Scientific Research Publishing

Journal of Biosciences and Medicines, 2026, 14(3), 396-406
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Sensory Nerve-Tumor Interplay: Mechanisms and Therapeutic Targets in Head and Neck Cancer

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How to cite this paper: Tian, M.M. and Qiang, B. (2026) Sensory Nerve-Tumor Interplay: Mechanisms and Therapeutic Targets in Head and Neck Cancer. *Journal of Biosciences and Medicines*, **14**, 396-406.
https://doi.org/10.4236/jbm.2026.143030

Received: January 31, 2026
Accepted: March 13, 2026
Published: March 16, 2026

Abstract

Head and neck cancer (HNC) represents a significant global health challenge, characterized by aggressive local invasion, frequent recurrence, and poor survival rates. Beyond its physical burden, HNC severely impacts patients' quality of life, often causing debilitating pain and functional impairments. Recent breakthroughs in cancer neuroscience have revealed that the peripheral nervous system is not a passive bystander but an active participant within the tumor microenvironment. A seminal study demonstrated that under immune pressure, cancer cells can hijack sensory nerves to establish an inter-organ neuroimmune circuit. This review aims to synthesize current knowledge on the multifaceted roles of sensory nerves in HNC progression, pain modulation, and immune regulation. It will provide an in-depth analysis of the underlying molecular mechanisms and explore the translational potential of targeting these neural pathways—such as repurposing CGRP receptor inhibitors—to develop novel strategies that concurrently inhibit tumor progression and alleviate cancer-induced pain.

Keywords

Head and Neck Cancer, Sensory Nerves, Cancer Neuroscience, Neuroimmune Interaction, Tumor Microenvironment, Therapeutic Target, Immunosuppression

1. Introduction

Head and neck cancer, particularly head and neck squamous cell carcinoma (HNSCC), ranks as the sixth most common cancer worldwide, with its incidence steadily rising [1]. Despite advancements in treatment modalities like surgery, ra-

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diotherapy, chemotherapy, and immunotherapy, the five-year survival rate for HNC patients remains disappointingly low, often ranging between 30% and 70% [2]. This poor prognosis is attributed to factors including late diagnosis, therapeutic resistance, and a high propensity for local recurrence and metastasis [3].

A hallmark of HNC's aggressiveness is perineural invasion (PNI), where cancer cells actively invade and spread along nerve sheaths. PNI is a well-established indicator of poor clinical outcomes [4]. While traditionally viewed as a mere pathway for dissemination, the intricate relationship between nerves and cancer is now recognized as a dynamic, bidirectional crosstalk [5]. The emergence of cancer neuroscience has shifted the paradigm, positioning the nervous system as a key regulator of tumor initiation, progression, and metastasis [6].

Sensory nerves, especially nociceptors responsible for pain sensation, form a crucial component of the HNC microenvironment [7]. Their role extends far beyond transmitting pain signals. Research indicates that tumor-infiltrating sensory nerves functionally connect to distinct brain areas, altering brain circuits and modulating behaviors related to well-being [8], such as reduced nest-building and voluntary running in mouse models. These behavioral changes are linked to neuronal hyperactivation and are not exclusively driven by pain, suggesting broader neuromodulatory effects of the tumor.

On the immune front, a groundbreaking discovery by Zhang *et al.* illustrates how HNSCC cells "hijack" sensory nerves [9]. Under pressure from tumor-associated macrophages (TAMs), cancer cells activate the ATF4-SLIT2 pathway, which stimulates tumor-innervating nociceptive neurons. This activation, in turn, stimulates sensory nerves in the TDLNs via a neural reflex arc. These nerves then secrete Calcitonin Gene-Related Peptide (CGRP), remodeling the TDLN into an immunosuppressive state by suppressing dendritic cell-mediated T cell activation and reducing CCL5 production. This cascade ultimately promotes M2-like TAM polarization in the primary tumor, creating a vicious cycle of immune suppression and tumor growth.

This review aims to provide a comprehensive overview of the complex interplay between sensory nerves and HNC. We will systematically explore the clinical evidence of nerve infiltration, detail the molecular mechanisms of nerve-tumor-immune crosstalk, and discuss emerging therapeutic strategies that target these neural pathways [10]. By integrating the latest clinical and preclinical findings, this article seeks to highlight the transformative potential of cancer neuroscience in improving outcomes for HNC patients [11].

2. Clinical Evidence of Sensory Nerve-Tumor Interaction in HNC

2.1. Distribution and Characteristics of Sensory Nerves in HNC

The head and neck region is densely innervated by sensory nerves, primarily derived from the trigeminal, facial, glossopharyngeal, and vagus nerves. HNC tissues often exhibit aberrant innervation, including perineural invasion (PNI), increased nerve density and overexpression of feurotrophic factors, as shown in **Table 1**.

Table 1. Clinicopathological features of neural involvement in head and neck cancer.

Feature	Incidence	Clinical significance	Associated neural markers
Perineural invasion (PNI)	30% - 50%	Increased local recurrence risk, reduced survival	GAP43, PGP9.5
Increased sensory nerve density	40% - 60%	Increased pain intensity, poor prognosis	TRPV1, CGRP
Overexpression of neurotrophic factors	50% - 70%	Accelerated tumor progression, enhanced invasiveness	NGF BDNF

Clinical pathology studies show significant upregulation of sensory nerve markers such as TRPV1 and CGRP in HNC tissues [12] [13]. Research on two clinical cohorts of head and neck squamous cell carcinoma (HNSCC) by Zhongshan Hospital found that tumor tissues were enriched with sensory nerves, and high sensory nerve abundance was correlated with stronger pre-operative pain in patients [9].

2.2. Clinical Significance of Perineural Invasion (PNI)

Perineural Invasion (PNI) is a critical pathological feature of HNC, referring to the invasion of tumor cells into the perineurium, perineural space, or endoneurium [14]. The incidence of PNI in HNSCC can reach 30% - 50%, particularly common in oral cancer and parotid gland cancer [15] [16]. The presence of PNI is closely associated with increased local recurrence, lymph node metastasis, and poorer prognosis. Quantification of PNI: The presence of Perineural Invasion (PNI) was primarily identified and confirmed through standard histopathological examination (Hematoxylin and Eosin staining). The diagnosis is based on the morphological criterion of tumor cells invading the perineurium, perineural space, or endometrium. Immunohistochemical markers such as GAP43 and PGP9.5 could serve as auxiliary tools for identification. The association between pretreatment pain and PNI remained statistically significant. This conclusion is robust because multivariate analysis confirmed that even after adjusting for key confounding factors like tumor site and T-stage, pretreatment pain persisted as a significant independent predictor of PNI [14].

Studies indicate that the five-year survival rate of HNC patients with PNI is reduced by approximately 20% - 30%. PNI not only provides a dissemination pathway for tumor cells but also creates a microenvironment conducive to their survival and proliferation [17]. Furthermore, PNI is strongly associated with pain symptoms, significantly impacting quality of life.

2.3. Nerve Density and Prognostic Correlation

Multiple clinical studies have confirmed that high nerve density in HNC tissues is an independent risk factor for predicting patient prognosis [18]. Immunohistochemical analysis of tumor specimens shows a significant correlation between nerve density and shortened disease-free survival and overall survival [19]. Some

papers used RNA sequencing analysis of human tumor tissue from a recent HNSCC clinical trial, proteomics of human nerves from HNSCC patients, and syngeneic orthotopic murine models of HPV-unrelated HNSCC to investigate how sensory nerves modulate the adaptive immune system [19].

As highlighted in a review by Professor Song XiCheng's team, a complex interaction network exists between HNC and the nervous system, involving not only locally frequent PNI but also triggering specific neurological symptoms and deeper "nerve-cancer crosstalk [10]."

3. Molecular Mechanisms by Which Sensory Nerves Regulate HNC Progression

3.1. Nerve-Cancer Cell Interactions in the Tumor Microenvironment

A bidirectional communication exists between sensory nerves and cancer cells in the HNC microenvironment. Cancer cells actively remodel their neural environment by secreting various axon guidance molecules, while activated sensory nerves release neuropeptides and neurotransmitters that modulate tumor biology [20].

3.1.1. Tumor-Derived Neuromodulators

Key factors include Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), and SLIT2 [21]. For instance, in HNSCC, tumor cells under pressure from tumor-associated macrophages can secrete SLIT2 via an ATF4-mediated mechanism, activating tumor-innervating sensory nerves and inducing pain.

3.1.2. Neuron-Cancer Cell Synaptic Connections

Recent studies in some cancers suggest the formation of functional synapses between neurons and cancer cells, allowing direct, rapid communication via neurotransmitters like glutamate. While direct evidence in HNC is limited, similar mechanisms may be applicable.

3.2. Regulatory Functions of Neurotransmitters and Neuropeptides

Upon activation, sensory nerves release various neuropeptides and neurotransmitters into the tumor microenvironment, as shown in **Table 2**, regulating tumor biology by binding to their respective receptors on tumor and immune cells [12].

3.2.1. Calcitonin Gene-Related Peptide (CGRP)

CGRP plays multiple roles in HNC progression. Recent research reveals that activating tumor-innervating sensory nerves can subsequently activate sensory nerves innervating the TDLN. The latter then secrete CGRP, reshaping the TDLN into an immunosuppressive state by reducing cDC-mediated (cDC: dendritic cells with antigen-presenting function) CD8+ T cell activation and inhibiting CCL5 production [9] [19].

Table 2. Functions of sensory nerve-derived factors in head and neck cancer.

Neuropathic factor	Primary receptor	Main functions in HNC	Expression status
CGRP	CLR/RAMP1	Induces immunosuppression, promotes pain and invasion	Upregulated
Substance P	NK1R	Promotes proliferation, angiogenesis, mediates pain	Upregulated
NGF	TrkA, P75^{NTR}	Axonal guidance, cell survival, differentiation	Upregulated
BDNF	TrkB	Enhances invasion, anti-apoptosis	Upregulated
VIP	VPAC1/VPAC2	Modulates immune response, promotes proliferation	Upregulated

3.2.2. Substance P

Substance P promotes tumor cell proliferation, migration, and angiogenesis via its primary receptor, NK1R. In HNC, activation of the Substance P/NK1R axis is also associated with therapy resistance.

3.2.3. Other Neuromodulators

This includes Vasoactive Intestinal Peptide (VIP), Neuropeptide Y (NPY), and Gastrin-Releasing Peptide (GRP).

3.3. Cross-Organ Neuro-Immune Regulatory Circuit

Recent research has uncovered a systemic regulatory network mediated by sensory nerves in HNC that extends beyond the local tumor microenvironment. The team from FuDan University elucidated a mechanism of "tumor-TDLN communication": Activation of tumor-innervating sensory nerves leads to the activation of TDLN-innervating sensory nerves, which, via CGRP secretion, inhibit dendritic cell-mediated T cell activation and reduce CCL5 production. This ultimately promotes M2-like polarization of tumor-associated macrophages (TAMs) in the primary tumor, aiding immune escape [9]. For example, the ATF4-SLIT2-CGRP pathway constitutes a clear, stepwise, inter-organ signaling cascade. This cascade originates in the primary tumor, is relayed via sensory neurons, and ultimately acts on immune cells within the tumor-draining lymph node to achieve systemic immunosuppression. The mechanism can be delineated into the following three key steps:

Step 1: The Tumor Senses Pressure and Emits a "Distress" Signal

Location: Primary Tumor Microenvironment.

Key Cell Types: Tumor cells (signal senders) and the terminals of intratumoral sensory neurons (nociceptors) (signal receivers).

Molecular Events (Receptor-Ligand Pair):

Trigger: Tumor cells experience immune pressure (e.g., attack by T cells), activating the endoplasmic reticulum stress pathway.

Core Transcription Factor: This stress leads to the stabilization and upregulation of the transcription factor ATF4 within tumor cells.

Signal Release: ATF4 drives tumor cells to secrete large amounts of the axon

guidance molecule SLIT2.

Cross-Cellular Dialogue: Secreted SLIT2 acts as a ligand, binding to the ROBO receptor expressed on the terminals of sensory neurons.

Downstream Effect: SLIT2-ROBO binding activates the intratumoral sensory neurons.

Step 2: Sensory Neurons Integrate the Signal and Initiate Long-Range Communication

Location: Peripheral Sensory Neurons (cell bodies located in the Dorsal Root Ganglia).

Key Cell Type: The same sensory neuron, whose branches innervate both the tumor tissue and the draining lymph node.

Molecular Events:

Signal Transduction: Activation at the tumor terminal generates an electrochemical signal that propagates along the neuronal axon toward the dorsal root ganglion cell body and continues to the central nervous system (causing cancer pain) and to the peripheral branch.

Antidromic Signal Release: This signal is antidromically conducted to another terminal of the same neuron that innervates the tumor-draining lymph node (TDLN).

Neurotransmitter Release: At the neural terminal within the lymph node, the neuron releases the key neuropeptide Calcitonin Gene-Related Peptide (CGRP).

Functional Role: The sensory neuron acts as a "bio-electrical relay," converting a local chemical signal (SLIT2) from the tumor into a remote chemical signal.

Step 3: The Neural Signal Suppresses Anti-Tumor Immunity in the Lymph Node

Location: Tumor-Draining Lymph Node (TDLN).

Key Cell Types: Specific immune cells within the lymph node (e.g., cDC1 dendritic cells) (signal receivers).

Molecular Events (Receptor-Ligand Pair):

Key Ligand: CGRP released from sensory nerve terminals.

Key Receptor: The CGRP receptor (composed of RAMP1 and CLR) highly expressed on the surface of immune cells like antigen-presenting cells within the lymph node.

Inhibitory Binding: CGRP binds to the CGRP receptor on immune cells.

Downstream Effects:

Inhibits the maturation and antigen-presenting function of dendritic cells.

Impairs the activation and proliferation of $CD8^+$ T cells.

Ultimately establishes an immunosuppressive microenvironment within the TDLN—a critical site for immune initiation—preventing the effective launch of a systemic anti-tumor immune response, thereby facilitating immune escape.

Points of Intervention for Therapeutic Strategies

Based on the above cascade, potential therapeutic interventions can precisely target the following nodes:

Intervention node	Target	Potential intervention strategy
1) Signal emission at the tumor site	Block SLIT2-ROBO interaction	Develop SLIT2-neutralizing antibodies or ROBO receptor blockers.
2) Neuronal signal conduction	Inhibit sensory neuronal activity	Use local anesthetics or specific sodium channel (e.g., NaV1.7/1.8) inhibitors.
3) Signal reception at the lymph node site	Block CGRP-RAMP1/CLR signaling	Use CGRP receptor antagonists (e.g., Rimegepant, already approved for migraine). This is currently the strategy with the highest clinical translation potential.

4. Therapeutic Strategies Targeting the Nerve-Tumor Interplay (Table 3)

4.1. Targeting Nerve Signaling Pathways

4.1.1. CGRP Signaling Pathway Inhibitors

Given the central role of CGRP, CGRP receptor inhibitors are promising. Notably, using CGRP receptor antagonists (already approved for migraine treatment) to block sensory nerve-mediated tumor-TDLN communication can significantly enhance the efficacy of immunotherapy and suppress cancer pain, achieving dual benefits.

Table 3. Therapeutic strategies targeting nerve-tumor interactions in head and neck cancer.

Therapeutic strategy	Representative agents	Mechanism of action	Development status
CGRP receptor antagonists	Telcagepant, rimegepant	Block CGRP-mediated immunosuppression and pain	Drug repurposing (Migraine)
NK1R antagonists	Aprepitant, fosaprepitant	Inhibit substance P signaling, induce apoptosis	Preclinical, drug repurposing (Antiemetic)
NGF antibodies	Tanezumab, fasinumab	Block NGF/TrkA signaling, reduce innervation	Preclinical/pain clinical trials
Beta-blockers	Propranolol, carvedilol	Inhibit catecholamine signaling, anti-angiogenic	Retrospective clinical studies
Local anesthetics	Lidocaine, ropivacaine	Block voltage-gated sodium channels, inhibit nerve conduction	Clinical use, anti-tumor effects under investigation

4.1.2. Substance P/NK1R Antagonists

NK1R antagonists like aprepitant, used clinically as antiemetics, have shown anti-tumor activity in preclinical HNC models.

4.1.3. Beta-Blockers

While primarily related to sympathetic nerves, retrospective studies suggest that beta-blockers like propranolol may improve outcomes in HNC patients.

4.2. Strategies Targeting Innervation

4.2.1. Local Nerve Blockade

Local nerve blocks are used for managing refractory cancer pain and may also

influence tumor progression.

4.2.2. Nerve Growth Factor Inhibitors

Targeting the NGF pathway is another promising strategy. Anti-NGF monoclonal antibodies (e.g., tanezumab) are under investigation.

4.3. Combination Therapies Targeting the Neuro-Immune Axis

Given the role of sensory nerves in shaping an immunosuppressive microenvironment, combining neuromodulatory drugs with immune checkpoint inhibitors holds significant promise. Preclinical studies confirm that blocking sensory nerve-mediated tumor-TDLN communication can significantly enhance the efficacy of immunotherapy [22].

5. Challenges and Future Directions

5.1. Limitations of Current Research

A significant challenge is the "double-edged sword" nature of sensory nerves in cancer progression, which highlights the complexity of these interactions. For instance, while ablation of sensory nerves has been shown to inhibit tumor growth in models of prostate, gastric, pancreatic, and head and neck cancer, their absence has paradoxically been reported to promote tumor growth and metastasis in models of breast, pancreatic, and gastric cancer, suggesting a context-dependent protective role.

These apparent contradictions may stem from several factors, including tumor-type specificity, the specific nerve subtypes involved (nociceptors vs. other sensory fibers), the model systems used, and the local heterogeneity of nerve fibers within the TME. This complexity must be carefully considered when moving discoveries from the bench to the bedside.

Furthermore, limitations in research models remain a hurdle. Current animal models and in vitro systems cannot fully recapitulate the complex human nerve-tumor-immune network, especially the recently discovered long-range, cross-organ communication.

5.2. Impact of Multi-Omics and Novel Technologies

Multi-omics technologies (transcriptomics, proteomics, metabolomics) and single-cell/spatial transcriptomics are powerful tools [23]. Advanced neuro-scientific tools such as optogenetics and chemogenetics are invaluable for establishing causality. By allowing precise manipulation of specific neuronal subpopulations in real-time, researchers can directly link neural activity to tumor biological outcomes. The fudan university team's use of sensory neuron-specific chemogenetic/optogenetic mice to confirm the functional link between tumor-innervating and TDLN-innervating nerves is a prime example of this approach [9].

5.3. Path to Clinical Translation: From Bench to Bedside

The translation of basic research on nerve-tumor interactions into clinical prac-

tice requires a deliberate, phased pathway involving multidisciplinary collaboration. A roadmap from fundamental discovery to clinical application includes target validation, drug development (novel compounds or drug repurposing), preclinical model verification, and clinical trial design.

Promising future directions include:

1) Biomarker Development: Identifying robust biomarkers predictive of response to nerve-targeting therapies is crucial. Candidate biomarkers include sensory nerve density in tumor biopsies, circulating levels of neuropeptides like CGRP or Substance P, or gene expression signatures related to neuronal signaling.

2) Optimization of Combination Therapies: Exploring the most effective sequencing and combinations of neuromodulatory drugs with existing standards of care, such as immune checkpoint inhibitors, chemotherapy, and radiotherapy. The synergistic effect observed between CGRP inhibition and immunotherapy is a prime example [19].

3) Integrated Management of Pain and Tumor Control: Developing dual-benefit strategies that simultaneously address cancer-related pain and tumor progression is a unique advantage of targeting sensory nerves. This approach could significantly improve the quality of life for HNC patients [24].

4) Neuroprotective Strategies: A critical future challenge is to achieve effective tumor killing while preserving normal nerve function to minimize treatment-related morbidity and deterioration of quality of life.

6. Conclusions

The bidirectional interplay between sensory nerves and HNC is a critical and active component of tumor progression, immune evasion, and pain. The recent discovery of a cross-organ neuro-immune axis provides a revolutionary perspective, revealing how tumors co-opt the peripheral nervous system to exert systemic immunosuppressive effects remotely via the TDLN [25].

Therapeutic strategies targeting key nodes of this interaction, such as the CGRP signaling pathway, show significant clinical potential, especially in combination with established immunotherapies. The repurposing of already-approved drugs like CGRP receptor antagonists offers a promising and expedited path to clinical translation, with the unique potential to deliver both tumor suppression and analgesia.

As our understanding of the molecular mechanisms deepens, propelled by multi-omics technologies and precise neural manipulation tools, Cancer Neuroscience is poised to establish new therapeutic paradigms for HNC patients. The future challenge and opportunity lie in achieving the dual goals of effective tumor control and the preservation of neurological function, ultimately improving survival and quality of life for patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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