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Review

Entangled cellular and molecular relationships at the sensory neuron-cancer interface

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https://doi.org/10.1016/j.neuron.2025.07.017

SUMMARY

Peripheral sensory neurons, once regarded merely as a passive route for nociceptive signals, are now acknowledged as active participants in solid tumor progression. This review explores how sensory neurons influence and are influenced by the tumor microenvironment (TME) through both chemical and electrical signaling, underscoring their pivotal role in the emerging field of cancer neuroscience.

We summarize recent findings indicating that cancer-neuron interactions vary among different organs and experimental models, highlighting the ways in which various tumors recruit and reprogram sensory neurons to establish mutual communication loops that foster malignancy. Clinically, the degree of sensory innervation and the level of neuropeptide signaling show promise as diagnostic and prognostic biomarkers, while targeting these pathways may enhance the efficacy of standard cancer treatments.

This review also highlights current knowledge gaps and proposes future research directions aimed at disrupting sensory neuron-tumor interactions, with the ultimate goal of improving clinical outcomes across multiple cancer types.

CANCER NEUROSCIENCE: SPOTLIGHT ON PERIPHERAL SENSORY NEURONS

Oncology research has traditionally focused on genetic mutations, signaling networks, and the tumor microenvironment (TME), particularly immune and stromal cells. However, accumulating evidence now indicates that the nervous system profoundly influences tumor initiation, progression, and metastasis, highlighting critical links between neuronal activity and oncogenic processes.[1–5] The nervous system controls nearly every physiological function, including organ development, tissue repair, and immune homeostasis.[3–5] While neuro-oncology has long centered on tumors of the central nervous system (CNS),[6,7] emerging studies emphasize that the peripheral nervous system (PNS), particularly peripheral sensory neurons, plays a pivotal role in extra-cranial tumor progression.[8–10]

Once viewed primarily as conduits for pain transmission, peripheral sensory neurons are increasingly recognized as active participants in the TME. Tumors recruit these neurons through neurotrophic factors and axonal guidance molecules, and the neurons in turn release neuropeptides and neurotransmitters, such as calcitonin gene-related peptide (CGRP) and substance P (SP), which support tumor growth and immune evasion.[11] These interactions are bidirectional: recent models suggest that direct electrical coupling between sensory neurons and tumor cells enables faster, more efficient communication than traditional paracrine or synapse-like signaling.[12,13] Such findings underscore the unique contributions of peripheral sensory neurons and establish their importance within the emerging field of cancer neuroscience.

Incorporating neurobiology, oncology, and immunology to investigate neuronal regulation of tumor growth challenges conventional views of cancer biology, potentially leading to novel strategies to disrupt harmful neural regulation in the TME. Although autonomic peripheral neurons are also known to modulate tumor growth, and sensory-autonomic co-regulation is well documented,[5,14,15] this review focuses specifically on the role of sensory neurons in cancer.

PERIPHERAL SENSORY NEURONS AND NEUROPEPTIDES

Peripheral sensory neurons constitute an extensive, highly adaptable network that is indispensable for normal organ and tissue homeostasis.[16] Their cell bodies reside in the dorsal root ganglia (DRGs), trigeminal ganglia (TGs), and nodose ganglia (NGs).[17] Because these ganglia lie outside the CNS and in close proximity to the glands and organs they innervate (Figure 1), sensory neurons are uniquely positioned to integrate and influence local physiology. DRG neurons gather sensory information from the trunk, limbs, and selected visceral organs[11,18,19]; TG neurons serve the face, oral mucosa, teeth, and eyes[20]; and NG neurons, which travel with the vagus nerve, innervate the heart, lungs, and gastrointestinal tract.[21,22] Although traditionally described as afferent detectors, these neurons also exert efferent effects by releasing neuropeptides in response to peripheral stimuli.

Within each ganglion, sensory neurons further diversify into functional subclasses: nociceptors, mechanoreceptors, and chemoreceptors. Nociceptors detect noxious stimuli that elicit pain,[23] whereas mechanoreceptors and chemoreceptors respond to mechanical or chemical cues, respectively.[24,25] This organ-specific innervation enables precise control of physiological processes: DRG and NG neurons regulate gut motility and blood flow[26,27]; TG fibers in facial tissues detect mechanical and thermal changes[19]; and DRG neurons create a dense cutaneous network that processes touch, temperature, itch, and pain.[19]

Sensory neurons are often classified as peptidergic (PEP) or non-peptidergic (NPEP) (e.g., IB4$^+$) on the basis of neuropeptide expression.[28,29] While this review concentrates on PEP nociceptors, emerging evidence shows that NPEP IB4$^+$ neurons mediate cancer-induced mechanical pain—particularly in squamous cell carcinoma (SCC)—and also display immunomodulatory capabilities, underscoring broader roles in tumor-immune crosstalk.[30,31] Strikingly, NPEP MrgprD$^+$ neurons can suppress mast cell activation through glutamate release, thereby preserving skin immune homeostasis.[32] This glutamatergic axis may represent a general mechanism by which NPEP neurons modulate immune responses in peripheral tissues, including tumors.[32]

Mechanosensitive ion channels, notably Piezo1, provide an additional layer of complexity. Piezo1 is expressed by large-diameter A-fiber neurons such as NEFM$^+$ mechanoreceptors,[33–35] enabling them to sense changes in tissue rigidity or pressure that could influence cancer cell behavior or immune cell recruitment.[36–38] Because Piezo1 also drives tumor-associated inflammation, metabolic rewiring, and stromal remodeling, it is plausible that these mechanoreceptors contribute to tumor progression by coupling mechanical cues to immune infiltration or fibroblast activation.[34] Consistent with this idea, Piezo1-expressing A-fiber neurons have been implicated in stromal remodeling and malignancies such as hepatoblastoma,[39] although their precise functions in the TME remain poorly defined and merit further investigation.[40]

Sensory neuron-released neuropeptides—including CGRP, SP, vasoactive intestinal peptide (VIP), somatostatin (SST), and pituitary adenylate cyclase-activating polypeptide (PACAP)—bind cognate G protein-coupled receptors (GPCRs) that couple to protein kinase A (PKA) and protein kinase C (PKC) pathways to govern nociception, vascular tone, and immune activity. CGRP engages the receptor-activity-modifying protein 1 (RAMP1) receptor to regulate pain, vasodilation, and immunity[41]; SP activates neurokinin-1 receptors (NK-1R) to enhance pain, vascular permeability, and immune cell recruitment[42]; VIP signals through VPAC1 and VPAC2 to modulate inflammation and blood flow[43]; PACAP acts via PAC1, VPAC1, or VPAC2 to orchestrate immune and neuroprotective responses[44]; and SST suppresses hormone secretion, cell proliferation, and immune functions through its five receptor subtypes (SSTR1–5; Figure 2).[45] Under inflammatory or tumor-promoting conditions, these neuropeptides are frequently upregulated, driving pain sensitization, vasodilation, inflammation, and immune cell infiltration—factors that collectively can accelerate disease progression.[46]

The transient receptor potential vanilloid 1 (TRPV1) cation channel is broadly expressed during development but becomes largely restricted in adults to unmyelinated CGRP$^+$ nociceptors that respond to noxious heat.[47] In cancer, inflammatory

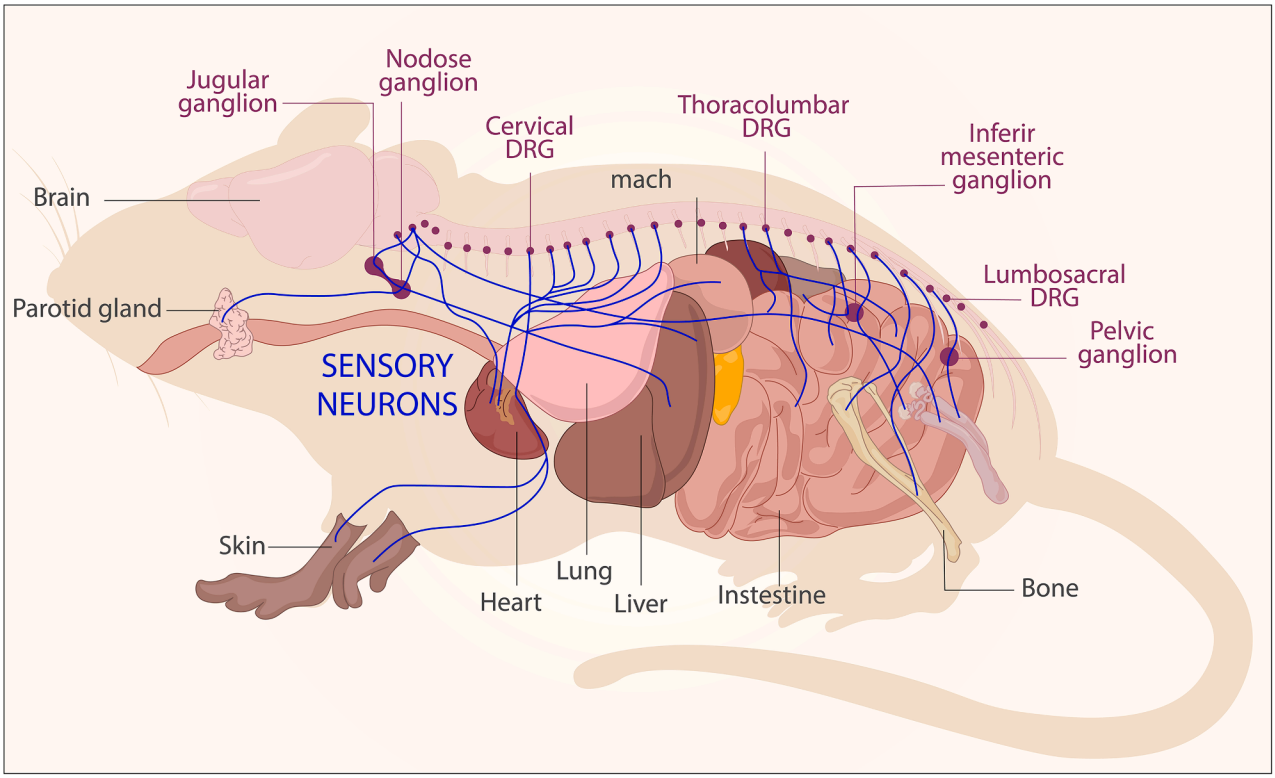

Figure 1. Sensory innervation of major primary sites of cancer formation in the mouse

This schematic shows sensory ganglia (purple) and sensory neurons (blue) innervating commonly studied organs where neural input has been linked to tumor progression. Visceral sensory fibers (blue lines) carry afferent signals from peripheral organs, including the parotid gland, skin, heart, lung, stomach, colon, ovary, and bone, to specific ganglionic structures along the neuroaxis. Cranial sensory input travels via the superior and inferior vagal ganglia to the upper visceral organs (lungs, heart, and stomach). Spinal sensory neurons, with cell bodies in the dorsal root ganglia (DRGs), are arranged segmentally and project to targets across the cervico-thoraco-lumbar axis. Cervical DRGs innervate upper thoracic organs, while thoracolumbar DRGs carry signals from mid-abdominal organs such as the stomach, liver, pancreas, and intestines. Lumbosacral DRGs transmit sensory information from the lower abdomen and pelvic structures, including the intestines, reproductive organs (e.g., ovaries), and bones. Additional integration occurs via the inferior mesenteric and pelvic ganglia, which handle feedback from the lower gut and urogenital system. This figure emphasizes the complex, region-specific architecture of visceral sensory innervation and how it can both influence and be influenced by tumor growth.

mediators and hypoxia activate TRPV1, provoking additional neuropeptide release.[48] While such responses normally foster tissue repair and regeneration, they may also augment tumor cell proliferation, migration,[49,50] and immune suppression.[51,52]

Sensory neurons transmit action potentials orthodromically toward the CNS and antidromically back to peripheral tissues, allowing them to shape local physiology and pathophysiology. Tumor-derived cytokines, extracellular vesicles (EVs), and hypoxia heighten neuronal excitability.[38] Cytokine receptors such as TNFR, IL-1R, and IL-17RA sensitize TRPV1 through mitogen-activated protein kinase (MAPK) pathways,[53–59] whereas protease-activated receptor 2 (PAR2) is activated by tumor proteases and recruits MAPK, PKCε, and PKA signaling to further amplify TRPV1 sensitization and neurogenic inflammation.[53,60] Co-expression of TRPV1 and PAR2 markedly amplifies pain signaling and local neuropeptide secretion.[61–63] Once activated, nociceptors release CGRP and SP, influencing central pain circuits and peripheral target cells—including immune and tumor cells.[64] Release can arise from full action potentials or from localized calcium microdomains sufficient to trigger vesicle fusion without a complete spike,[49,50] providing dual mechanisms by which sensory neurons govern tumor biology, immunity, and vascularity.

The involvement of TRPV1 in cancer is nuanced and context dependent.[65–68] Whereas multiple studies link TRPV1 activity to tumor progression[69,70] and pain, others report counter-intuitive results in which TRPV1 inhibition or genetic deletion actually accelerates tumor growth or metastasis in certain models.[71–75] Such discrepancies may reflect differences among tumor types, cell-autonomous roles of TRPV1 in cancer cells, or compensatory pathways engaged when TRPV1 is absent.[76,77] Consequently, TRPV1 remains an intriguing therapeutic target whose modulation must be approached with caution.

Anatomical, neuropeptidergic, and functional investigations now converge to show that sensory neuron activity can foster tumor growth. Contemporary research extends beyond peripheral innervation to encompass central structures, including the DRG, spinal cord, and vagal circuits, in order to map the neuro-immune networks that govern tumor dynamics. These insights may ultimately enable the development of therapies that disrupt neuron-tumor interactions and improve clinical outcomes.

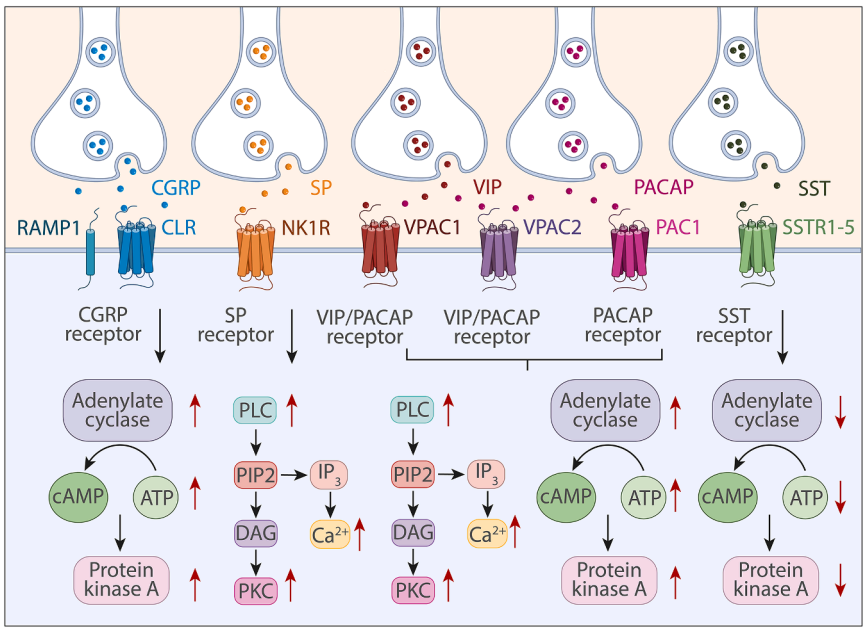

Figure 2. Signal transduction pathways mediated by sensory neuropeptides

Schematic representation of the major sensory neuropeptides (CGRP, SP, VIP, PACAP, and somatostatin [SST]) that activate specific receptors to trigger intracellular signaling cascades. CGRP binds the CALCRL–RAMP1 receptor complex and activates the Gs pathway, which stimulates adenylate cyclase and increases cAMP, ATP turnover, and protein kinase A (PKA) activity. SP binds neurokinin-1 receptor (NK1R), activating Gq-mediated phospholipase C (PLC). PLC cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol (DAG), elevating intracellular calcium levels and activating protein kinase C (PKC). VIP and PACAP signal through VPAC1, VPAC2, and PAC1 receptors via both Gq and Gs pathways, thus influencing PLC-dependent calcium flux as well as cAMP-dependent pathways. SST binds to somatostatin receptors (SSTR1–5) and inhibits adenylate cyclase via Gi/Go, lowering cAMP levels and reducing downstream kinase activity.

THE TME AND SENSORY NEURON-TUMOR CROSSTALK

The TME comprises cancer cells, infiltrating immune cells, cancer-associated fibroblasts (CAFs), endothelial cells, the extracellular matrix (ECM), and invading nervous system components,[15,78,79] all of which communicate via cytokines, growth factors, neuropeptides, and EVs.[80] Cancer cells secrete inflammatory cytokines, chemokines, and growth factors, which drive their own proliferation and invasion through autocrine and paracrine loops.[81] Immune constituents—including T cells, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and innate lymphoid cells (ILCs)—either promote immune escape or orchestrate antitumor immunity.[82] CAFs release protumorigenic mediators and remodel the ECM,[83,84] whereas endothelial cells integrate angiogenic cues to build a vasculature that supplies nutrients, removes waste, and facilitates metastasis.[85,86]

Sensory neurons have emerged as pivotal TME regulators, modulating vascular permeability, immune cell trafficking, and tumor cell behavior. Tumors emit signals that induce neurite extension and neuronal hyperexcitability, creating a reciprocal feedforward circuit; interrupting this neuron-tumor dialogue can slow disease progression. In pancreatic cancer, for example, sensory nerve infiltration accelerates tumor growth, whereas surgical or chemical denervation in animal models retards it, and heightened neuronal recruitment in patients predicts poorer outcomes.[87]

Neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF), together with axon-guidance molecules like netrin-1 and SLIT2, are secreted by tumor cells, CAFs, and immune cells. These cues attract sensory fibers into the tumor, raise intratumoral nerve density, and often presage an unfavorable prognosis.[49,88–93] Netrin-1 from tumor or stromal sources engages the DCC receptor to foster sensory nerve ingrowth and cancer-associated pain,[90–93] while endothelial SLIT2 expression is indispensable for sensory nerve recruitment in breast cancer, where elevated nerve density correlates with greater metastasis and worse clinical outcome in both murine models and human cohorts.[94,95] NGF binding to TrkA on nociceptors activates phosphatidylinositol 3-kinase (PI3K)/Src signaling, phosphorylates TRPV1, promotes its membrane insertion, and acutely sensitizes the neuron.[96,97] NGF also drives TRPV1 translocation via p38 MAPK in DRG neurons, boosting TRPV1 abundance independently of transcription.[54] Collectively, these mechanisms stimulate axonal sprouting, intensify cancer pain, and heighten neuronal excitability within the TME.

Once sensory fibers infiltrate the tumor, nociceptors discharge neuropeptides and neurotransmitters that influence lymphangiogenesis and immune polarization. SP, CGRP, and VIP act on immune subsets that express their cognate receptors (Figure 3). Single-cell RNA sequencing (scRNA-seq) shows that the CGRP receptor subunit RAMP1 is highly enriched in certain intratumoral $CD3^+CD4^+FOXP3^-$ T cells, and CGRP together with SP skews macrophages toward an M2 phenotype while impairing cytotoxic T cell recruitment and function.[51,98,99] In the gut, activation of $Trpv1^+$ nociceptors modulates ILCs, macrophages, and $ROR\gamma^+$ regulatory T cells, whereas CGRP suppresses Th2 differentiation and promotes Th1 polarization via CREB and ATF3.[100]

Neuropeptide signaling also bridges sensory neurons and CAFs. In oral carcinoma, CAFs abundantly express CGRP receptors; CGRP thereby stimulates CAF proliferation and activation, which escalates ECM remodeling.[106] In pancreatic ductal adenocarcinoma (PDAC), CGRP prompts fibroblasts to secrete NGF, fueling further sensory axon outgrowth and establishing a feedforward loop that accelerates tumor progression.[107] RNA-seq analyses of co-cultured PDAC cells and CAFs confirm that

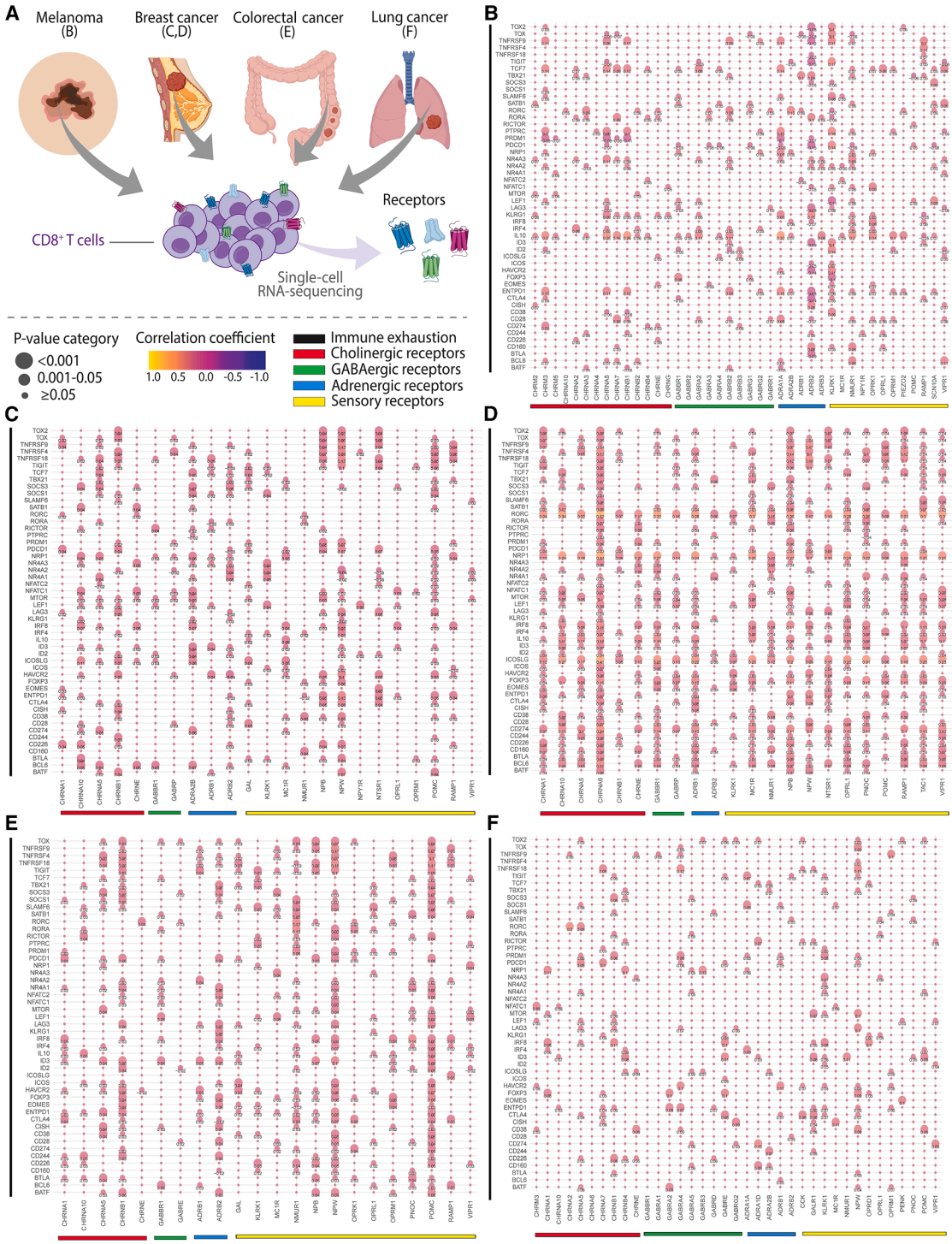

Figure 3. Correlation between neuron receptor expression and T cell exhaustion

In silico analysis was conducted on single-cell RNA sequencing (scRNA-seq) data from tumor-infiltrating CD8$^+$ T cells in melanoma[101] (A), breast cancer[102,103] (B and C), colorectal cancer[104] (D), and lung cancer[105] (E). We calculated Spearman correlations between genes encoding adrenergic, cholinergic, sensory, and GABAergic receptors and those associated with immune exhaustion, presenting the results as heatmaps (correlation range: 1 to 1). Circle size indicates the relative *p* value based on the Spearman rank correlation test. A second target selection strategy was developed using the Broad Institute's single-cell BioPortal (https://singlecell.broadinstitute.org/single_cell). We queried all available human cancer scRNA-seq datasets for tumor-infiltrating lymphocytes, ultimately identifying five datasets covering four cancer types: melanoma, colorectal, lung, and breast. As a proof of concept, we focused on cytotoxic CD8$^+$ T cells, which play central roles in antitumor immunity, and examined the expression of adrenergic, cholinergic, sensory, and GABAergic receptors. We then generated a Spearman correlation matrix that compared the expression of these receptor genes with genes linked to CD8$^+$ T cell exhaustion.

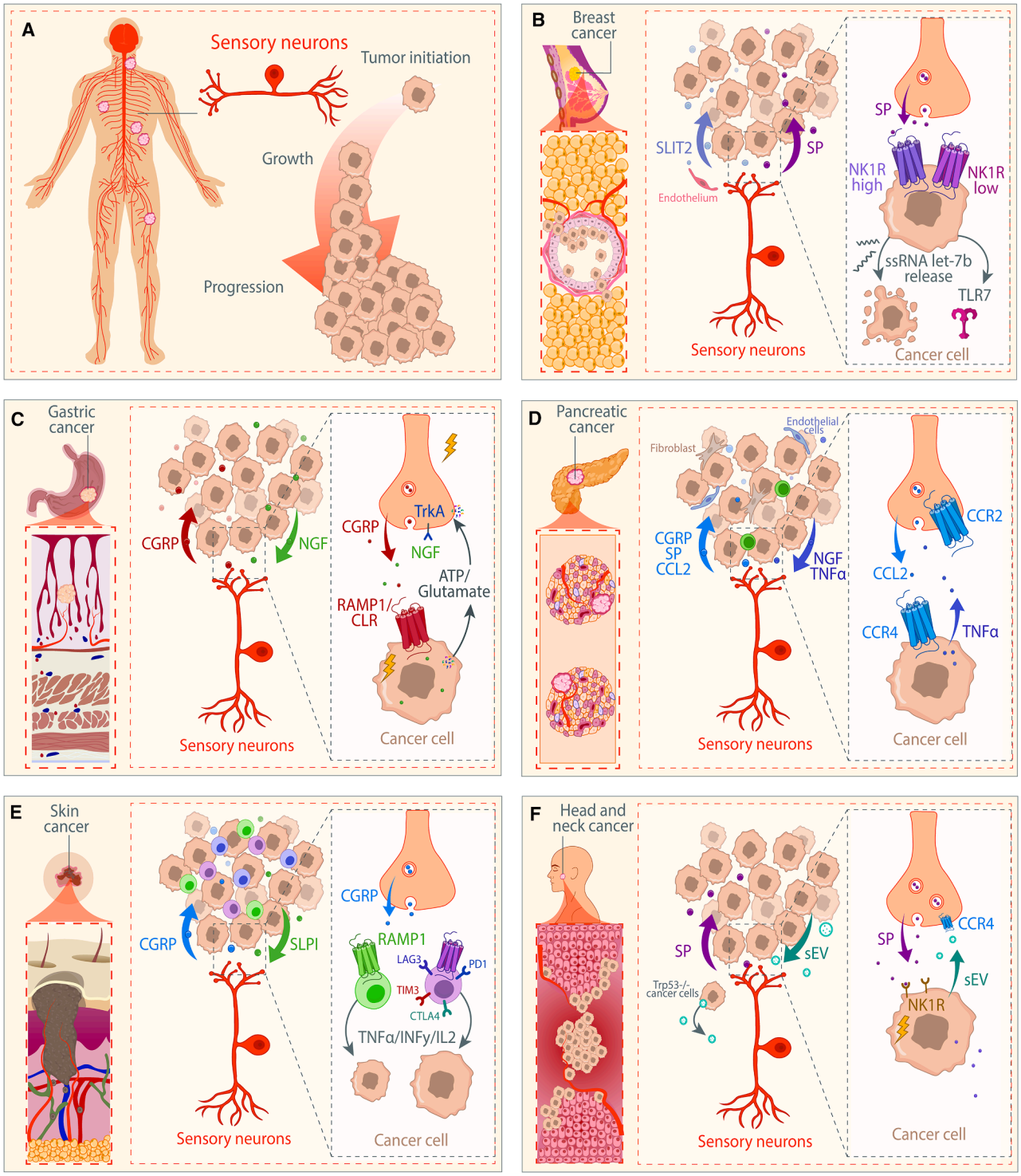

Figure 4. Sensory neurons crosstalk with tumors that develop in distinct organs

(A) Schematic showing how sensory neurons influence tumor initiation and progression.

(B) In breast cancer, sensory neurons release the neuropeptide substance P (SP), which preferentially binds to tumor cells that overexpress the neurokinin-1 receptor (NK1R). Activation of NK1R drives the cancer cells to expel single-stranded RNA (ssRNA), including microRNAs such as let-7b that carry a GUUGUGU motif capable of engaging Toll-like receptor 7 (TLR7) on neighboring tumor cells. This paracrine loop heightens inflammatory signaling and accelerates tumor growth.[125] Endothelial cells reinforce the circuit via Slit2, further enhancing neural-tumor communication, and local invasion.

(legend continued on next page)

neuronal cues markedly enhance CAF proliferation.[108] Tumors often recruit specific sensory neuron subsets that, in concert with CAFs, boost cancer cell proliferation, migration, and invasion; dampen immune infiltration; and ultimately worsen clinical outcomes.[108]

Endothelial cells too respond to neuronal mediators: SP and CGRP bind endothelial receptors to provoke vasodilation, raise vascular permeability, and stimulate endothelial migration and proliferation.[109–112] These changes enhance tumor perfusion, nutrient supply, and metastatic dissemination. Reciprocally, endothelial cells secrete axon-guidance molecules that attract additional sensory fibers.[50] Such bidirectional interactions underscore the elaborate network connecting sensory neurons, tumor cells, CAFs, immune elements, and the vasculature within the TME.

PARACRINE AND ELECTRICAL SIGNALING IN SENSORY NEURON-TUMOR COMMUNICATION DURING TUMOR PROGRESSION

Neurons secrete neuropeptides that regulate stemness in non-tumor settings.[113] For example, CGRP-dependent CFTR signaling maintains progenitor niches in cystic fibrosis,[114] and CGRP binding to the RAMP1-CALCRL receptor complex on hematopoietic stem cells (HSCs) activates the Gαs → adenylate cyclase → cAMP cascade, thereby promoting HSC mobilization.[115] Gastric isthmus and other epithelial stem cell compartments also express CGRP receptors, suggesting that sensory neurons can influence epithelial stem cells even before malignant transformation.[49] By detecting early pathological changes, sensory neurons shape stem cell programs: in $Gli1^+$ progenitors, Hedgehog-pathway activation drives tumorigenesis, whereas denervation reverses this effect.[116] Similar neuronal control of progenitor activity has been documented in the liver,[117] intestine,[118] and stomach,[119] and capsaicin-mediated stimulation of intestinal sensory nerves alters progenitor behavior.[120] Together, these data indicate that sensory neurons can influence malignancy at its inception by modulating stem and progenitor cells.

Although paracrine signaling was long viewed as the dominant mode of neuron-tumor interaction, recent studies reveal a rapid, bidirectional electrical component. In CNS gliomas, tumor cells form synapse-like contacts with glutamatergic neurons, allowing for direct electrochemical transmission that fuels malignancy.[121,122] Roughly 5%–10% of glioma cells exhibit AMPA-receptor-dependent synaptic activity that enhances tumor growth and invasion. Evidence is accumulating that peripheral tumors also establish electrical synapses with sensory neurons. Breast cancer-brain metastases express glutamatergic NMDA receptors, and electron microscopy shows pseudo-tripartite synapses in both primary and metastatic lesion.[123] Head-and-neck SCC (HNSCC) and high-grade serous ovarian cancer (HGSOC) likewise display elevated synaptic marker expression and neuronal-like electrical activity within malignant tissues; this activity diminishes when TRPV1-lineage sensory neurons are ablated, implicating those neurons in the phenomenon.[124] In gastric cancer (GC), tumor cell depolarization triggers CGRP release from sensory neurons, which then stimulates tumor cells, CAFs, and immune cells, creating a pro-tumor electrochemical feedback loop.[49] These neuron-tumor connections are highly specific, guided by neurotrophins and other axonal guidance cues. Although the junctions differ from classical synapses—separated by ~200 Å instead of 20–30 Å and transmitting signals over 1–2 s rather than 0.1–0.5 ms—they are distinct from conventional paracrine signaling. Multiple lines of evidence now substantiate electrical communication between sensory neurons and tumor cells.[49] *In vivo*, optogenetic depolarization of GC cells in mice elicited synchronous depolarization of jugular-nodose complex (JNC) sensory ganglia, detected via GCaMP6s imaging; single-cell patch-clamp recordings corroborated this coupling. Additional experiments demonstrated that cancer cells activate sensory neurons through adenosine and glutamate receptors. Conversely, chemogenetic depolarization of sensory neurons *in vitro* induced GCaMP6s-detected depolarization of GC cells—a response abolished by CGRP signaling inhibition.

THE ROLE OF SENSORY NEURONS IN SPECIFIC PERIPHERAL TUMOR TYPES

Sensory neurons play critical roles in tumor initiation, growth, and progression (Figure 4A). Although neuronal signaling can drive cancer, selectively targeting these pathways may offer therapeutic benefits. Each organ's sensory innervation has distinct functions, so understanding the precise neuron-cancer mechanisms is vital for designing targeted interventions. Because completely ablating sensory neurons carries the risk of significant adverse effects, more refined strategies that focus on molecularly distinct populations or tissue-specific pathways are needed. Below is an overview of recent findings on how sensory neurons contribute to various peripheral tumors (Figures 4B–4F).

Breast cancer

Breast tumors display increased sensory innervation

Breast tissue is primarily innervated by sensory nerves originating from DRG at C3-C4 and T3-T6, and by sympathetic

(C) In GC, tumor cells secrete high levels of NGF to recruit nociceptive sensory neurons, forming direct neuron-cancer contacts through the CGRP-RAMP1/CALCRL axis. Upon neuronal stimulation, cancer cells release excitatory factors (ATP/glutamate) that re-engage TrkA on neurons, establishing a self-reinforcing loop that drives tumor progression.
(D) Pancreatic ductal adenocarcinoma (PDAC) shows extensive neuronal reprogramming and PNI. Cancer cells, fibroblasts, and endothelial cells produce NGF and TNF-α, promoting a phenotypic shift in neurons. Sensory neurons respond by secreting neuropeptides (CGRP and SP) and chemokines (Ccl2), which engage Ccr4 on cancer cells, further stimulating TNF-α release. This loop intensifies tumor-related inflammation and neuronal recruitment.
(E) In melanoma, cancer cells closely interact with sensory neurons via calcitonin gene-related peptide (CGRP). CGRP binds Ramp1 receptors on $CD8^+$ T cells, inducing functional exhaustion (high LAG3, PD1, TIM3, CTLA4 and low TNF-α, IFN-γ, IL-2). This neuronal-immune interplay fosters an immunosuppressive environment that promotes melanoma progression and resistance to therapy.
(F) In head-and-neck SCC, tumor cells—particularly those with a Trp53 mutation—release small EVs (sEVs) that remodel adjacent sensory neurons. These neurons then release SP, acting on neurokinin-1 receptors (NK1R) on cancer cells, fueling tumor growth, neural invasion, and inflammation. Sensory neurons can also differentiate into adrenergic neurons producing norepinephrine (NE), exacerbating tumor aggressiveness and immune evasion.

nerves from T1-T5.[126] Normal human breast tissue has relatively sparse innervation, but studies reveal increased nerve infiltration in tumors, detectable by pan-neuronal markers.[69,127] Recent work shows elevated TRPV1$^+$ sensory nerve density in human breast cancers,[70] while CGRP$^+$ fibers are present in hormone receptor-positive tumors.[50] High expression of neuronal markers and TRPV1 correlates with poor prognosis.[50,69,70,127]

Mice have ten mammary glands extending from cervical to inguinal regions, innervated by more DRGs than in humans.[128] Retrograde labeling confirms that abdominal xenograft tumors receive sensory inputs from T10-L4 DRGs.[50] In xenograft models of triple-negative breast cancer (TNBC) (4T1, EO771 LM2, HCC1806, MDA-MB-231), higher CGRP$^+$ innervation parallels greater metastatic potential.[50,129] In the MNU-induced rat breast cancer model, thoracic and abdominal tumors are innervated by T5-T6 and L1-L2, respectively.[130]

Perineural invasion (PNI), in which tumor cells infiltrate nerves, appears in 1%–25% of breast cancer patients, although its prognostic value remains debated. Some studies show no effect on survival,[131,132] whereas others link PNI to increased tumor size, recurrence, and shorter metastasis-free intervals.[133,134] The specific role of sensory nerves in PNI and prognosis thus remains uncertain.

Mechanism of increased innervation in breast cancer

Breast tumors often secrete factors that promote sensory outgrowth, including VEGF, NGF, and axon-guidance molecules. In one study, deleting the endothelial cell-specific gene for *Slit2* reduced CGRP$^+$ sensory innervation in a 4T1 tumor model.[50] Blocking VEGFR or NGFR, or applying anti-VEGFR2 antibodies, also decreased neuronal density in rat breast tumors. *In vitro* experiments show that MCF-7, MDA-MB-231, and 231-BR breast cancer cells can induce substantial neurite outgrowth in PC12 cells, emphasizing the ability of tumor-secreted factors to foster sensory innervation.[130]

MCF-7 and MDA-MB-231 cells particularly enhance neurite formation in neuronal-like cells, whereas HER2$^+$ lines (BT474, JIMT-1) have minimal effects.[127] MCF-7 cells secrete NGF, and anti-NGF antibodies can reduce cancer cell-induced neurite growth.[127] Moreover, conditioned media from MCF-7 and MDA-MB-231 cells increases neurite outgrowth and axonal branching in the 50B11 sensory neuronal cell line through VEGF-A/VEGFR2 signaling and ARP2/3-mediated filopodia formation.[129]

A second proposed mechanism involves doublecortin$^+$ (DCX$^+$) cells from the brain's subventricular zone, detected in PyTM-MMTV mouse breast tumors.[135] However, it remains unclear whether these cells differentiate into sensory neurons.

Effect of sensory nerves on breast tumor progression

Studies consistently show that sensory neurons influence breast tumor growth and metastasis. Co-injecting tumor cells and DRG neurons into the mammary gland increases nerve density in the primary tumor and significantly enhances tumor progression.[50,70] However, findings on sensory denervation differ, possibly due to variations in denervation techniques and tumor implantation sites. For example, a single neck injection of capsaicin 7 days before 4T1 cell implantation had no effect on primary tumor growth but increased lung and cardiac metastases.[136] Although an eye-wipe test confirmed some denervation, direct evidence of nerve loss in breast tissue was lacking. In contrast, intraductal capsaicin delivery visibly reduced mammary gland innervation, and ongoing capsaicin treatment after 4T1 cell injection suppressed tumor growth and lung metastasis.[50]

Mechanistically, sensory nerves induce transcriptional changes and facilitate tumor cell migration. Co-culture of mouse DRG neurons with human or mouse TNBC cells increases tumor cell migration along neuronal processes, mediated by the semaphorin receptor Plexin B3.[70] Sensory nerves also upregulate genes linked to cell movement and adhesion,[70] and sensory denervation alters tumor gene expression associated with invasion while reducing SP levels in the lung and heart.[137] In turn, sensory nerves secrete factors that affect tumor cells; SP, for example, can kill a subset of cancer cells through tachykinin receptors (TACR1/NK1R), releasing single-stranded RNAs that activate Toll-like receptor 7 (TLR7) in neighboring cells and drive a pro-metastatic profile.[50] Aprepitant, a TACR1 antagonist used clinically for nausea, decreases tumor growth and metastasis in multiple breast cancer models.[50] There is also evidence that sensory neurons reduce antitumor immunity, as the TRPV1 agonist olvanil reduces lung and liver metastases in 4T1 models and increases T cell infiltration into the primary tumor.[138]

Although direct electrical signaling between sensory neurons and breast tumors remains unconfirmed, xenograft TNBC tumors exhibit measurable electrical activity in mice.[139] Lidocaine abolishes this activity, but whether sensory neurons underlie or sustain it is unclear.

Several questions persist. Breast cancer includes multiple subtypes with distinct molecular profiles and clinical behaviors, yet it is unknown if all subtypes exhibit similar nerve infiltration or depend on the same neuron-derived signals. Additionally, mouse models often focus on abdominal mammary glands innervated by many DRG levels, whereas human breast tissue primarily connects to cervical and upper thoracic DRGs. Future studies must clarify whether these anatomical differences alter tumor-nerve interactions.

GI tumors

The human gastrointestinal (GI) tract houses up to 600 million neuronal cell bodies, making it the most densely innervated peripheral organ system. It receives input from DRGs, nodose or jugular ganglia, and intrinsic primary afferent neurons of the enteric nervous system (ENS).[140] This extensive innervation reflects the GI tract's vital role as the primary interface between the body and the external environment, where it must simultaneously enable nutrient absorption and protect against pathogens. GI sensory neurons respond to ingested nutrients, microbial metabolites, and toxins, regulating immune cells and local inflammation.[141]

GI tumors often develop in a setting of chronic inflammation, which promotes strong neuron-tumor interactions. In GC, prolonged *Helicobacter pylori* infection leads to sustained inflammation that alters sensory circuits. *H. pylori* activates CGRP$^+$ sensory neurons, inducing somatostatin release that briefly suppresses histamine and stomach acid.[142] It also triggers lasting structural and functional changes in gastric sensory circuitry, even after bacterial clearance, and recruits M2-like macrophages and type 2 ILC2s, fueling persistent infection and tumorigenesis.[143–145]

Early studies linked GC to cholinergic signaling. Vagotomy, which disrupts muscarinic inputs, significantly decreases tumor

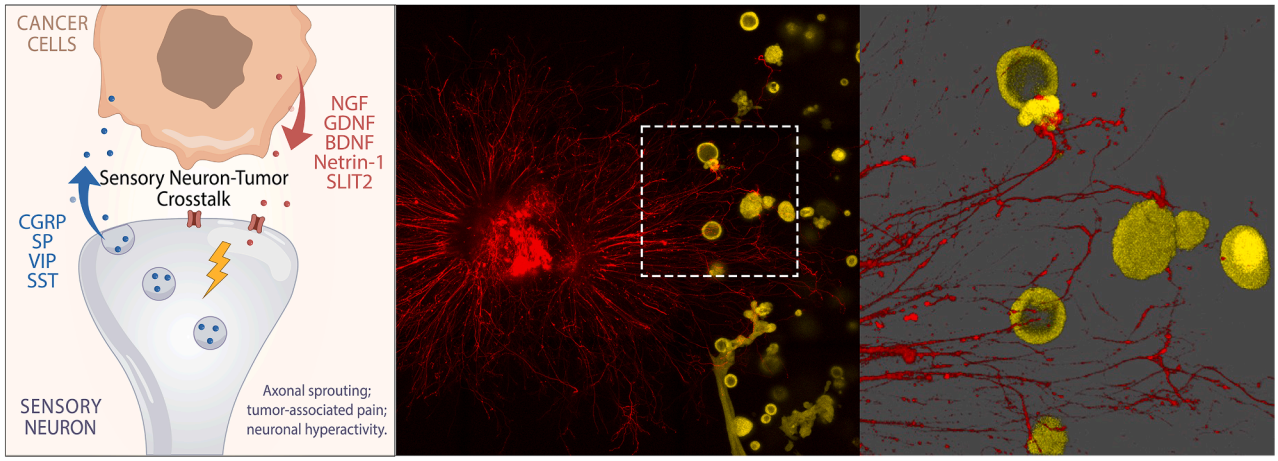

Figure 5. Direct interaction between GC cells and sensory neurons

Left: schematic illustrating bidirectional interactions between nociceptive neurons and GC cells. Neuropeptides, including substance P (SP) and calcitonin gene-related peptide (CGRP), released by nociceptive neurons, modulate tumor cell behavior. Tumor cells in turn secrete factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), netrin-1, and SLIT2. This reciprocal signaling loop promotes tumor progression, axonal sprouting, neuronal hyperactivity, and tumor-associated pain. Right: confocal microscopy images showing direct physical contact between dorsal root ganglion (DRG) sensory neurons and GC spheroids. DRG neurons labeled in red were isolated from *Trpv1-cre; tdTomato* mice, while GC spheroids labeled in yellow were derived from *Atp4b-cre*; *Cdh1fl/fl*; *KrasG12D*; *Trp53fl/fl*; *YFP* mice. The left portion of the image shows an overview of GC spheroids growing toward nearby sensory neuron axons. The dotted box highlights a magnified region on the right, illustrating the close proximity and apparent synapse-like connections between sensory nerve fibers and GC cells.[49] These findings support the presence of direct electrochemical communication within the gastric tumor microenvironment.

burden and inhibits Wnt and Notch pathways.[119] More recently, work has shown that tuft cell-derived acetylcholine can stimulate NGF secretion, promoting axon outgrowth.[146] Although vagal nerves contain both autonomic and sensory fibers, the specific role of sensory neurons in GC was only clarified more recently.

Recent data indicate that RAMP1, a CGRP receptor subunit, is present on gastric chief cells and in isthmus-localized stem/progenitor cells.[49] TRPV1$^+$ sensory neuron activation in the stomach enhances epithelial proliferation, and CGRP directly drives GC organoid growth[49] (Figure 5). Under normal conditions, such neurotrophic pathways aid tissue repair; in an ulcer model, sensory nerve stimulation accelerated healing.[49] However, these same processes can be co-opted by tumor cells. New findings show that GC cells secrete NGF, BDNF, and GDNF to recruit sensory fibers, forming synapse-like contacts and establishing functional, bidirectional electrochemical loops.[49] When tumor cells depolarize, they release neurotransmitters (e.g., glutamate, adenosine), which further activate adjacent sensory neurons, sustaining a self-amplifying electrical circuit. Concurrently, nociceptor stimulation raises CGRP output, enhancing tumor and stromal cell interactions via PI3K-AKT and Ca^{2+}/calmodulin-dependent protein kinase (CaMK) pathways, as well as RAMP1.[49] Blocking RAMP1 with the antagonist rimegepant significantly reduces tumor growth, showing that both cancer cells and the TME rely on these neurogenic mechanisms.[49] This mirrors findings in CNS gliomas, demonstrating that peripheral tumors also exploit direct electrical and chemical signaling to advance malignancy.

Pancreatic cancer

Origins of sensory neurons and how to trace them in pancreatic cancer

PDAC is notable for its aggressive behavior and extensive PNI.[147] Although PDAC hijacks local neural networks to facilitate cancer cell migration, proliferation, and immune evasion, the precise neurobiological mechanisms remain incompletely defined.[87] Sensory innervation of the pancreas primarily arises from DRG neurons at thoracic levels T6-T9, which detect noxious stimuli and transmit pain signals to the CNS.[148,149] Parasympathetic sensory inputs via the nodose ganglion and sympathetic fibers from the celiac ganglia also innervate the pancreas.[150,151] Investigating these neuronal subpopulations is challenging because the pancreas's deep location complicates molecular analyses of its sensory nerves.[152] Consequently, retrograde tracing is key for identifying and characterizing pancreatic-innervating neurons. In this approach, tracers such as cholera toxin subunit B (CTβ) are injected into the pancreas, taken up by local nerve terminals, and transported back to the neuronal cell bodies for visualization. Alternatively, genetically engineered viral vectors (e.g., adeno-associated viruses [AAVs]) can deliver fluorescent reporters to label and map these neurons at high resolution.

Functional impact of sensory neuron subtypes

Molecular profiling of PDAC models reveals that DRGs comprise three principal sensory neuron subpopulations. Neurofilament-positive (NEFM) neurons are large, myelinated fibers responsible for mechanosensation and proprioception. PEP neurons, in contrast, are small, unmyelinated fibers that release CGRP and mediate pain and inflammation. NPEP neurons, which are also small, participate in pain signaling and neuro-immune regulation.[153,154]

Beyond the DRGs, the celiac ganglia contain sympathetic neurons that secrete noradrenaline, thereby regulating vascular tone, metabolism, and immunity, while parasympathetic afferents convey visceral sensory information to the brainstem.[155] Current evidence indicates that DRG nociceptors and sympathetic neurons generally promote PDAC progression, whereas

vagal cholinergic signaling may exert an opposing, tumor-restraining effect.[87,156–160] Interactions among these neuronal subtypes likely modulate PDAC further, but their precise contributions remain under active investigation.[87]

Despite progress in PDAC, a comprehensive map of DRG sensory subtypes across diverse cancers is still missing. The neurons involved extend beyond nociceptors, and their discrete roles in tumor growth, immune modulation, and cancer-associated pain require deeper study. Emerging approaches, such as retrograde tracing coupled with spatial transcriptomics,[11–13] are beginning to chart organ-specific patterns of sensory innervation, underscoring that tumor-neuron crosstalk is shaped by the unique DRG composition innervating each tissue. Future work should prioritize functional dissection of these sensory neuron subtypes to clarify their impact on cancer progression, host immunity, and pain pathophysiology.[16–18]

Neurotransmitter signaling in PDAC

Spinal visceral afferent neurons projecting to DRGs include small myelinated (Aδ) and unmyelinated (C) fibers that convey mechanical and nociceptive signals.[161] Many are capsaicin-sensitive and express SP or CGRP.[162,163] Parasympathetic afferents from the NGs are also primarily capsaicin-sensitive and release SP and CGRP.[162,164] In PDAC, neural sprouting and hypertrophy are accompanied by shifts in neurotransmitter expression.[108] Trace-n-seq assays show that glutamate is the main excitatory neurotransmitter in PDAC-innervating DRG neurons,[108] in line with abundant glutaminase (GLS) expression in small and medium DRG neurons.[165–167] PDAC samples also exhibit elevated ionotropic glutamate receptor subunits,[168] suggesting a functional role for glutamatergic signaling. CGRP, SP, and serotonin (5-HT) are present in PDAC as well. Although CGRP is upregulated in chronic pancreatitis, it may be less central in PDAC.[149] SP, via the NK1R receptor, can promote progression of pancreatic intraepithelial neoplasms (PanINs), stimulate proliferation and invasion, and drive MMP-2 expression contributing to PNI.[169,170] 5-HT and its receptor HTR2B are also elevated in human PDAC, potentially aiding glycolysis under stress.[171]

What sensory neurons detect in the tumor tissue

PDAC is associated with severe pain, and the degree of neural infiltration correlates with neuropathic pain.[149] Tissue injury and inflammation release NGF and other mediators that activate nociceptors.[172] Peripheral nerve damage can then trigger reactive sprouting and remodeling in DRG neurons.[108,173] Thiel and colleagues observed elevated sensory neuron density in PDAC but could not confirm increased functional neuronal activity or identify changes in central pain pathways.[108] Ablating sensory neurons in a PKC-driven PDAC mouse model via neonatal capsaicin injections reduced astrocyte activation, neuronal injury, and PNI, delaying PanIN formation and improving survival.[87] These data suggest that sensory neurons not only detect tissue damage but also shape disease outcomes. However, exactly how they sense and respond to PDAC remains under investigation.

Mechanosensitive neurons in PDAC

Mechanosensitive neurons expressing the Piezo1 receptor play roles in chronic pancreatitis.[174] Piezo1 antagonists protect against pressure-induced pancreatic injury, supporting a link between channel activation and inflammation.[174] In PDAC, Piezo1 inhibition slows tumor progression, whereas its activation worsens it.[175] Piezo1 also partners with other mechanosensitive channels to drive durotaxis (migration directed by ECM thickness) in pancreatic stellate cells, which contribute to PDAC's fibrotic stroma.[176] Targeting these mechanoreceptors is emerging as a therapeutic strategy in PDAC.

Neuron-PDAC communication

Neurons typically communicate with adjacent cells via electrical signaling, neurotransmitter release, paracrine interactions, gap junctions, or synapse-like contacts.[177] Similar to conventional synapses, these junctions involve presynaptic release of neurotransmitters and receptor-mediated responses in the postsynaptic cell.[178] Electron microscopy studies in glioma and breast cancer-brain metastases show that tumor cells can form synapse-like junctions with glutamatergic neurons, promoting malignancy.[121,123] In PDAC, transcriptomic analyses point to upregulated glutamatergic and synaptic signaling pathways, consistent with axonal sprouting.[108] While direct evidence of synapse-like structures in PDAC remains elusive, these gene signatures raise the possibility of electrical or electrochemical crosstalk between sensory nerves and cancer cells.

Targeting sensory neurons in PDAC

Sensory neurons innervating PDAC exhibit transcriptional reprogramming that accelerates tumor progression and worsens survival.[87,108] Thiel and colleagues showed that celiac ganglionectomy or neurotoxin-based sympathetic denervation (using 6-hydroxydopamine [6OHDA]) in PDAC models reduced tumor size. Transcriptomic profiles of denervated tumors indicated upregulated inflammation and TCA cycle pathways. Combining 6OHDA with the immune checkpoint inhibitor (ICI) nivolumab further suppressed tumor burden, suggesting that denervation potentiates immunotherapy.[108] Nab-paclitaxel, commonly used in PDAC chemotherapy, disrupts sensory axonal growth and can eliminate sensory neurons from the TME. Patient samples confirm reduced nerve density in tumors treated with nab-paclitaxel but not FOLFIRINOX (a combination regimen composed of leucovorin, 5-fluorouracil, irinotecan and oxaliplatin). Simultaneous sympathetic ablation with 6OHDA and sensory denervation by nab-paclitaxel diminished tumor size over 16-fold, opening the door for dual denervation approaches in PDAC, an otherwise immunologically "cold" tumor.

Skin cancer

The skin and mucosal epithelia are densely innervated by sensory and autonomic fibers whose signals convey pain, temperature, and other environmental cues while sustaining tissue homeostasis, wound repair, inflammation, and immunity.[179,180] Over the past decade, these cutaneous sensory nerves have been recognized as active architects of skin cancer biology, influencing the initiation, growth, and dissemination of basal cell carcinoma, SCC, and melanoma. In mouse models of basal cell carcinoma, for example, innervated progenitor epithelia within mechanosensory touch domes are markedly more tumorigenic than interfollicular epidermal stem cells, a disparity driven in part by sensory nerve-mediated Hedgehog signaling.[116]

Ultraviolet radiation (UVR) is a well-established carcinogen, yet the impact of UVR-induced damage to cutaneous nerves on tumorigenesis remains largely unexplored.[181,182] After UVR

exposure, sensory fibers release CGRP, SP, and NGF, mediators that can exert both pro- and anti-inflammatory effects.[183,184] Clinically, a direct association between denervation and skin cancer is difficult to confirm. Individuals with spinal cord injury display higher incidences of bladder SCC as well as colorectal, hepatic, and esophageal cancers, but not skin cancer.[185,186] Nevertheless, spinal cord injury compromises neuronal regulation of wound healing and predisposes patients to chronic pressure ulcers[187]; chronic wounds, long-standing scars, or non-healing ulcers that have an elevated risk of malignant transformation into Marjolin's ulcers.[188] A systematic review reported a modest increase in SCC arising from burn scars, and a retrospective study linked physical trauma to acral melanoma.[189] Comprehensive epidemiological analyses are therefore needed to clarify how sensory denervation influences cutaneous oncogenesis and progression.

Although melanoma primarily spreads through lymphatic and vascular routes, cutaneous sensory neurons directly engage melanoma cells to create a tumor-promoting microenvironment.[190] Human biopsies and mouse models reveal that primary melanomas exhibit lower nerve density than normal skin, while inducing a nerve activation program in melanoma-associated DRG neurons.[191] Melanoma can reprogram sensory fibers and associated glia into a state resembling Wallerian-like degeneration, initiating a persistent repair response that favors tumor growth. This nerve injury fosters M2-macrophage polarization, ECM remodeling, malignant cell motility, and overall tumor progression.[191] Transforming growth factor β (TGF-β)—a central driver of peripheral nerve repair—contributes to this reprogramming[192] by upregulating neuronal 12/15-lipoxygenase and cyclo-oxygenase-2, thereby increasing prostaglandin E_2 and lipoxin A_4/B_4 production, which dampen T cell-mediated antitumor immunity.[193,194]

Although most studies report that tumor-associated sensory neurons promote melanoma progression,[51,190,195–198] others describe inhibitory effects.[72,199–201] This discordance highlights the intricacy of neuro-immune crosstalk within the TME. Cutaneous nociceptors influence immunosurveillance.[16,51,72,190,195–197] Surgical or pharmacological ablation of sensory neurons in melanoma models augments antitumor immunity by enhancing effector $CD8^+$ T cell infiltration, reducing regulatory T cells and MDSCs, increasing intratumoral T cell clonality, and inducing tertiary lymphoid structures—all features associated with improved responses to immunotherapy.[195,202,203] Melanoma cells can provoke sensory neurons to secrete CGRP, which binds RAMP1 on cytotoxic $CD8^+$ T cells and drives their functional exhaustion, thereby fostering tumor growth.[51] Because most cutaneous PEP fibers express the TRPV1 channel, genetic or pharmacological silencing of $TRPV1^+$ nociceptors slows melanoma growth and reinforces protective immunity,[51,195] and RAMP1 overexpression on tumor-infiltrating $CD8^+$ T cells correlates with poorer patient survival.[49] Ultimately, the impact of tumor-associated sensory nerves on immunity may vary with (1) the sensory neuron subtype targeted—PEP neurons that release CGRP and/or SP versus NPEP populations; (2) the tumor stage at which neuronal modulation occurs, from early seeding to late outgrowth; and (3) microenvironmental factors such as inflammation, immune cell infiltration, and neuropeptide receptor expression. Future studies must disentangle this biologically meaningful heterogeneity with cell-type-specific neuronal tools and carefully refined experimental designs.

Head and neck cancers

Head and neck cancers arise from epithelial, glandular, odontogenic (oral cavity), or mesenchymal tissues in the oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx. More than 90% are SCC, with oral cavity SCC (OSCC) accounting for ~43% of these cases.[179,180] OSCC, which originates from the oral cavity's surface epithelium, has a high incidence of PNI.[204,205] Other head and neck cancers, such as adenoid cystic carcinoma of the salivary glands, also show notable PNI but occur less frequently and need further study to clarify the mechanisms and consequences of nerve invasion.

Like many extracutaneous and extra-mucosal solid tumors, OSCC often presents with pain and involves nociceptive neurons, both of which correlate with worse clinical outcomes.[94,206] Elevated adenosine in OSCC promotes CGRP release via trigeminal A2A receptors, enhancing tumor growth.[207] Tumor-produced tumor necrosis factor alpha (TNF-α) induces nerve activation and OSCC progression, whereas TNF-α blockade reduces cancer proliferation, cytokine production, and nociception in mice.[208] Genetic alterations can also affect tumor innervation; for instance, CCND1 amplification in HNSCC enhances tumor innervation by altering the packaging of axonogenesis-related microRNAs (miRNAs) into small EVs (sEVs).[209] PNI is a well-established negative prognostic factor across cutaneous, head and neck, and OSCC tumors.[210] Since nerve involvement enables cancer cells to spread locally and distantly, such cancers receive aggressive treatment.[205] PNI, defined as tumor surrounding at least one-third of a nerve or invading the nerve,[211] is an independent risk factor for poor survival in OSCC.[204,212] To prevent locoregional recurrence, OSCC with PNI is often managed with elective node dissection and/or radiotherapy.[213,214] However, as PNI definitions have evolved, retrospective studies must re-examine archival tissues rather than rely solely on older pathology reports.

Growing insights into cancer-nerve interactions suggest that other neural phenotypes also have prognostic value in OSCC. Besides PNI, factors such as large nerve diameter, high nerve density, and short nerve-tumor distance correlate with worse survival.[204,212,215] Increased nerve density can stem from axonogenesis (neurite outgrowth), neurogenesis (formation of new neurons), or neurotropism (infiltration of nerves by cancer cells).[94,216] OSCC is neurotropic and exhibits both neurogenesis and neuritogenesis.[94,204,205,212] Spatial transcriptomics in human OSCC tissues, supported by *in vitro* findings, shows that OSCC induces an injury/repair phenotype in nearby nerves, which intensifies with tumor proximity.[204] This suggests that parameters beyond PNI alone, such as nerve-tumor distance, merit attention. Since the oral cavity is densely innervated, especially in high-risk OSCC sites like the tongue, multiple nerves may be involved.[215] Immunohistochemical analyses using nerve-specific markers (e.g., Nav1.8 for sensory, tyrosine hydroxylase for sympathetic, nNOS for parasympathetic) reveal that OSCC is predominantly associated with sensory or mixed sensory sympathetic innervation.[217] Sensory or mixed sensory sympathetic fibers are more common in the tumor bulk than at the margin,

while parasympathetic or triple-positive nerves occur more frequently at the tumor margin. Studies in transgenic mice further confirm that tongue SCC is mainly innervated by Calca$^+$ PEP nociceptors.[217–219]

Nerves and OSCC cells both release factors including neuropeptides, neurotransmitters, chemokines, and neurotrophins that drive neurite outgrowth and neurotropism. Because nerves are conduits of axons wrapped by cellular and matrix layers, cancer-nerve interactions involve both neuronal and non-neuronal cells (especially Schwann cells). These interactions are mediated by substances secreted into the microenvironment, such as galanin (GAL), or transported via small EVs (sEVs, including miRNAs.[209,220,221]

GAL was first identified as a 29-amino acid neuropeptide in porcine intestine,[222,223] and it is produced by various cells, including OSCC cells, exerting cell-type-dependent functions.[220,224–226] A meta-analysis of OSCC datasets showed that GAL correlates with poor 3-year survival ($p < 0.003$).[220] In OSCC, GAL released by neurons and cancer cells supports bidirectional signaling that promotes neuritogenesis and invasion.[180] Further findings indicate that GAL secreted by SH-SY5Y cells activates GAL receptor 2 in OSCC cells, driving NFATc2-mediated transcription of COX2 and GAL, which releases PGE2 and GAL to fuel cancer invasion and neuritogenesis.[180] Another study revealed that dietary palmitic acid upregulates GAL in OSCC cells by altering histone trimethylation; the cancer cells then release GAL to stimulate intratumoral Schwann cells to form a pro-regenerative matrix that facilitates distant metastasis.[227] In the absence of this matrix, OSCC progresses locally but does not metastasize.

Neurons can also promote OSCC progression via immunosuppression. For instance, CGRP inhibits cytotoxic CD8$^+$ T cells, CD4$^+$ T cells, and NK1.1$^+$ natural killer (NK) cells in a mouse model.[228] A high proportion of trigeminal sensory neurons innervating OSCC secrete CGRP, which increases proliferation and migration of OSCC cells; in patients, elevated plasma CGRP correlates with PNI and lymph node involvement.[52,228,229] In HNSCC models, tumor-derived sEVs interact with DRG neurons and induce T cell exhaustion.[197]

Additional work suggests a role for SP and NK-1R in early HNSCC development.[230] Mutations in *TP53*, among the most common in OSCC,[231] heighten neuritogenesis in DRG and trigeminal neurons by reducing miR-34a release in EVs.[221] Conversely, OSCC cells that secrete more ephrin-B1 in sEVs promote neurite outgrowth in PC12 cells.[219] Co-culture experiments with BDNF-deficient or -enriched media indicate that both OSCC and Schwann cells express tropomyosin receptor kinase B (TrkB), supporting possible two-way communication.[232] Although TrkB is classically associated with neuronal survival and plasticity in the CNS, BDNF-TrkB signaling also contributes to peripheral sensory neuron function, particularly under inflammatory or tumor-associated conditions.[233–235] With expanding knowledge of nerve-cancer interactions in OSCC, it is becoming clear that PNI alone may not be sufficient to guide treatment decisions. Other factors such as nerve diameter, distance between tumor and nerves, nerve density, and nerve subtype may also influence tumor behavior and could be important for tailoring therapy.

Cancer in the bone

Epidemiology of bone cancer

The bone's rich vasculature and abundant stromal factors create a highly supportive environment for tumor growth. Osteosarcoma, the most common primary bone cancer, has an annual incidence of 0.4–0.7 per 100,000, peaking in adolescence and again after age 65.[236] In contrast, metastatic lesions, primarily from breast, prostate, and lung cancers, are far more prevalent in bone than primary bone tumors.[237] Because bone is densely innervated by sensory and sympathetic fibers, there is growing interest in how tumor cells and nerves interact in this niche. Breast, prostate, and lung cancers account for over 80% of metastatic bone disease and often metastasize to highly vascularized bone marrow regions such as the skull, spine, ribs, pelvis, and the proximal ends of long bones.[238–240]

Innervation of bone

Somatosensory innervation is present throughout rodent and human bones across the lifespan.[241] The highest nerve density is found in the periosteum, followed by the bone marrow, with fewer fibers in cortical bone.[242,243] Most somatosensory fibers in bone express CGRP, the neurotrophin receptor Ntrk1/TrkA, and the capsaicin-sensitive ion channel TRPV1.[244–246] This profile matches PEP Aδ and C-fiber nociceptors, many of which are encoded by *Calca*.[247] CGRP, a principal product of *Calca*, is essential for normal bone function by promoting osteogenesis (Figure 6).[248]

Bone pain and neuronal plasticity

Bone metastases frequently precipitate hypercalcemia, anemia, pathologic fractures, and intense pain, all of which markedly diminish quality of life.[249,250] Standard interventions—opioids, radiotherapy, and bisphosphonates—provide only partial and transient relief.[251] Cancer-induced bone pain is multifactorial: nerve compression, fractures, and direct neuronal injury (reflected by heightened ATF3 expression in sensory ganglia) intersect with aberrant bone remodeling.[252] In many metastases, hyperactive osteoclasts create osteolytic lesions that liberate protons, cytokines, and growth factors, thereby amplifying nociceptor activity.[253,254] Conversely, prostate-cancer lesions are usually osteoblastic, and metastatic breast tumors often display mixed osteolytic-osteoblastic features. Compounding the problem, reduced bone mineral density—although uncommon—can emerge as a debilitating adverse effect of doxorubicin chemotherapy and immune checkpoint blockade with agents such as anti-PD-1,[255,256] further destabilizing bone architecture and exacerbating pain.

In preclinical models of prostate and breast cancer, bone-invading tumors drive pathological sprouting of PEP sensory fibers that sometimes coalesce into neuroma-like structures, intensifying pain.[257,258] Newly ingrown afferents within metastatic bone lesions underlie pronounced hypersensitivity,[259–262] while peripheral and central circuitry is reprogrammed, as demonstrated by reactive gliosis and other injury-like responses in the spinal cord.[263,264] Multiple mediators heighten sensory neuron excitability in this context. Osteoclasts secrete netrin-1 and shed EVs that, via epidermal growth-factor signaling, promote neurite outgrowth and pain.[92,265] NGF stimulates nerve sprouting, tumor vascularization, and nociception and simultaneously supports tumor expansion[258,266–270]; accordingly,

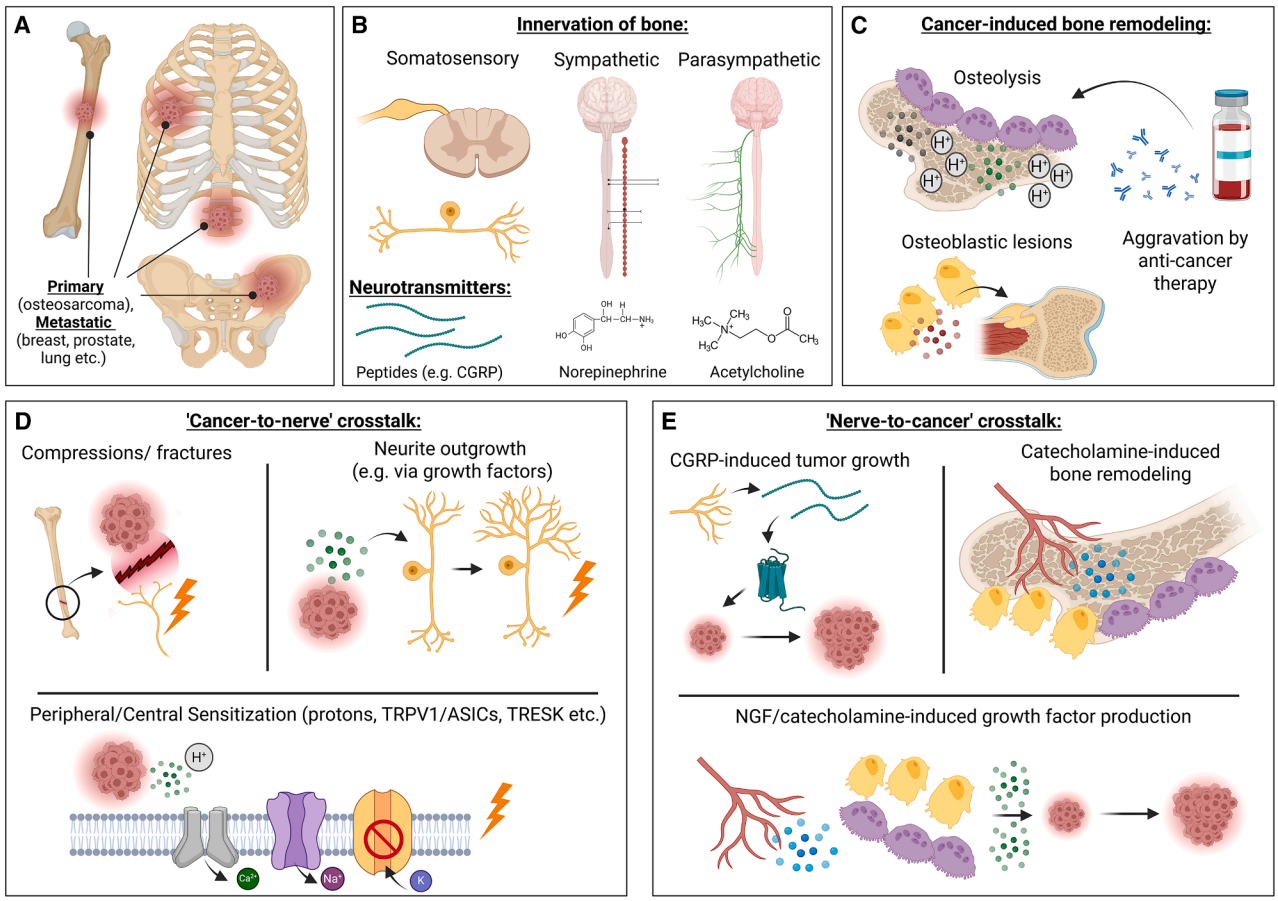

Figure 6. Cancer-nerve crosstalk in bone

Metastatic lesions preferentially arise within the axial skeleton (A). This environment is richly supplied with somatosensory and autonomic nerve fibers (B) and is continuously remodeled by osteoclasts and osteoblasts (C), a dynamic that releases plentiful growth factors for colonizing cancer cells. Tumor-induced alterations in bone architecture then precipitate structural weakening, pathologic fractures, peripheral-nerve hyperexcitability, and pronounced pain (D). Neurotransmitters liberated from these activated fibers feedback to amplify tumor proliferation, perpetuate aberrant bone remodeling, and further enhance growth factor availability (E).

many emergent bone-innervating fibers express TrkA and GAP-43, and NGF blockade curtails both sprouting and pain.[266–268] VEGF, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor exert analogous pro-neuritogenic, pro-nociceptive effects,[269,271] while osteoclast-derived insulin-like growth factor-1 fuels neuroinflammatory processes that intensify pain in metastatic breast cancer.[272]

Acidosis provides a further excitatory drive. Osteoclast-mediated bone resorption lowers extracellular pH, activating TRPV1-positive afferents—possibly ASIC3 as well—and fostering hyperexcitability.[261,273] In parallel, diminished expression of the potassium channel TRESK in CGRP-positive neurons raises their intrinsic excitability in bone metastasis models.[274] Collectively, these mechanisms intertwine aberrant bone remodeling with maladaptive neuronal plasticity to produce the severe, often refractory, pain characteristic of skeletal metastases.

Neuronal activity and cancer growth

Greater density and heightened excitability of sensory fibers can actively fuel tumor proliferation.[275,276] CGRP, acting through the calcitonin receptor-like receptor (CRLR) and downstream p38 MAPK-HSP27 signaling, correlates with shorter recurrence-free survival in patients.[257,269] In a breast cancer-bone metastasis model, TRPV1$^+$ sensory neurons secrete elevated levels of hepatocyte growth factor (HGF), thereby facilitating tumor colonization.[277] Pharmacological blockade of CGRP or TRPV1 alleviates bone pain and simultaneously restrains tumor progression.[273,278]

Neurotrophins such as NGF and BDNF, together with their cognate receptors, are expressed in both osteosarcoma and bone-metastatic breast cancer.[279,280] Injured bone releases NGF, which induces robust neurite sprouting; stimulates stromal growth-factor production; and drives vascular regeneration—conditions that malignant cells readily exploit.[281–284] Within osteosarcoma, NGF further amplifies primary tumor growth and lung metastasis by upregulating MMP2 and recruiting immunosuppressive M2-like macrophages.[285] Accordingly, anti-Trk therapeutics such as larotrectinib show promise in curbing osteosarcoma progression and dissemination.[269,286]

Conversely, several myeloproliferative neoplasms prosper when the hematopoietic niche is denervated.[287–289] Standard chemotherapy can aggravate this situation by injuring sympathetic fibers, thereby slowing hematopoietic recovery.[290] Enhanced adrenergic signaling worsens outcomes in multiple myeloma, whereas high cholinergic receptor expression predicts poorer prognosis—observations that imply parasympathetic activity may drive specific disease subsets.

Collectively, sensory innervation in bone orchestrates a complex dialogue among neurons, bone cells, and cancer cells, underpinning tumor establishment, progression, skeletal destabilization, and debilitating pain. Therapeutic strategies that disrupt these neuron-tumor interactions could simultaneously improve analgesia, strengthen antitumor immunity, and impede cancer growth within the bone microenvironment.

Metastasis

Metastasis is a major driver of cancer morbidity and mortality worldwide. Sensory nerves and nociceptive neuropeptides influence multiple metastatic steps, including tumor cell migration and invasion, hematogenous spread, premetastatic niche formation, and metastatic cell survival. Although studies associate sensory innervation with higher tumor grade, aggressiveness, and metastasis,[50,291–294] the mechanisms remain incompletely understood. Sensory axons may serve as physical conduits for dissemination and secrete neuropeptides that promote tumor cell motility and microenvironment remodeling. Tumor cells invading nerve bundles can spread along perineural routes, often predicting poor outcomes.[295–298] Neuropeptides such as SP and GAL stimulate cancer cell migration and direct them toward nerve endings,[50,169,299] while also elevating matrix-degrading enzymes MMP-2 and MMP-9.[169,299,300]

CGRP and SP act on blood and lymphatic endothelium, enhancing vasodilation and capillary permeability,[112,301–305] and induce cancer cells to release factors such as VEGF.[300,306] Increased vascular flow and permeability can facilitate extravasation and metastasis.[307–309] Sensory nerve signaling also appears crucial for metastatic outgrowth; in a clinical series, 33% of cancer patients with idiopathic sensory neuropathies developed metastases, regardless of tumor origin.[310] Animal models suggest that vagotomy can heighten metastatic burden in breast, colorectal, and pancreatic cancers,[311–314] although these findings are complex because vagotomy removes both sensory and autonomic fibers.[315] Elevated SP after vagotomy has been proposed as one mechanism for increased metastatic spread.[313] Conversely, boosting vagal activity with semapimod reduced metastases in breast cancer models, possibly through cholinergic inhibition of inflammatory mediators.[314]

Sensory nerve ablation studies with high-dose capsaicin in breast cancer models highlight the complexity of these interactions. Desensitizing Trpv1$^+$ nerves can enhance metastasis to the lung and heart without changing primary tumor size,[136,137] although short-term nerve hyperexcitation and neuropeptide release may condition the tumor niche. Other Trpv1 agonists, such as olvanil, can reduce metastatic burden and boost local T cell responses.[138] Chronic capsaicin treatment started before tumor implantation, and continued post-tumor implantation decreased metastasis in breast cancer models,[50] suggesting that tumor-infiltrating sensory innervation may support metastasis. Similarly, in PDAC, blocking *de novo* axonogenesis by inhibiting the Sema3D-PlexinD1 axis lowered PNI and metastasis.[291] Conversely, co-injecting tumor cells with DRG neurons increased metastatic burden.[50,70] One proposed mechanism involves SP-mediated apoptosis in a subset of tumor cells, releasing single-stranded RNAs that activate TLR7 in neighboring cells, driving an invasive and metastatic phenotype.[50]

It remains unknown whether primary tumors trigger sensory signaling in distant organs to create a pro-metastatic niche. Lymph node metastases, for instance, indicate aggressive behavior and poor outcomes.[316–318] Tumor cells often first colonize the node's hilum and capsule,[319–321] which are sites of sensory fiber innervation.[110,322–324] By responding to inflammation in the node, these fibers can alter stromal and immune cell gene expression, supporting ECM deposition, lymphangiogenesis, and axonogenesis.[110] Nociceptive signals also induce immunosuppressive phenotypes in neutrophils and dendritic cells,[325–328] raising the possibility that sensory-driven immunomodulation might favor metastatic colonization in distant tissues. In the brain, meningeal nociceptors releasing CGRP promote immunosuppression by meningeal macrophages.[329,330] Analogous mechanisms could potentially facilitate metastatic spread to the brain and meninges, although more evidence is needed to confirm this hypothesis.

Influence of tumor heterogeneity on the role of sensory neurons in specific peripheral tumor types

The emerging body of work on sensory neuron-tumor interactions already highlights clear differences among tumor entities, yet even greater complexity arises from the functional and phenotypic heterogeneity that exists within a single neoplasm. High-coverage single-cell sequencing of human cancers has revealed extensive genetic diversity among intratumoral clones and among the non-malignant cells that may engage infiltrating sensory fibers.[331] Genomic instability fuels this clonal diversity,[332] but it remains unclear whether differentiated and undifferentiated subclones respond identically to sensory input inside the same tumor. Likewise, microenvironmental conditions vary widely across a lesion: highly vascularized or immune-enriched niches may interact with sensory neurons in ways that differ fundamentally from interactions occurring in poorly vascularized or immune-desert regions.

The field must therefore progress from the early "one-size-fits-all" perspective toward a context-dependent framework that accounts for the continuous, tumor-specific evolution of neuron-cancer crosstalk. Future studies aimed at dissecting these relationships will need to probe the mechanistic basis of sensory neuron signaling while factoring in inter-patient variation in oncogenic mutations, microenvironmental composition, and disease stage.

Sensory neurons likely play distinct roles in pain generation and tumor regulation at different stages of cancer progression and across tissue types. Such variation may reflect differences in innervation density as well as the repertoire and concentration of algogenic mediators released by each tumor. Early-stage cancers, for example, can be painless because they induce minimal

tissue damage, elicit less inflammatory infiltration, impose lower mechanical stress, and produce fewer nociceptor-sensitizing molecules; under these conditions, neuronal engagement is limited. As tumors grow, however, changes in the immune compartment and in the biochemical milieu may progressively heighten nociceptor excitability, reshape neuro-immune interactions, and alter the balance between tumor-promoting and tumor-restraining neuronal signals.

CANCER-INDUCED SENSORY PLASTICITY AND NEUROPATHIC CHANGES

scRNA-seq has revealed remarkable structural and molecular diversity among sensory neurons in DRGs, TGs, and jugular-NGs (JNGs).[333–338] Under physiological conditions, many of these neurons are chiefly nociceptive,[339] yet tumor-driven inflammation or injury can sensitize or damage them, initiating maladaptive pain signaling. Such cancer-induced nociceptor activation aligns with the intricate anatomy of peripheral nerves that convey information through distinct spinal or cranial pathways to higher brain centers[340,341]: DRG neurons innervate the body and visceral organs, TG neurons serve head and neck tissues, and nodose neurons relay visceral input via the vagus nerve.[335,342,343]

Tumors remodel neurons along three principal dimensions. First, they can heighten neuronal excitability. CNS tumors form excitatory synapses with glutamatergic neurons, thereby accelerating cancer cell growth,[121,122] and breast cancer-brain metastases similarly exploit glutamate receptors.[123] Peripheral tumors also establish synapse-like contacts that sustain malignancy.[121,122] Second, cancer cells secrete neurotrophic factors that induce dense neural infiltration; prostate cancer and GC, for example, rely on NGF, GDNF, and related molecules to maintain bidirectional tumor-nerve crosstalk.[49,146] Third, these remodeled circuits influence tumor metabolism, immune evasion, and overall progression,[49,146] implying that interventions targeting cancer-induced sensory plasticity could curb both tumor expansion and cancer pain.

Neural progenitor cells (NPCs) from the brain can migrate to peripheral prostate tumors, differentiate into neurons, and foster tumor growth.[135] Nevertheless, whether adult NPCs truly leave their cerebral niche and enter the circulation remains debated,[344] and further work is required to clarify the prevalence and impact of NPC-derived tumor-infiltrating neurons. Transcriptional programs within such infiltrating sensory neurons are just beginning to emerge, pointing to organ- and tumor-specific gene expression patterns that drive neural remodeling. In head-and-neck cancer, trigeminal neurons from tumor-bearing mice upregulate genes linked to synaptic signaling, neuronal function, and nerve injury or pain.[345] Cancer-related nociceptor reprogramming also correlates with elevated NGF, which increases Calca under low-glucose conditions and reshapes neuronal gene profiles to sustain tumor viability.[196]

Tumor heterogeneity further complicates these processes. Distinct oncogenic mutations sculpt the immune microenvironment[346–348] and impose unique patterns of neuronal remodeling. In head-and-neck cancer, TP53 loss provokes an adrenergic shift in tumor-associated sensory neurons via miR-34a downregulation[221]; preventing this conversion through targeted sensory denervation or pharmacologic adrenergic receptor blockade hinders tumor progression, whereas removing preexisting adrenergic nerves yields little benefit.[221] These observations underscore the tissue- and genotype-specific nature of tumor-nerve interactions. Comprehensive mechanistic studies—leveraging genome-wide transcriptomic profiling and refined mouse models that capture the full diversity of neurons and tumors—are essential for deeper insight into how sensory innervation and adrenergic reprogramming drive cancer progression.

EARLY CANCER NOCICEPTIVE SIGNALING RESEARCH

Clinicians once attributed cancer pain primarily to mechanical processes such as local tissue infiltration, nerve compression, and bone involvement. However, early rodent studies proposed a more complex scenario driven by tumor-secreted molecules, inflammation, and neuronal sensitization. The current view posits that tumor-derived factors can directly activate or sensitize primary afferent nociceptors, making neuron-tumor communication a key driver of pain, particularly in oral cancer.[349–351]

Rodent models have helped identify tumor-derived mediators that generate cancer pain, although differences in cell lines and behavioral tests can complicate data interpretation. Several crucial factors have emerged. Endothelin-1 (ET-1), a powerful vasoconstrictor, signals via ETAR and ETBR and can induce pain through ETAR on sensory neurons in preclinical models.[352] ETAR antagonists alleviate pain in OSCC by reducing nociceptor firing and increasing endogenous opioid release.[353–355] Yet clinical trials with atrasentan in prostate cancer have yielded mixed outcomes, reflecting tumor-specific variability.[356]

ATP released by tumor cells activates purinergic receptors (P2X, P2Y) on nociceptors,[357] and blocking P2X2 or P2X2/3 diminishes pain-like behavior in rodents,[358] although species differences in purinergic signaling may limit clinical translation.[359] Exosomes and miRNAs contribute to nociception by acting on both immune cells and sensory neurons, modulating neuroinflammation, ion channel expression, and pain sensitivity.[209,360] Neurotrophic factors (e.g., NGF, BDNF) drive neuronal growth and hyperexcitability,[361] enhancing pain perception through Trk receptors.[362,363] Proteases (serine proteases, legumain, cathepsin S) can activate sensory neurons via PAR2, intensifying pain.[61] TNF-α further raises nociceptor activity,[61–63] and its inhibition reduces pain in cancer models.[364]

PAIN AND SENSORY DYSFUNCTION IN CANCER PATIENTS

Pain is one of the most common and disabling cancer symptoms, profoundly affecting patients' quality of life. Despite diagnostic and therapeutic advancements, the neurobiological mechanisms of cancer pain remain only partially understood. Treatments borrowed from other pain conditions can be less effective in cancer,[221] and opioids may even accelerate tumor growth in certain cases.[365,366] Many preclinical models rely on non-orthotopic tumors or cancer cells without key human mutations, further limiting our knowledge of cancer pain. These issues underscore the need for more accurate pain assessment and disease-specific cancer models.

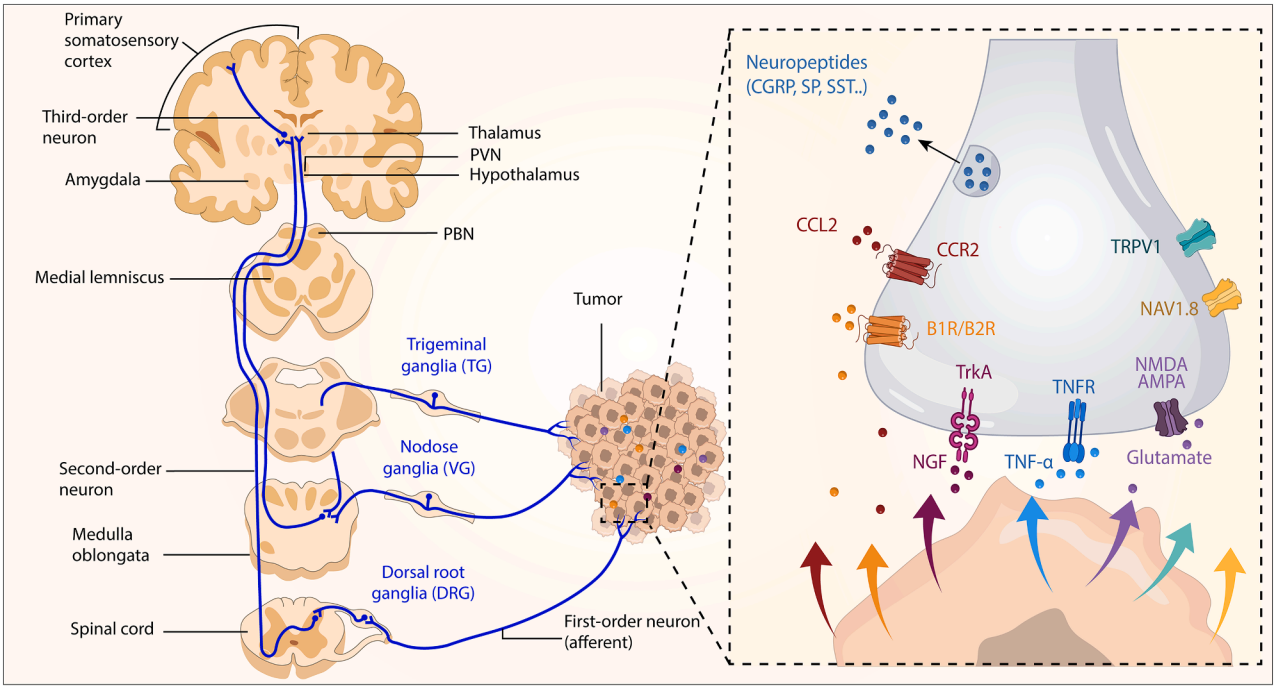

Figure 7. Cancer-induced modulation of central nociceptive pathways

Schematic illustrating how tumors can remodel CNS circuits involved in pain processing. The tumor microenvironment (TME)—encompassing tumor cells, vasculature, immune cells, and secreted factors (e.g., cytokines, metabolites)—modulates the excitability of sensory neurons. Sensory innervation of visceral tissues arises from neurons in the trigeminal ganglia (TGs), vagal ganglia (VGs), and dorsal root ganglia (DRGs). Trigeminal and vagal afferents project directly to brainstem nuclei, whereas nociceptive DRG neurons relay signals through the spinal cord dorsal horn. Second-order neurons then ascend to higher centers via pathways such as the spinothalamic tract. Key regions implicated in cancer-associated pain include the parabrachial nucleus (PBN), medial amygdala, and paraventricular nucleus (PVN) of the hypothalamus, which integrate nociceptive, affective, and autonomic responses. Tumor-driven spinal cord alterations, such as astrocyte hypertrophy and elevated dynorphin expression (indicated by red arrows), illustrate the neurochemical changes that promote central sensitization in the context of cancer.

Local activation of sensory neurons

Cancer elevates numerous cytokines and chemokines, even though only some directly stimulate tumor-infiltrating sensory nerves. TNF-α, for instance, is highly expressed in human oral cancers and activates pain-related primary afferent fibers in OSCC.[350] Blocking TNF-α in mouse OSCC models reduces pain behaviors and T cell infiltration,[350] suggesting that modulating TNF-α can alleviate nociception while affecting local immunity.

Another study found that inhibiting TNF-α in oral cancer decreased tumor proliferation, Schwann cell activation, and pronociceptive signaling, thereby relieving pain.[208] However, because TNF-α may also have antitumor functions, complete neutralization could be detrimental in certain cancers, highlighting the importance of tumor-specific approaches.

Tumor cells undergo substantial metabolic shifts that can influence neuron-tumor interactions. For example, pancreatic cancer cells can boost NGF production to recruit sensory fibers and acquire essential metabolites like serine.[367] Whether tumor-derived metabolites in turn alter sensory neuron activity is still unclear. Acidification within the tumor may also heighten nociceptor excitability by activating acid-sensing ion channels such as TRPV1 and ASICs.[367–369] In bone cancer, osteoclast-mediated bone resorption lowers pH and depolarizes nociceptors, intensifying pain.[370] Mechanical factors add to the pain as tumor expansion stretches or compresses nearby tissues. Many organs contain mechanoreceptive neurons expressing channels like PIEZO2, which can further exacerbate pain when stimulated by tumor growth.[371–373]

Central sensitization

Nociceptive signals originate in peripheral sensory neurons located in the DRG, then project to second-order neurons in the spinal cord's dorsal horn (Figure 7). From there, pain signals travel through the spinothalamic tract to the brainstem and thalamus, eventually reaching higher-order areas such as the somatosensory cortex (for localization), the insula and anterior cingulate cortex (for affective processing), and the prefrontal cortex (for cognitive and emotional integration).

Tumor-driven immune and metabolic changes (e.g., elevated cytokines, altered metabolites) can profoundly alter CNS circuits.[374–376] In head-and-neck cancer models, tumor-innervating sensory neurons engage brain regions like the central medial amygdala and parabrachial nucleus, leading to heightened calcium signaling and behavioral signs of anhedonia, and analgesics partly reverse these effects.[345]

In orthotopic pancreatic cancer, visceral pain correlates with diminished firing of GABAergic neurons in the paraventricular nucleus (PVN); artificially boosting these neurons relieves pain.[377] Bone cancer models demonstrate similar reorganization in spinal pain pathways, including astrocyte hypertrophy, reduced

expression of glutamate transporters, and elevated dynorphin levels that paradoxically intensify nociceptive signals.[378] Blocking osteoclast-mediated bone degradation normalizes spinal neurotransmission and mitigates pain, reinforcing the notion that tumors can remodel nociceptive networks at multiple CNS levels.

CLINICAL SIGNIFICANCE AND TRANSLATIONAL OPPORTUNITIES

Discoveries emerging from cancer neuroscience are transforming our grasp of malignancy and revealing novel diagnostic, prognostic, and therapeutic avenues. By clarifying the molecular and cellular dialogue between tumors and peripheral sensory neurons, clinicians and researchers can refine risk prediction, tailor treatment, and design targeted interventions. In mice, TRPV1$^+$ neurons are confined to PEP nociceptors, whereas in humans TRPV1 appears in both PEP and NPEP DRG neurons.[32,379] This broader expression pattern implies that TRPV1-directed therapies could influence a wider spectrum of sensory neuron subtypes in patients than murine studies alone would suggest, underscoring the need for careful translational interpretation.[40] Although no completed clinical trials have yet tested agents that directly disrupt sensory neuron-cancer crosstalk—likely because these findings are still recent—an ongoing phase I/II study in China (ClinicalTrials.gov identifier NCT06999252) is evaluating the combination of a CGRP receptor antagonist with anti-PD-1 therapy in patients with colorectal-cancer liver metastases, thereby directly targeting neural-tumor interactions mediated by sensory neurons.

Diagnostic and prognostic biomarkers

Tumor innervation—particularly the density of CGRP$^+$ and SP nerve fibers and the proximity of nerves to malignant cells—may predict clinical outcomes. Immunohistochemical or immunofluorescent analysis of patient biopsies can quantify neuronal infiltration and refine prognostic assessment. Elevated circulating concentrations of neuropeptides such as CGRP and SP correlate with more aggressive tumor behavior.[229,380] Advanced imaging techniques capable of visualizing neuropeptide receptors or nerve architecture promise earlier detection, more precise treatment planning, and better surgical margins, especially in cancers notorious for extensive PNI, including pancreatic and head-and-neck malignancies.[381,382]

Therapeutic strategies targeting sensory neuron-tumor interactions

Pharmacological blockade of neuropeptide signaling is a particularly promising strategy. CGRP receptor antagonists such as rimegepant, already approved for migraine prophylaxis, might be repurposed for tumors with high CGRP activity—for example, certain GCs.[49] Anti-NGF antibodies originally created for chronic pain indications can reduce tumor innervation and growth,[367] with successful preclinical results in oral cancer, Ewing sarcoma, and pancreatic adenocarcinoma.[196,207,383] Direct neural disruption approaches (e.g., sympathectomy or vagotomy) have slowed tumor progression in several experimental models,[119] although their broad off-target effects warrant caution. Combining neuron-focused agents with immunotherapies is also attractive, because neuropeptides such as CGRP and SP modulate immune cell function.[51,384,385]

Pain management and tumor control

Cancer-related pain, particularly in tumors that exhibit extensive PNI (for instance, PDAC and HNSCC), remains a formidable clinical challenge. Conventional analgesics—opioids and non-steroidal anti-inflammatory drugs (NSAIDs)—can prove inadequate and may even foster tumor progression.[357,358] Recent clinical trials indicate that anti-NGF agents may provide effective pain relief in cancer patients who fail standard opioid-based regimens.[386,387] Opioids acting through the μ-opioid receptor suppress antitumor immunity by dampening NK and CD8$^+$ T cell activity, impairing antigen presentation, and bolstering regulatory T cell function.[388–390] Conversely, κ-opioid receptor activation curtails tumor angiogenesis and thereby restrains growth.[391] Precisely targeting nociceptive signaling at its origin could therefore deliver localized analgesia while diminishing nerve-driven tumor support.[392]

Modulating immune status via pain control

Effective pain control may simultaneously enhance antitumor immunity. Widely used non-steroidal and steroidal anti-inflammatory agents that inhibit the COX-2/PGE_2/EP2-4 pathway—central to pain and inflammation—also improve the efficacy of immune checkpoint blockade in murine cancer models.[393] Nevertheless, caution is warranted: recent evidence shows that morphine fosters a pro-tumor, immunosuppressed state via peripheral OPRM1 signaling; peripheral OPRM1 antagonism preserves central analgesia while mitigating these detrimental effects, offering a promising therapeutic strategy.[394] Chronic pain and neurogenic inflammation can directly impair cytotoxic T cell function and recruit immunosuppressive cell subsets such as MDSCs. Interventions that disrupt sensory neuron-tumor communication—such as CGRP or SP antagonists—may therefore reduce pain and relieve immunosuppression, potentially enhancing immunotherapy responses. Early clinical trials are already assessing these dual benefits, although final data are still forthcoming. Approaches that alleviate pain while invigorating anticancer immunity hold the promise of improving both patient quality of life and therapeutic success.

CONCLUSION

Mounting evidence highlights the pivotal role of peripheral sensory neurons and their neuropeptides in solid tumor progression. These neurons do more than relay sensory signals, they actively shape inflammation, immune evasion, and metastasis within the TME. Although mechanisms differ by cancer type, a recurring pattern involves pathological, self-reinforcing loops of neuron-tumor crosstalk. Tumor cells recruit and reprogram local sensory neurons to form neural niches that drive growth, invasion, and therapy resistance, often via chemical (neuropeptides, neurotransmitters) and electrical signaling.

Therapeutic interventions aimed at neuron-tumor interactions show promise. Preclinical data indicate that pharmacological agents, localized neuromodulation, and neuroablative approaches can disrupt these tumor-promoting circuits. Such strategies may work synergistically with immunotherapies and other

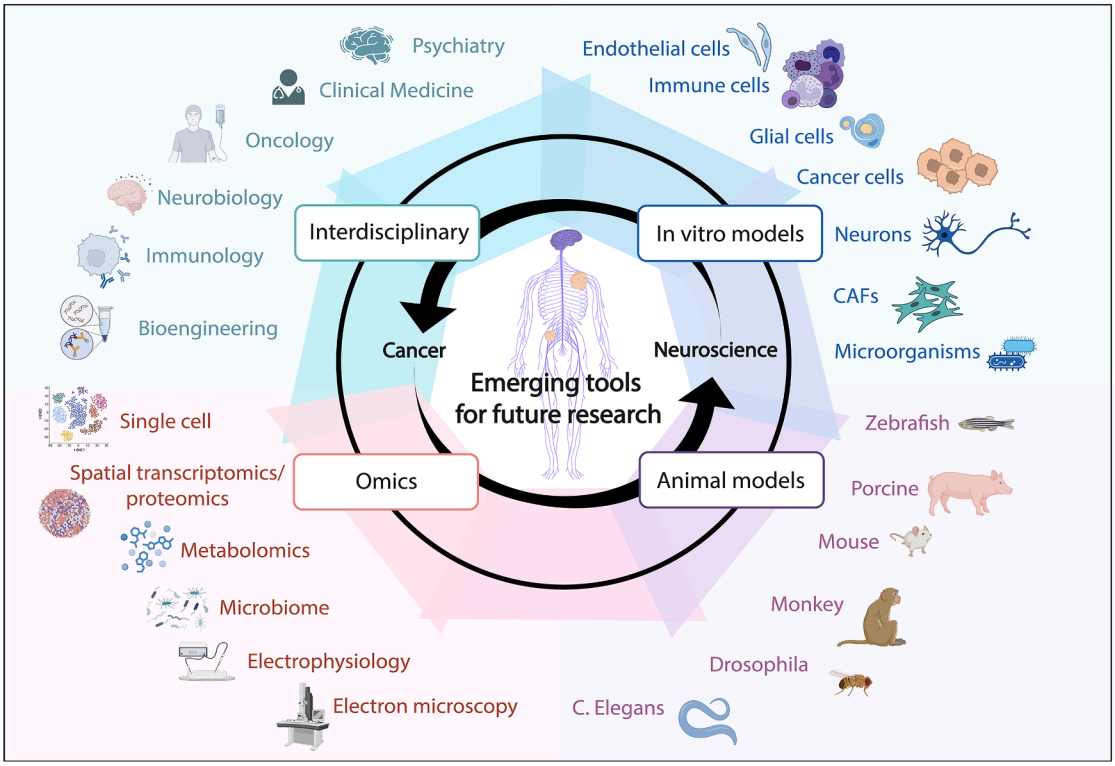

Figure 8. Emerging tools for future research in cancer neuroscience

A schematic highlighting emerging methods and collaborative efforts guiding future cancer neuroscience research. *In vitro* techniques use advanced 3D co-culture platforms that combine cancer cells, neurons, cancer-associated fibroblasts (CAFs), endothelial cells, immune cells, and microbial consortia to replicate the complexity of the TME and allow real-time functional studies. *In vivo* investigations leverage diverse animal models—ranging from mice, zebrafish, and non-human primates to swine, *Drosophila*, and *Caenorhabditis elegans*—for imaging, gene editing, viral tracing, and functional assays to verify neuron-tumor pathways and potential therapies. Multi-omics analyses integrate single-cell RNA sequencing (scRNA-seq), ATAC-seq, proteomics, and spatial transcriptomics/proteomics with metabolomics, microbiome profiling, electrophysiology, and high-resolution electron microscopy, providing deep insights into the molecular underpinnings of neuron-tumor interactions. Successful progress depends on cross-disciplinary collaborations among oncologists, neurobiologists, immunologists, bioengineers, clinicians, and mental health experts, enabling comprehensive approaches to cancer therapy and improved patient well-being.

anticancer treatments, potentially improving both therapeutic potency and precision. Targeting sensory neurons may also significantly alleviate cancer-associated pain, delivering the dual benefit of enhanced tumor control and better patient quality of life.

Rapid advances in imaging, multi-omics, and experimental models are illuminating the molecular and functional interfaces between neurons and cancer cells (Figure 8).[395] These insights will be critical for developing novel therapeutic targets and precision medicine approaches tailored to the neural characteristics of specific tumors. Continued interdisciplinary collaboration among oncologists, neuroscientists, immunologists, bioengineers, and clinicians is essential to translate these basic findings into effective human therapies. Novel techniques for precisely manipulating human sensory neurons will be key to fulfilling the potential of cancer neuroscience. Although recent progress has greatly expanded our understanding of sensory neuron roles in tumors, the most transformative discoveries and treatments still lie ahead.

ACKNOWLEDGMENTS

We apologize to those whose work could not be included due to space limitations. This work is supported by grants from the UW-Skin Disease Research Center (AAJ9318), American Cancer Society (134105-IRG-19-146-54-IRG), Wisconsin Partnership Program (AAN4246), Carbone Cancer Center Critical Pilot (144-AAL7122), 2025 Cancer Center Support Grant (CCSG) Program Pilot (P30CA014520), and U.S. Department of Defense (ME240045) to A.B. S.T.'s work is supported by the Canadian Institutes of Health Research (193741, 407016, 461274, and 461275), the Canadian Foundation for Innovation (44135), the Canadian Cancer Society Emerging Scholar Research Grant (708096), the Knut and Alice Wallenberg Foundation (KAW 2021.0141 and KAW 2022.0327), the Swedish Research Council (2022-01661), the Natural Sciences and Engineering Research Council of Canada (RGPIN-2019-06824), and the NIH/NIDCR (R01DE032712). A.T.'s work is supported by the Canadian Institute of Health Research (186176). J.P.C.-J.'s work is supported by the Minas Gerais Research Foundation – FAPEMIG, Brazil (REMITRIBIC, RED-00031-21). N.J.D.'s work is supported by NIH/NIDCR R35 DE027551 and NIH/NCI R01 CA250214. Y.L.B.'s work is supported by the National Institutes of Health grant R01CA266529. I.A.-S.'s work is supported by the Simons Foundation and Howard Hughes Medical Institute. A.J.S.'s work is supported by 1R61NS140684-01. T.C.W. is supported by grants from the NIH, including R35CA210088, R01CA272901, and DK128195.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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