neural pathways may influence several of these steps through effects on tumour-cell motility, adhesion, angiogenesis, inflammation and stromal support. The breast cancer and prostate cancer studies in the selected literature provide examples of neural involvement in metastatic or progressive behaviour [8,10]. Nevertheless, the exact contribution of neural signalling in human metastasis remains to be quantified for each cancer type.

VIII. PHARMACOLOGICAL AND DRUG-DEVELOPMENT CONSIDERATIONS

8.1 Target validation

A neural pathway should not be considered a drug target solely because it is associated with tumour progression. Target validation requires evidence that the pathway is functionally necessary, that its manipulation changes tumour behaviour, and that the effect is reproducible across relevant models. Genetic perturbation, pharmacological inhibition, rescue experiments and independent replication can strengthen causal inference. Investigators should also determine whether the pathway is active in patient tumour samples and whether activity correlates with clinically meaningful outcomes.

8.2 Selectivity and therapeutic window

Many neurotransmitters and synaptic proteins are essential to normal physiology. A drug that blocks a widely expressed receptor may produce neurological, cardiovascular or gastrointestinal adverse effects. The therapeutic window may be improved by targeting a tumour-enriched receptor subtype, a disease-specific protein interaction, a downstream dependency or a local delivery route. The aim should be selective interruption of pathological communication rather than global neural suppression.

8.3 Delivery to the central nervous system

For brain tumours, drug delivery is a major challenge. The blood–brain barrier restricts entry of many molecules, although its integrity may be altered in parts of a tumour. Drug distribution can vary between the enhancing tumour

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core, infiltrative margins and surrounding brain. Therapeutic development must therefore assess brain penetration, target engagement in infiltrating cells and exposure in normal neural tissue. A compound that reaches the tumour core but not invasive margins may have limited clinical value.

8.4 Biomarkers and patient stratification

Potential biomarkers include nerve density, neural subtype markers, expression of neurotransmitter receptors, abundance of synaptic proteins, NLGN3 pathway activity and molecular signatures of neural response. Imaging approaches may also help characterize innervation or neural activity, although these methods require validation. Biomarkers could identify patients whose tumours depend on a particular neural pathway and help avoid exposing patients unlikely to benefit.

8.5 Preclinical models

Conventional tumour-cell cultures do not reproduce the full neural microenvironment. More informative systems may include neuron–tumour co-cultures, organoids, brain slices, engineered neural networks, patient-derived models and animal models with intact innervation. Each model has limitations. Co-cultures can isolate specific interactions but may lack immune and vascular components; animal models provide systemic context but may not fully reproduce human disease. Combining complementary models is likely to produce stronger evidence.

IX. CLINICAL TRANSLATION AND CURRENT LIMITATIONS

Cancer neuroscience is a rapidly developing research area, but the clinical translation of neural-targeted therapy remains at an early stage. Reviews and perspectives emphasize the need to connect mechanistic discoveries with patient-based studies, clinical specimens and carefully designed trials [1,2,7,11–13]. The presence of a plausible neural mechanism does not establish that blocking it will improve survival, quality of life or treatment response in humans.

A first limitation is biological heterogeneity. Different tumour types, molecular subgroups and anatomical sites may use distinct neural pathways. Even within a single tumour, invasive margins and central regions may differ in innervation, receptor expression and activity. A second limitation is pathway redundancy: malignant cells may compensate for blockade of one transmitter or growth factor by activating another pathway. A third limitation is safety, because neural targets often participate in normal organ function.

A further challenge is separating direct neural effects from systemic stress responses. Studies of chronic stress and cancer may involve endocrine, immune, behavioural and metabolic changes in addition to local nerve signalling. Observational associations in humans can be confounded by disease severity, treatment exposure, sleep, physical activity and other factors. Mechanistic experiments are needed to clarify causality, and clinical studies must avoid implying that patients are responsible for cancer progression because of their emotional state.

Finally, the field requires standardized methods for measuring tumour innervation and neural activity. Nerve density alone may not reflect functional signalling, and expression of a neurotransmitter receptor does not prove that the receptor is activated in vivo. Better spatial and functional profiling will help connect neural anatomy with tumour behaviour and treatment response.

X. FUTURE PERSPECTIVES

Future work should move from broad descriptions of tumour innervation toward precise maps of the neural circuits and molecular signals that matter in each cancer. Single-cell and spatial transcriptomic methods can identify receptor expression and cell states in their tissue context. Spatial proteomics, electrophysiology and advanced imaging may reveal functional contacts between neurons and malignant cells. These data should be integrated with tumour genomics and clinical outcomes.

Another priority is to define whether neural signalling is an early driver, a late progression mechanism or a treatment-induced adaptation. Longitudinal models could determine how innervation and neuronal activity change during tumour development, surgery, radiotherapy and systemic treatment. This may reveal windows during which neural pathway modulation is most effective.

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The development of selective agents is essential. Rather than broadly inhibiting neuronal activity, future drugs may target tumour-specific synaptic dependencies, activity-regulated secreted factors or receptor configurations enriched in malignant tissue. Drug delivery systems, local administration and targeted biologics may improve exposure at the tumour while limiting systemic effects. Any such approach will require rigorous safety evaluation.

Combination therapy deserves particular attention. Neural pathway inhibitors may be paired with standard anticancer treatments if preclinical evidence demonstrates complementary mechanisms. For example, a neural-targeted intervention might reduce a growth-supporting signal while radiotherapy or chemotherapy damages tumour cells through an independent mechanism. Combination studies should include pharmacodynamic biomarkers to confirm that the neural target is actually inhibited.

The field should also include patient-centred outcomes. Neurological function, cognition, pain, fatigue and quality of life are particularly important when targeting pathways that intersect with normal neural activity. A therapy that modestly slows tumour growth but causes substantial neurological impairment may not provide meaningful overall benefit. Early trials should therefore assess functional outcomes alongside tumour response and survival.

XI. DISCUSSION

The literature reviewed here supports a revised view of cancer biology in which the nervous system is an active participant in the tumour microenvironment. The strongest mechanistic evidence in the selected references comes from glioma studies demonstrating activity-dependent NLGN3 signalling and functional synaptic integration [4–6]. These findings provide direct evidence that neuronal activity can influence malignant-cell behaviour and that tumour cells can receive neural input.

The peripheral cancer studies broaden the concept by showing that autonomic and sympathetic pathways can affect tumour progression, angiogenesis and metastatic traits in experimental models [8–10]. Together, these observations suggest that neural communication is not a single pathway but a family of context-dependent interactions involving nerve subtype, transmitter, receptor, tumour genotype and local tissue environment.

From a pharmaceutical perspective, the most promising opportunities are those in which a specific neural dependency can be identified and pharmacologically modified with acceptable selectivity. NLGN3-related signalling in glioma is an illustrative example because it links neuronal activity to a defined secreted mediator and tumour response [5,6]. In peripheral cancers, autonomic receptor pathways may be relevant in selected settings, but systemic effects require particular attention.

The evidence should nevertheless be interpreted cautiously. Many findings are based on preclinical models, and a mechanism that is important in a mouse model may not be equally important in human disease. The therapeutic value of altering neuronal communication will depend on demonstrating target engagement, clinical benefit and safety. At present, cancer neuroscience should be viewed as a promising source of therapeutic hypotheses rather than a replacement for established oncology treatment.

XII. CONCLUSION

Neuronal communication is an important and increasingly recognized regulator of cancer biology. Tumour–nerve interactions occur through electrical activity, synaptic contacts, neurotransmitters, neuropeptides, neurotrophic factors and activity-dependent secreted molecules. In glioma, neuronal activity can promote tumour growth through NLGN3, and malignant cells can become functionally integrated into neural circuits. In selected peripheral cancer models, sympathetic and autonomic signalling has been associated with tumour progression, angiogenesis and metastatic behaviour.

These findings create opportunities to develop therapies that selectively interrupt tumour-promoting neural pathways. Potential approaches include blocking neurotransmitter receptors, inhibiting activity-dependent factors, disrupting pathological synaptic signalling, modulating autonomic pathways and limiting tumour-associated nerve recruitment. Such approaches may ultimately complement conventional cancer treatments. However, clinical use requires stronger

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human evidence, validated biomarkers, tumour-selective drug delivery and careful monitoring of neurological and systemic adverse effects. The future of this field lies in precision targeting of pathological tumour–nerve communication while preserving normal neural function.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this review article.

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