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Sensory neurotransmission and pain in solid tumor progression

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Abstract

Sensory nerves form a crucial component of the tumor microenvironment (TME) that relays vital information to the central nervous system and modulates tumor progression via immunosurveillance. Afferent activity processed by the brain can sensitize brain circuitry and influence host behaviors. Peripheral sensory signaling (e.g., release of neuropeptides in the TME) can drive phenotypic changes in the tumor immune response, such as increased exhaustion markers and inhibited effector cell activity, which promote cancer progression. In this review we highlight the most recent evidence demonstrating the pivotal role of the sensory nervous system in cancer, with a focus on primary tumor pain, and we discuss the extent to which pain can influence cancer progression and treatment response, including immunotherapeutic strategies.

The role of peripheral nerves in solid tumor progression is evident [1]. The primary focus to date has been on the autonomic nervous system owing to its relationship with stress [2]; physical and psychological stressors associated with cancer diagnosis and clinical treatment are thought to result in robust sympathetic signaling throughout the body [1]. However, pain is also considered to be a hallmark of cancer [3]. Sensory neurons, including a subtype which encodes painful (i.e., nociceptive) stimuli, comprise a large percentage of peripheral nerve endings in target tissues (skin, breast, oral cavity) that detect stimuli in the environment and propagate these signals to the central nervous system. Sensory neurons can also mediate efferent signaling by releasing neuropeptides into the TME to modulate tumor cells, immune cells, and stromal cells [4,5].

The impact of cancer on peripheral sensory neurons and subsequent nociceptive signaling has been studied for decades in the context of cancer pain. Pain before treatment has been shown to be a prognostic marker for poor outcome. For example, pretreatment pain is reported in >70% of oral and 40% of cutaneous squamous cell carcinoma (SCC) patients as well as at least 20% of non-small cell lung cancer patients, and it is thought to predict locoregionally advanced disease, perineural invasion, and poor prognosis [6–8]. In addition, experiments using preclinical cancer pain models have identified numerous neuroactive

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mediators that are released from tumor cells and have elucidated the impact of nociceptive signaling in tumor-associated inflammation in the context of cancer pain [9–11].

However, recent attention has shifted to the impact of the sensory nervous system on cancer [4] and immunity [5]. The importance of sensory neuron signaling within the TME and its regulation may play a pivotal role in tumor progression and treatment response, including immunotherapeutic strategies. We review here the role of the sensory nervous system in the TME, with a focus on pain arising from the primary tumor site, and discuss whether pain as a functional output of sensory nerve activity can be used to suggest therapeutic strategies to treat cancer.

Clinical and preclinical assessment of cancer pain

Cancer patients can report pain before treatment, which likely arises directly from the tumor [7,12]. Pretreatment cancer pain is most common in bone, oral, and pancreatic cancers and can indicate perineural invasion and increased tumor progression. For example, referred pain in the abdominal region or low back are considered to be indicators of advanced disease for visceral cancers such as pancreatic cancer [13] and ovarian cancer [14]. There are many hypothesized drivers of primary tumor-evoked pain, including tumor mass, necrosis of surrounding tissue, tumor-secreted mediators, and nerve injury [15]. However, these factors do not consistently apply across cancer types; for example, human papilloma virus (HPV)-derived head and neck cancers are less painful than HPV-negative head and neck cancers, even though the location of the tumor is similar [16]. In addition, the skin is densely innervated with sensory nerves, particularly nociceptors, but the prevalence of pain in melanoma and cutaneous basal cell carcinoma is minimal. The intensity of pain can be used clinically in differentiating cutaneous SCC from basal cell carcinoma [17], suggesting that the tumor cell type or cell of origin may play a significant role in the activation of pain-producing fibers, thus emphasizing the complexity of cancer pain. Unfortunately, assessment of cancer-related pain is most frequently initiated following treatment (e.g., surgery, chemotherapy, radiation), given the tissue damage that often follows these procedures [18]. Tracking cancer pain as early as diagnosis may inform and improve treatment strategies.

The relationship between primary tumor pain before treatment and recurrence has not yet been explored. Defining whether targeting pain is sufficient to slow cancer progression is challenging in patients owing to the routine use of analgesic medications during cancer treatment [19] and the influence of standard treatment paradigms (e.g., surgery, radiation) on local sensory nerve signaling. In addition, opioids remain the current therapeutic regimen for cancer-related pain, despite being well documented to be immunosuppressive [20], raising concerns about their potential to interfere with the efficacy of immunotherapeutic strategies such as immune checkpoint inhibitors (ICIs). Alternative strategies directly targeting the sensory nervous system are being explored for chronic cancer pain. Botulinum neurotoxins (BoNTs), that are commonly used for cosmetic purposes, have emerged as potential interventions following cancer treatment because the evidence suggests that they can inhibit neuropeptide release from peripheral endings; however, the clinical outcomes across different cancer types to date have been inconclusive [21,22].

How the nervous system signals cancer pain: orthodromic and antidromic propagation

Sensory neurons are pseudounipolar in structure with (i) peripheral projections that innervate somatic and visceral peripheral tissues organized by vertebral level, and (ii) central projections that extend into the spinal cord and/or brainstem. The cell bodies, which contain the genetic material, are housed in bilateral clusters called ganglia located within the spinal vertebral column (dorsal root ganglia), the floor of the middle crania fossa (trigeminal ganglia), or the jugular fossa (nodose and jugular ganglia) (Figure 1). A key feature of sensory neurons is their ability to generate action potentials from peripheral input that can be transmitted in both directions, referred to as orthodromic and antidromic propagation. Both types of electrical signal have been shown to impact on cancer pain and tumor progression [23,24]. We review them independently because each directional transmission engages with distinct mechanisms that impact on tumor progression and cancer pain.

Afferent (orthodromic) signaling in cancer pain

In healthy conditions, nociceptive signaling is protective, allowing sensation and host response to damaging stimuli. During tumor growth, however, nociceptors in the TME may become sensitized or damaged, resulting in aberrant sensory signaling. The currently accepted theory for the etiology of cancer pain is that mediators secreted by tumor cells and tumor-associated immune cells directly activate or sensitize primary afferent nociceptors in proximity to the TME [25]. The mediators released by cancer have primarily been identified using secretomic and proteomic approaches and have been implicated in the cancer pain pathway based on *in vitro* neuronal activity assays in dissociated sensory neurons, acute nociceptive behavioral assays, and receptor pharmacology, all primarily in rodents. Many reviews have discussed and graphically demonstrated the large variety of mediators that can activate innervating sensory neurons in the TME [25,26]; however, few studies have translated to targetable clinical options. Current interest in sensory neuron sensitization in the TME related to tumor progression has resulted in recent findings demonstrating sensory afferent activity in response to cancer-secreted extracellular vesicles (EVs) and neurotrophic factors (Figure 1).

Extracellular vesicles and miRNAs. EVs containing proteins, nucleic acids (i.e., DNA, miRNA, rRNA), and lipids are produced by all cells and serve as a means of intercellular communication [27]. Recently, EVs have been implicated as a driving force for perineural invasion [28], although the type of neuron involved (i.e., sympathetic, sensory) was typically not elucidated. Current investigations into vesicle contents reveal nociception-related proteins such as intercellular adhesion molecule 1 (ICAM-1) and complement component 5a (C5a) [29]; however, the primary focus to date has been on microRNAs (miRNAs) in oral cancers. Isolated EVs from oral SCC cell culture media evoked nociceptive behaviors when injected into the glabrous skin of the hindpaw; EV depletion from the oral SCC media abolished nociceptive behaviors [30–32]. RNA sequencing data from tumor tissue of metastatic oral cancer patients revealed genes possibly related to nociceptive signaling whose transcripts were predicted to be present in exosomes [31]. Oral SCC EVs contained high levels of miRNAs, in particular miR-22 and miR-221 [30], which

have been previously implicated in non-cancer pain [33]. Furthermore, EVs containing miRNAs from p53-deficient oral SCC cell lines were shown to drive a regeneration phenotype in trigeminal neurons, an effect that was reduced by lingual nerve denervation; however, no pain behaviors were assessed [34]. Notably, many of the studies have utilized non-orthotopic transplant models and genetically modified cell lines, which may impact on the translatability of the results.

Neurotrophic factors. Neurotrophins (e.g., nerve growth factor, NGF; and brain-derived neurotrophic factor, BDNF) promote neurite outgrowth, neuronal cell differentiation, and post-mitotic survival [35]. The expression of neurotrophic factors and their receptor tropomyosin receptor kinases (i.e., TRKA, TRKB) can drive neural remodeling of the TME and increase perineural invasion. Cancer cell-secreted NGF and BDNF can sensitize sensory neurons that likely contribute to the release of sensory neurotransmitters, substance P (SP) and calcitonin gene-related peptide (CGRP), into the tumor [36]. Anti-NGF treatment attenuated pain behaviors in animal models of metastatic cancer pain and bone cancer pain [37]. BDNF and corresponding TRKB have been implicated in both tumor progression and tumor-evoked pain [38,39]. Injection of anti-BDNF reduced mechanical allodynia, and TRKB knockdown in TG tissue attenuated mechanical allodynia and increased food intake in a xenograft oral SCC rodent model [38]. An effect of neuronally released BDNF cannot be excluded and may contribute to nociceptive processing in these studies [40].

Efferent (antidromic) signaling in cancer pain: impact on tumor progression and immunity. Sensory neurons have recently been implicated in tumor progression, with a focus on a sub-population of sensory neurons expressing transient receptor potential vanilloid 1 (TRPV1) [41–45] (Table 1). Considered to be a polymodal pain sensor, TRPV1 serves as an embryonic marker for most nociceptive neurons during development. TRPV1 expression is then restricted in adulthood to a specialized population of unmyelinated peptidergic neurons encoding noxious thermal sensation [46]. There is evidence that TRPV1-expressing nociceptors can be activated by a wide range of proinflammatory mediators [46], EVs, and the hypoxic TME [23]; these neurons can also be potentiated by signaling through other sensory neuron receptors such as PAR2 [47]. Upon activation, TRPV1-expressing nociceptors can release neuropeptides and glutamate into the spinal cord and into the periphery [48]. The primary neuropeptides studied in efferent sensory signaling are CGRP and SP. There are two proposed mechanisms for sensory neuropeptide release: (i) propagation of electrical impulses towards the soma which, once aggregated at the spike initiation zone, will trigger action potential firing that spreads towards the brain (orthodromic) as well as back towards the peripheral terminal (antidromic signaling), resulting in potential vesicle release at both terminals, and (ii) local elevations in Ca^{2+} influx in the bulk cytoplasm of the afferent terminal independently of action potential generation sufficient for vesicle release [48] (Figure 2).

CGRP signaling has been directly linked to increased tumor growth by promoting cytoprotective autophagy in cancer cells [49] and indirectly via the tumor-associated immune response. There are two CGRP isoforms; αCGRP, derived from the *CALCA* gene, that is present in the central and peripheral nervous system, and βCGRP, derived from

the *CALCB* gene, that is predominantly found in the enteric nervous system [50]. There is some evidence for non-neuronal sources of CGRP; however, their biological relevance is still undetermined. Both isoforms act as potent vasodilators in peripheral tissues and can play a pro- or anti-inflammatory role depending on the environment [51]. Because CGRP-expressing neurons comprise the majority of sensory afferent innervation [52], CGRP signaling has been the main focus in orthotopic mouse models of head and neck cancer [49,53–55]. The consensus from the recent literature is that cancer-secreted mediators can trigger CGRP release in sensory nerves innervating the TME, resulting in increased tumor growth; germline *Calca* knockout, lingual nerve denervation or systemic treatment with CGRP receptor antagonists substantially slowed tumor growth, increased the infiltration of tumor-infiltrating lymphocytes, and reduced exhaustion markers in CD8 T cells [53–55]. Similarly, in an orthotopic syngeneic transplant melanoma model, nociceptor ablation using *Trpv1–cre/DTA (diphtheria toxin A chain)* [41] or systemic resiniferatoxin (RTX) treatment [56] slowed B16F10 tumor growth. These treatment groups also showed an increased incidence of cytotoxic immune cells (including CD4 and CD8 T cells) and a decreased abundance of regulatory T cells and myeloid-derived suppressor cells [41,56]. Single-cell RNA sequencing from head and neck cancer and melanoma patients revealed elevated *RAMP1*, encoding a component of the CGRP receptor, in $CD8^+$ T cells which was linked to diminished responsiveness to immune checkpoint blockade [41,55]. In addition to the immune system, CGRP receptors have also been identified on tumor cells, and recent evidence suggests that CGRP supports tumor cell survival in low-glucose environments [49]. A similar mechanism has been proposed for serine release from sensory neurons in pancreatic cancer [57], further suggesting a connection between cancer-associated nerves and cancer metabolism in the TME. FDA-approved drugs that target the RAMP1–CGRP axis, including existing migraine treatments, could be repurposed to mitigate the immunomodulatory effects of CGRP and impact on cancer metabolism, and this presents a promising therapeutic approach to enhance immunosurveillance.

SP has also been implicated in sensory neuron-induced immune responses associated with allergens [58], but the impact of neuronal SP signaling on tumor immunity is less clear. SP has been linked to increased tumor proliferation, migration, and an inflammatory microenvironment directly through NK1R receptors on cancer cells, although most of these effects were observed in *in vitro* studies with SP antagonists [23,59]. Sinah *et al.* demonstrated that postnatal $TRPV1^+$ fiber ablation using systemic RTX treatment also resulted in impaired pancreatic intraepithelial neoplasia (PanIN) lesion development in an inducible pancreatic cancer model, and propose a mechanism in which SP released from sensory neurons could aid lesion proliferation via NK1-R receptors [45]. Notably, RTX-induced systemic denervation before tumor inoculation in the 4T1 orthotopic mouse model of breast cancer did not significantly alter intratumoral SP concentration [60], suggesting that there are substantial non-neuronal sources of SP. For example, SP has been detected in human fibroblasts, keratinocytes, and immune cells, and its expression levels are increased in epithelial cells and macrophages during chronic inflammation [61]. In addition, SP is a splice variant encoded by the *TAC1* gene which can also undergo post-translational processing to yield neurokinin A, neuropeptide K, and neuropeptide Y, the latter being

highly expressed in sympathetic neurons. These divergent sources render selective genetic targeting of SP challenging.

TRPV1-expressing sensory nerve signaling has also been shown to inhibit tumor progression, due at least in part to a neurogenic inflammatory response that is required for the elimination of pathogens and cancerous cells [62]. In addition, chronic inflammation has been associated with the initiation, growth, progression of cancer [63], as well as with the response to cancer therapies [64]. Activation of TRPV1-expressing sensory neurons was shown to reduce breast cancer metastasis and enhance intratumoral recruitment of $CD8^+$ T cells in a syngeneic murine breast carcinoma model [65]. Although sensory neurons have also been shown to drive migratory behaviors of breast tumor cells *in vitro* and metastatic potential *in vivo* [66–68], these differential results were suggested to be due to loss of capsaicin-sensitive vagal afferent fibers of the jugular and nodose ganglia; surgical vagotomy also resulted in enhanced breast cancer metastasis [62]. However, the vagus nerve is not thought to supply sensory innervation to somatic tissues below the cervical level [69]. Given the anatomical location of the mammary fatpad in rodent models, it is likely that vagotomy and systemic TRPV1 fiber ablation result in global indirect effects. In addition, in humans, a retrospective *in silico* analysis of melanoma biopsies revealed that increased expression of sensory neuron-related genes within the tumor was associated with improved survival. Importantly, sensory neuron genomic material is not located within the TME, and therefore neuron-related genes detected in the periphery are likely not of neural origin. Tumor growth and angiogenesis were found to be accelerated following inhibition of sensory neuron activity in a B16F10 melanoma model [70,71]. Conversely, activation of NaV1.8 sensory neurons enhanced CD4 and CD8 T cell recruitment and reduced T cell exhaustion [70]; however, the magnitude of cytotoxic immune cell infiltration into the tumor following neural targeting limits the biological validity of the model.

Tumor–brain circuitry in response to nociceptive signaling in the TME

The central nervous system (e.g., brain) is important in triggering stress and trauma responses because it plays a predominant role in interpreting input from the environment and regulating the autonomic nervous system. Stress has been shown to strongly influence tumor progression (as reviewed previously [72]). Stress and pain are also positively correlated; chronic pain patients have reported enhanced pain during stress whereas stress-reducing strategies can alleviate pain in patients [73]. Recently, pharmacogenetic and chemogenetic activation of the central medial amygdala increased anxiety-like behaviors and exacerbated tumor growth in a mouse breast cancer model, suggesting a direct brain–tumor connection [74] triggered by activation of a brain area imperative for emotional processing and fear. However, this brain region is also well known for pain processing because the nociceptive signals from trigeminal and spinal nerves converge at the central medial amygdala. Activation of sensory nerves by the TME may occur before the onset of physical and psychological stressors that trigger an autonomic nervous system response from the brain. Transneuronal tracing has demonstrated that sensory neurons innervating the TME activate brain circuits involved in processing pain and stress in orthotopic mouse models of oral SCC [42]. Tumor-bearing mice had heightened calcium activity as measured by *in vivo* imaging with the GFP/calmodulin-based Ca^{2+} sensor GCaMP in

the central medial amygdala and parabrachial nucleus compared to sham; this effect and tumor-evoked anhedonia behavior were partially attenuated with analgesic pharmacology [42], suggesting that tumor-evoked nociceptive signaling activates tumor–brain circuitry. Similarly, visceral pain in a syngeneic orthotopic pancreatic cancer model was paired with decreased firing frequency of inhibitory GABAergic neurons in the paraventricular nucleus (PVN) of the hypothalamus [75], a known autonomic control center in the brain [76]. Although chemogenetic activation of GABAergic neurons in the PVN alleviated pain induced by pancreatic cancer, the stress response was not evaluated. Lastly, painful nerve injury has been linked to changes in an anterior cingulate cortex–ventral tegmental area feedback loop that results in anxiodepressive-like behaviors [77], as well as to changes in glutamatergic neurons in the primary somatosensory cortex and GABAergic neurons in the central nucleus of the amygdala. This region is implicated in regulating peripheral immune responses via projections to the spleen [78]. Together, these data suggest the possibility that tumor-associated nociceptive signaling could impact directly on brain circuitry to drive autonomic output and even splenic immunity (Figure 3). Local norepinephrine signaling can drive cellular proliferation and increase tumoral algogenic mediator release, thereby exacerbating tumor-evoked pain signaling [24], thus implicating a vicious cycle that affects tumor growth and response to therapeutic treatments.

Concluding remarks and future perspectives

In summary, there is a fundamental interest in understanding sensory nerve plasticity in the TME for the development of analgesic strategies to treat cancer pain and progression. The cancer neuroscience field has begun to expand beyond pain signaling to include broader consequences of nociceptive activation on cancer development, tumor immunity, and response to treatment (see Outstanding questions). However, many studies are limited by evaluating nociceptive signaling in the TME using models for cancers that have a low clinical incidence of primary tumor-associated pain (e.g., melanoma, breast cancer) [3]. Because pain perception and subsequent behaviors (e.g., guarding, freezing, hyper/hypo-grooming) [79] are behavioral outputs of sensory neuron activity, examining nociceptor activity itself in the absence of pain-related behaviors raises significant concerns about the translatability of these findings. The impact of sensory neurotransmission may differ considerably in cases where constant firing results in central pain perception compared to cases where peripheral sensory stimulation results in subthreshold activity within the TME. Thus, appropriate animal modeling and corresponding neuroanatomy must be used for *in vitro* and *in vivo* manipulations to reliably recapitulate the clinical condition, accurately study tumor biology, and test the efficacy of anticancer agents.

Current evidence suggests that TRPV1-expressing sensory neurons produce immunomodulatory neuropeptides that can inhibit effector cell activity and promote immune evasion. However, targeting TRPV1 has been one of the only approaches used preclinically, but has yielded inconsistent results. Although the channel activation is evident in response to hypoxic environments (i.e., acidic solutions), TRPV1-expressing neurons also likely express receptors for many other mediators that are present in the TME, such as neurotrophins, TNF-α, and PAR2, which modulate afferent excitability [5,25]. Tools that target the TRPV1 population are also imperfect, and this impacts on the conclusions made from work that

has focused on nociceptor-derived neuropeptide signaling. Many fail to consider the early developmental expression of *Trpv1* and transcriptomic overlap between *Trpv1* and various peptides across neuron subtypes [80]. In addition, compensatory mechanisms of whole-body nerve ablation are possible. Using systemic RTX administration to ablate the TRPV1 fiber population in the adult mouse can induce a stress response [81] as well as altering splenic function [82], which may indirectly alter tumor progression. $TRPV1^+$ neurons also release several signaling mediators such as CGRP, SP, pituitary adenylate cyclase-activating neuropeptide (PACAP), and glutamate [46]. Given that the majority of recent research focuses on neuronally derived peptides that modulate tumorigenesis, targeting the specific peptide of interest (e.g., CGRP) provides a more compelling line of inquiry than manipulating the neuron that expresses it (see Outstanding questions).

Because clinical treatment increasingly focuses on immunotherapeutic strategies [18], and basic research continues to highlight neural invasion, systematic analysis of the sensory neural influences on pain and immunosuppression within the tumor will be essential for targeted therapies to induce tumor regression.

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Highlights

Sensory neurons, including those that encode painful stimuli (i.e., nociceptors), comprise a large percentage of peripheral nerve endings across several tissues and function to detect stimuli in the environment and propagate these signals to the brain.

Bidirectional interactions between cancer cells and sensory neurons can result in pain as well as influencing stages of tumorigenesis, including tumor initiation, growth, and metastasis.

Sensory neurons expressing the TRPV1 ion channel produce immunomodulatory neuropeptides that, when released into the tumor, inhibit effector cell activity and promote immune evasion.

Targeting signaling by the sensory neuropeptide, calcitonin gene-related peptide (CGRP), in the tumor can reduce pain, improve antitumor immunity, and increase the response to immune checkpoint inhibitors, suggesting that CGRP is a viable target for both cancer pain and tumor progression.

Outstanding questions

How does the variety of sensory neuron types and their distribution across tissues influence their role in modulating tumor progression? Studies have primarily focused on neuropeptides as signaling molecules that modulate immunity, but the true complexity of the sensory signaling interactome with tumor cells remains unknown.

Perineural invasion is a common prognostic indicator of survival. Given data suggesting a bidirectional interaction between tumor cells and sensory neurons, are nociceptors the primary nerve type over autonomic nerves to be affected by perineural invasion?

Given that sensory neuron signaling has been studied in tumor models that do not evoke a strong nociceptive response in animals, is a behavioral pain phenotype necessary to confirm nociceptive signaling in the TME?

There is bidirectional crosstalk between immune cells and neurons, as evidenced by neural checkpoint protein expression and immune neuropeptide receptor expression. What is the impact of the immune system on activating or inhibiting sensory neurons during tumor progression?

Nociceptive signaling is protective because it allows sensation and host response to damaging stimuli. Is denervation/ablation before inoculation the best strategy to understand the impact of sensory neurons on the TME?

Stress and pain are closely linked clinically, and sympathetic signaling can modulate sensory nerve sensitization directly via adrenergic signaling. Do the sympathetic and sensory nervous systems interact to modulate the TME?

There is extensive evidence indicating sex differences in pain processing, but data are lacking in the context of disease. How does the interaction between sensory nerves and the TME differ between the sexes and with age?

Exogenous opioids have both analgesic (central) and immunosuppressive (peripheral) properties. Does opioid use for the treatment of pain aid or inhibit tumor progression?

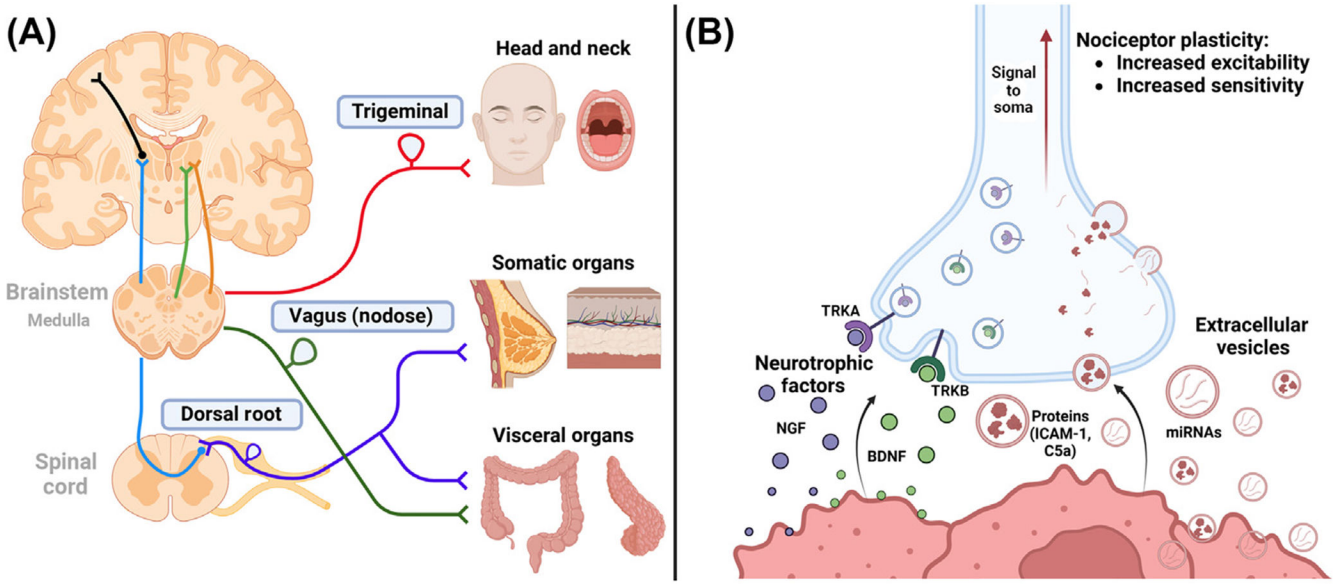

Figure 1. Anatomical overview sensory innervation and cancer-secreted algogenic triggers in the tumor microenvironment (TME).

(A) The sensory neurons in the trigeminal, vagal, and dorsal root pathway are localized in the respective ganglia and their central axons project to nuclei in the brainstem (trigeminal, vagal) or to the spinal dorsal horn (dorsal root). From there the signals are relayed to various cortical regions via the thalamic nuclei to encode the sensory and affective components of cancer-induced pain. (B) Cancer-secreted mediators can directly activate and sensitize the peripheral axons of the afferent neurons. Highlighted are the tumor cell-derived neurotrophins, nerve growth factor (NGF), and brain-derived growth factor (BDNF), as well as extracellular vesicles (EVs) containing algogenic mediators (ICAM, C5a) and microRNAs (miRNAs). NGF and BDNF bind to their receptors TRKA and TRKB, respectively, and are internalized via clathrin-mediated endocytosis for retrograde transport to the soma for further signaling. EVs fuse with the plasma membrane to release proteins and miRNAs into the extracellular space for intracellular signaling, resulting in increased excitability and sensitization.

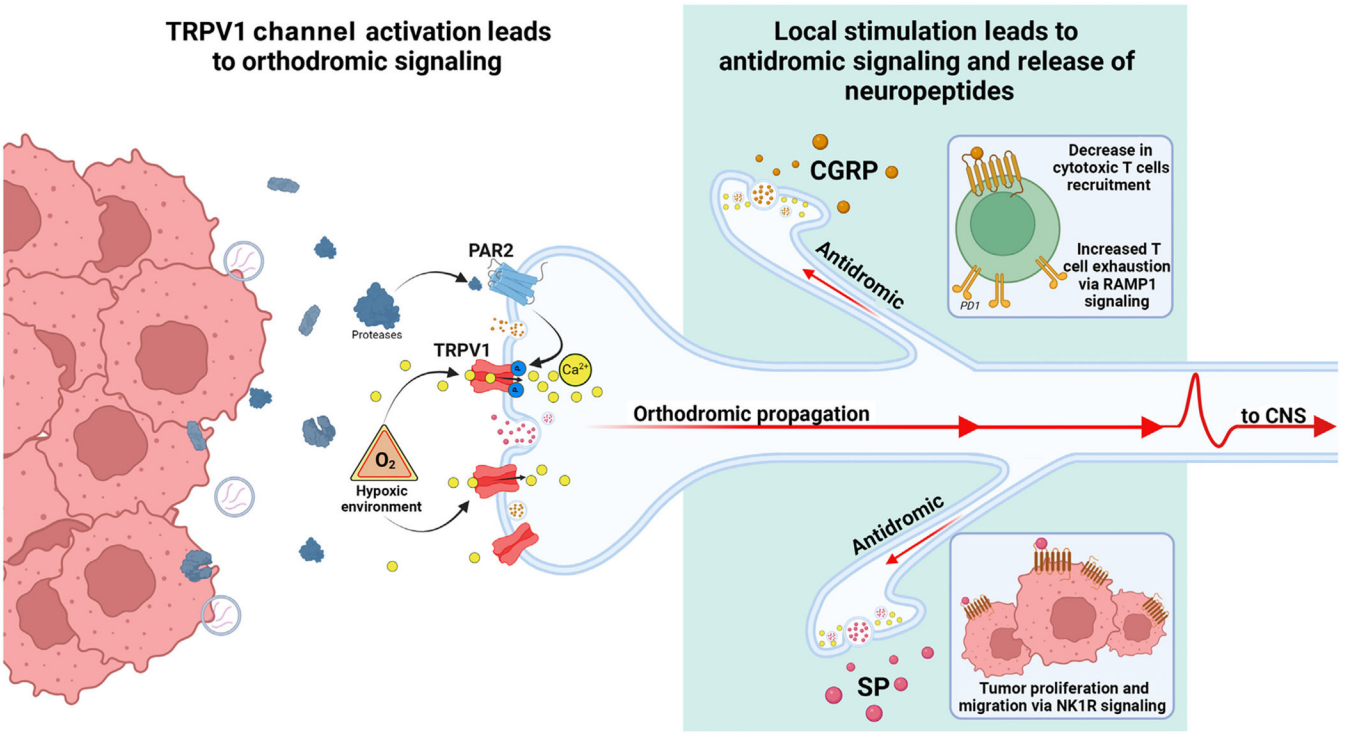

Figure 2. Two proposed mechanisms for sensory neuropeptide release.

The nutrient-deprived tumor microenvironment is hypoxic and is enriched in algogenic mediators, including proteases, that trigger the activation of receptors on primary afferent endings, often via transient receptor potential vanilloid 1 (TRPV1), a nonselective cation channel. Activation of TRPV1 results in Ca^{2+} and Na^{+} influx to depolarize the neuron ending and trigger an orthodromic action potential; this also invades local collaterals and terminal endings that were unaffected by the original insult. When these action potentials enter the terminal, they trigger local voltage-gated calcium channels, Ca^{2+} entry, and subsequent neuropeptide release. Neuropeptides may cause suppression of the immune system or drive the proliferation and migration of tumor cells. Neurotransmitters are released from different axons, but are shown at the top and bottom, respectively, of this schematic. Abbreviations: CGRP, calcitonin gene-related peptide; NK1R neurokinin-1 receptor; PAR2, protease activated receptor 2; PD1, programmed cell death 1; RAMP1, receptor activity-modifying protein 1, SP, substance P.

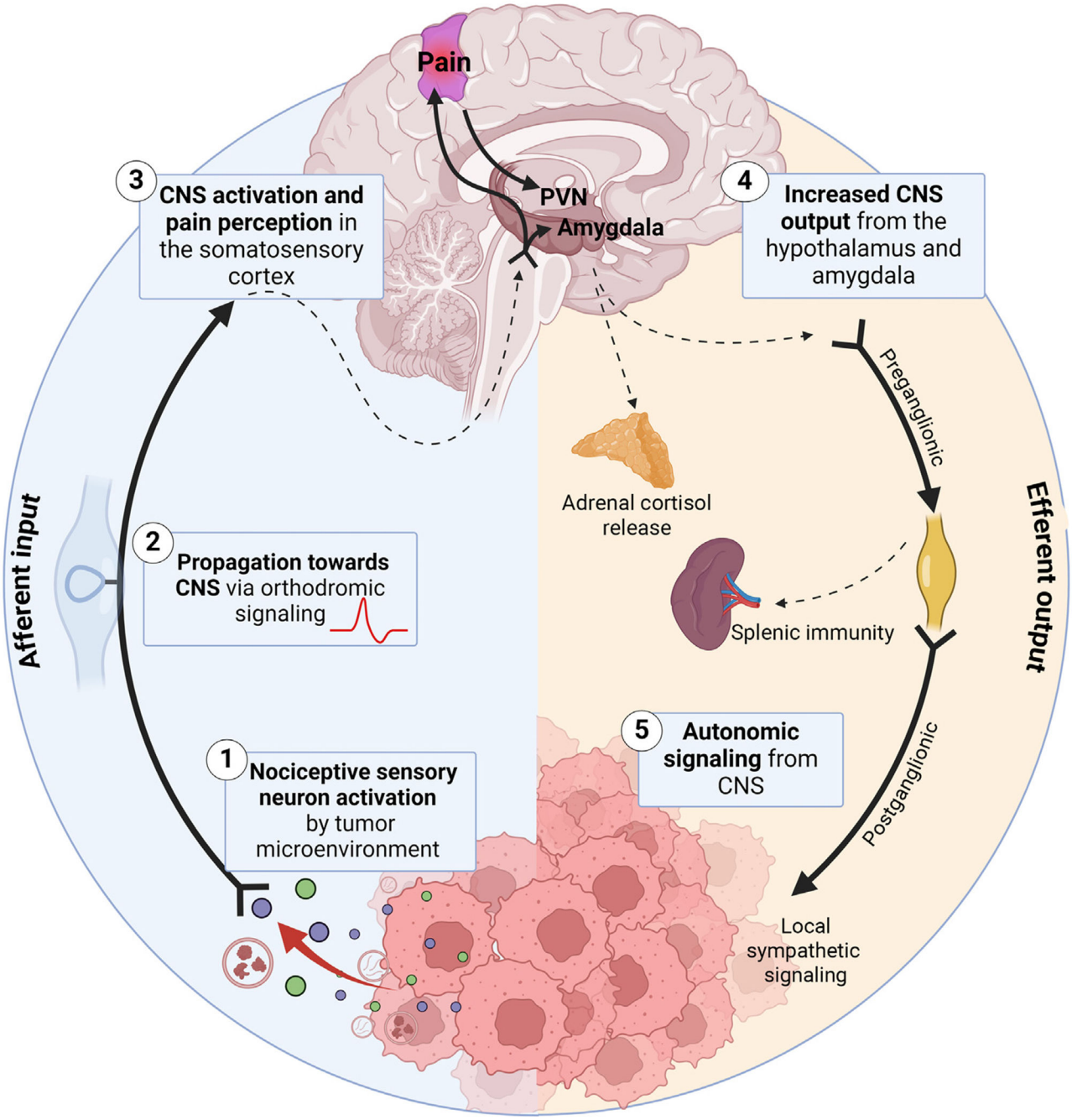

Figure 3. Proposed cycle between nociceptive input and autonomic output in cancer.

Sensitization of nociceptive sensory neurons by the tumor microenvironment leads to propagation of orthodromic signaling towards the central nervous system (CNS). The cognitive processing of this information via the brainstem, through the thalamus and into the somatosensory cortex, results in the perception of pain as well as activation of the amygdala and hypothalamic regions such as the paraventricular nucleus, both of which are involved in the processing of pain and stress. Increased thalamic and hypothalamic signaling results in autonomic output via the hypothalamic–pituitary–adrenal (HPA) axis

and sympathetic preganglionic neurons. It is possible that autonomic output can modulate sympathetic signaling in the spleen to change splenic immunity, as well as activating sympathetic postganglionic efferents innervating tumor tissues, resulting in local release of norepinephrine that is thought to drive cell proliferation, migration, and increased algogenic mediator release via adrenergic signaling. Abbreviation: PVN, paraventricular nucleus of the hypothalamus.

Table 1.

Impact of sensory neurons on tumor growth and associated immune responses in rodent models published in the period 2020–2024[a]

Cancer	Tumor model	Manipulation	Neuropeptide	Immunity	Pain behaviors	Overall effect	Refs
Melanoma	B16F10	*Trpv1–cre/DTA*; local silencing; CGRP antagonism	CGRP	$CD8^+$ T cells	N.D.	Reduced $CD8^+$ T cell exhaustion and reduced tumor growth	[41]
	B16F10	Surgical denervation; RTX ablation	N.D.	CD4 T cells B cells	N.D.	Reduced tumor growth, increased T cell clonality, and expanded the B cell repertoire	[56]
	B16F10	RTX ablation; *Nav1.8–cre/DTA*	N.D.	N.D.	N.D.	Increased tumor growth	[71]
	B16F10	*Nav1.8–cre*/hM4Di *Nav1.8–cre*/hM3Dq	CGRP	Neutrophils MDSCs Dendritic cells $CD4^+$ T cells $CD8^+$ T cells	Capsaicin-induced behavior	Chemogenetic inhibition accelerates tumor growth and proliferation Chemogenetic activation decreases tumor growth while increasing dendritic cells and promoting $CD4^+$ and $CD8^+$ T cell infiltration	[70]
Oral SCC	HSC-3; OSC-20	Depletion of EVs	N.D.	N.D.	Mechanical hypersensitivity; thermal hyperalgesia	Reduced mechanical and thermal hyperalgesia	[30]
	mEERL	EV depletion; RTX ablation	N.D.	N.D.	Mechanical hypersensitivity; grimace behavior	sEV depletion leads to reduced mechanical hypersensitivity and grimace behavior RTX ablation leads to reduced mechanical hypersensitivity and grimace behavior, but no change in tumor volume	[32]
	PCI-13; $Krt5^{cre}Trp53^{fl/fl}$	Coculture with cancer-derived EVs; lingual denervation	N.D.	N.D.	N.D.	Coculture with EVs leads to sensory neuron reprogramming Lingual denervation reduced tumor growth	[34]
	MOC2-7	*Trpv1–cre/DTA*; RTX ablation; analgesics	N.D.	N.D.	N.D.	Ablation reduced tumor growth Analgesic gave no change in tumor growth	[42]
	4NQO-induced OSCC; orthotopic tongue xenografts (Cal27, B16F10) in Balb/c-Nu mice	CGRP antagonism, knockdown of CLR/RAMP1; Calca knockout; *Trpv1–cre/DTA*	CGRP	N.D.	N.D.	Reduced tumor growth	[49]
	MOC2-OVA	Facial nerve axotomy; CGRP antagonism;	CGRP	$CD8^+$ T cells $CD4^+$ T cells	N.D.	Reduced tumor growth and increased	[53]

Cancer	Tumor model	Manipulation	Neuropeptide	Immunity	Pain behaviors	Overall effect	Refs
		Trpv1 knockout; gabapentin				$CD8^+$ and $CD4^+$ T cell activity	
	HSC-3; CAL27	Adenosine receptor antagonism; CGRP antagonism	CGRP	N.D.	N.D.	Reduced tumor growth	[54]
	MOC1; MOC2; HSC3	Cgrp knockout	CGRP	$CD8^+$ T cells $CD4^+$ T cells	N.D.	Reduced tumor growth and increased infiltration of $CD8^+$ T cells, $CD4^+$ T cells and $NK1.1^+$ cells	[55]
Breast	4T1	RTX ablation	CGRP; substance P; somatostatin	CD31, CD45, and CD3	N.D.	Increased tumor growth in early stages with no change in immune profile	[60]
	MDA-MB-231; SUM-159, PyMT	Neuron/cancer cell coculture	N.D.	N.D.	N.D.	Increased tumor cell migration and adhesion	[66]
	4T1	*Slit2* knockout; capsaicin denervation	Substance P	N.D.	N.D.	Reduced tumor growth and proliferation	[80]
	4TBM	Olvanil treatment	N.D.	$CD8^+$ T cells	N.D.	Reduced metastasis, no change in tumor growth, enhanced $CD8^+$ T cell recruitment	[65]
Pancreatic	PDAC cells (K8484)	Chemokine knockdown in DRG	N.D.	T cells Neutrophils	Mechanical Hypersensitivity	Chemokine knockdown reduced tumor migration and nociceptive behaviors; no effect on T cell and neutrophils	[26]
	PANC-1; ASPC-1; *KRAS/p53*$^{m/+}$	Tumor exosome blockade (GW4869)	N.D.	N.D.	N.D.	Exosome blockade reduced perineural invasion	[83]
	PANC-1: *LSL–KRAS*$^{G12D/+}$: *LSL–TP53*$^{R172H/+}$; and *PDX-1–cre*$^{+/+}$	Knockdown of PIAT and YBX1 in cancer-associated fibroblasts	N.D.	N.D.	N.D.	Knockdown of RNAs reduced PNI	[84]
Gastric	Inducible gastric models (MNU; *Cck2r–creERT; Kras; Atp4b–cre; Cdh1*$^{fl/fl}$; *Kras*^{G12D}; *Trp53*$^{fl/fl}$; *YFP*) Syngeneic orthotopic allograft model	*Trpv1–cre/DTR; Trpv1–cre*/ hM3Dq chemogenetic	CGRP	N.D.	N.D.	TRPV1 activation increased tumor growth TRPV1 ablation decreased tumor growth	[85]
Lung	Lewis lung carcinoma (in hindpaw)	Germline *Calca* knockout; germline *Trpv1* knockout	CGRP	N.D.	Flinches; limb use; mechanical hypersensitivity	Loss of CGRP and TRPV1 globally reduced tumor growth and cancer pain	[86]
Bone	Orthotopic xenograft transplant (human	TRKA inhibition (*Trka*^{F592A})	CGRP	N.D.	None	TRKA inhibition reduced tumor growth and metastasis, and impaired CalcaR signaling	[87]

Cancer	Tumor model	Manipulation	Neuropeptide	Immunity	Pain behaviors	Overall effect	Refs
	osteosarcoma 143B)						
	4T1 cells into bone marrow	TRPV1 antagonism; I-RTX	N.D.	N.D.	Mechanical hypersensitivity	Reduced tumor growth and metastasis as well as reduced mechanical hypersensitivity	[67]
Mixed	Lewis lung carcinoma; AXT osteosarcoma and B16F10 melanoma cell lines	Sciatic nerve expression of hM3Dq	CGRP; substance P	N.D.	Hargreaves; mechanical hypersensitivity	Neuronal activation increased tumor growth and increased Calca and *Tac1* expression	[88]
	HNC: mEERL, MOC7; Ovarian cancer: *Trp53* knockout; Pten knockout	*Trpv1–cre/DTA*	Substance P	N.D.	N.D.	Ablation of TRPV1 reduced tumor growth	[23]

[a]Abbreviations: DTA, *diphtheria toxin* A chain; DTR, *diphtheria toxin* receptor; EVs, extracellular vesicles; HNC, head and neck cancer; mEERL, mouse E6/E7/hRas oropharynx epithelial luciferase cell line; MNU, *N*-methyl-*N*-nitrosourea; N.D., not determined; 4NQO, *4-nitroquinoline 1-oxide*; PNI, perineural invasion; PyMT, polyomavirus middle T antigen; RTX, resiniferatoxin; sEVs, small extracellular vesicles.