HHS Public Access

Author manuscript

Trends Neurosci. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Trends Neurosci. 2016 December ; 39(12): 880–889. doi:10.1016/j.tins.2016.10.002.

Can Stopping Nerves, Stop Cancer?

Jami L. Saloman[1,*], **Kathryn M. Albers**[1], **Andrew D. Rhim**[2], and **Brian M Davis**[1]

[1]University of Pittsburgh, Center for Pain Research and Dept. of Neurobiology, Pittsburgh, PA, 15261

[2]Zayed Center for Pancreatic Cancer Research and Department of Gastroenterology, Hepatology and Nutrition, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030

Abstract

The nervous system is viewed as a tissue affected by cancer and as a conduit for transmission of cancer pain and perineural invasion. Here, we review recent studies that indicate a more direct role. Several studies have shown that reducing stress or suppressing sympathetic drive correlates with improved outcomes and prolonged survival. Recent studies using animal models of visceral and somatic cancer further support a role for the nervous system in cancer progression. Specifically, nerve ablation had a profound impact on disease progression including delayed development of precancerous lesions, decreased tumor growth and metastasis. This review summarizes new evidence and discusses how future studies may address the role of neural signaling in the modulation of tumorigenesis.

Keywords

sensory neurons; autonomic; peripheral nervous system; tumorigenesis

Nerves are more than reporters of cancer pain

Neuroscientists have a long-standing interest in **cancer** (Glossary). This research has primarily focused on understanding mechanisms of pain, a common feature of several cancers [1-4]. Additionally, cancer pain can also be compounded by pain induced by treatments that damage nerves (e.g. chemotherapy or surgery) [5-8]. However, recent evidence suggests that nerves may play another critical role in the development and progression of cancer. One example of this is illustrated by perineural invasion (**PNI**), a common feature of visceral and soft tissue cancers [3, 9, 10]. PNI involves tumor cells invading nerves and causing structural damage and changes in the neuronal milieu that can drive cancer associated inflammatory and **neuropathic pain**. Moreover, preclinical studies have shown that individual neoplastic cells invade neural tissue prior to tumorigenesis [11], suggesting that nerves are utilized as a means of cancer cell dissemination and **metastasis**.

[*]Correspondence: jls354@pitt.edu (J.L. Saloman).

Such an interaction has been highlighted in a recent study where peripheral nerve Schwann cells exhibited affinity for pancreatic cancer cells and engaged in directed cancer cell outgrowth and migration [9]. These observations have contributed to the concept that the peripheral nervous system (**PNS**) is an important constituent of the tumor microenvironment. Recognition of the importance of nerve-cancer interactions resulted in the National Cancer Institute (NCI) convening its first meeting to explore the "Role of Nerves in Cancer Progression" (March, 2015). Two emergent areas of cancer research identified at the NCI meeting will be examined in this review: 1) The influence of neuroactive molecules on cancer risk or prognosis and, 2) The role of peripheral nerves in cancer progression.

Neuroactive molecules and cancer

Exposure to a variety of compounds, such as nicotine, is associated with *increased* cancer risk [12-14]. Previously, it was assumed that the site of action of these molecules was on precancerous tissue or tumor cells. With respect to the tumor or tumor microenvironment, nicotine can stimulate angiogenesis and the epithelial to mesenchymal transition, a critical step in cancer progression [15-17]. *In vitro* studies show that nicotine also increases the growth, migration, and spread of pancreas and ovarian cancer cells [12, 13]. However, nicotinic receptors are also expressed in both the peripheral (**PNS**) and central (**CNS**) nervous systems. In the CNS, cholinergic signaling modulates stress and anxiety, which are risk factors for cancer, making it difficult to determine how nicotine contributes to cancer risk.

Other neuroactive substances used for the treatment of various neurological illnesses are associated with *reduced* cancer risk. Not surprisingly, the receptors for these compounds are also expressed on both neurons and developing cancer cells. For example, anti-psychotics tend to antagonize both dopamine and serotonin type 2 receptors [18, 19]. Long-term exposure to anti-psychotic agents for the treatment of schizophrenia was associated with significantly lower risk for cancer [20-23]. Similarly, lithium intake, a common treatment for bipolar disorder, has also been associated with a decreased risk for cancer [24]. Tricyclic antidepressants primarily act as serotonin-norephinephrine reuptake inhibitors, but they also antagonize serotonergic, adrenergic, glutamatergic, and histaminergic receptors [25]. Multiple cohort studies describe an association between tricyclic anti-depressant use and a reduction in risk and incidence of colorectal cancer as well as glioma [26-28]. Although these epidemiological studies report a correlation between neuroactive therapies and a reduced cancer risk, experimentally driven studies are necessary to pinpoint the actual underlying mechanisms.

Whereas the above studies suggest neuroactive molecules can influence cancer risk, other reports suggest neuroactive compounds may also affect progression, once disease is established. The sympathetic nervous system, through the release of norepinephrine and epinephrine (in addition to various neuropeptides like NPY and VIP) plays a major role in regulating homeostatic mechanisms related to stress and anxiety. Drugs that target stress and anxiety are associated with improved prognosis, including increased survival times [29-32]. Under high stress conditions, sympathetic nerves release additional epinephrine and

norepinephrine (**NE**), that has been shown to increase **IL-6** and reactive oxygen species, all of which promote cancer cell survival and proliferation [33-36]. *In vitro,* cancer cell survival and proliferation are effectively inhibited by incubation with adrenergic receptor antagonists [37, 38]. These observations may explain why patients taking adrenergic antagonists (α1 or β blockers) for the treatment of conditions such as hypertension have significantly lower rates of soft tissue cancers including melanoma, breast, prostate and colorectal cancer [39-42].

Furthermore, common therapies for stress and anxiety disorders, such as benzodiazepines and SSRIs, also inhibit proliferation and migration of cancer cells *in vitro* [43-45]. Studies using *in vivo* models have confirmed that stress enhances tumor growth and that stress reduction, either via behavioral or pharmacological means, retards disease progression [39, 46, 47]. These findings support the idea that manipulation of the nervous system is a potential avenue for adjuvant treatment of cancer.

The role of peripheral nerves on cancer progression

Denervation has profound effects on cancer progression

The epidemiological reports as well as the preclinical studies discussed above all suggest that the nervous system contributes, in some way, to cancer risk and prognosis (disease progression). Although this can be attributed to its role in coordinating virtually every aspect of homeostasis, including immune and autonomic function, recent studies provide new evidence that portions of the nervous system actually drive tumorigenesis. Specifically, in multiple preclinical models, ablation of different portions of the peripheral nervous system (**PNS**) prevented cancer development [11, 36, 48-51].

With the exception of tumors of the brain and spinal cord, all solid tumors of the body are innervated by nerve fibers arising from the PNS as part of the tumor microenvironment (Fig. 1). These fibers include axons originating from the autonomic nervous system (both sympathetic and parasympathetic) and axons of primary sensory neurons. They all can synthesize and release small molecules (e.g., glutamate, ATP, norepinephrine (**NE**), serotonin, acetylcholine (**Ach**) and substance P (**SP**)) that can bind membrane receptors expressed on cells of normal, precancerous and cancerous tissues, affecting multiple processes associated with cellular homeostasis, including proliferation. Tumor cells also release molecules that bind to receptors on sensory and autonomic nerve fibers, providing two-way communication that can modulate growth of the developing tumor and function of the peripheral nervous system (Fig. 2).

Recent studies using rodent models of prostate cancer, gastric cancer, basal cell carcinoma (**BCC**) and pancreatic ductal adenocarcinoma (**PDAC**) evaluated the requirement of the PNS for tumor development. The most compelling finding across all the reports was that surgical or chemical ablation of nerve fibers innervating affected organs dramatically reduces either precancerous lesions and/or slows tumor progression. One recent study utilized both a **xenograft** and a genetically engineered mouse model (**GEMM**) to investigate the role of nerves in prostate cancer [48]. In these experiments, 6-hydroxy dopamine (6-HODA) was administered to chemically ablate sympathetic fibers innervating the prostate. This was

compared to surgical denervation of the prostate that removed both sympathetic and a portion of the sensory innervation to the prostate. Chemical or surgical denervation of neonates or one month-old mice significantly reduced the number of precancerous lesions, slowed tumorigenesis and decreased metastasis. When a similar 6-HODA-sympathectomy technique was employed prior to xenografting fibrosarcoma or malignant melanoma cells, tumor incidence was reduced and survival significantly improved [36, 51]. Comparable results were also reported in a study investigating the role of vagal innervation in gastric cancers [49]. These studies showed that subdiaphragmatic vagotomies affecting one side of the stomach reduced tumorigenesis by 57% (83% vs. 25%) [49]. Although similar in outcome, this study differs in a number of important ways. First, the cancer model used is slow growing, requiring up to 12 months for tumorigenic changes (compared to 3-6 months for the slowest of the prostate models). Second, the nerve under investigation, the vagus nerve (**VN**), is comprised of both sensory (80-90% in mouse [52]) and preganglionic parasympathetic fibers. Third, these experiments were able to exploit stomach anatomy such that it was possible to denervate the entire organ or the posterior and anterior regions separately, allowing for within animal controls.

Another recent study was the first to examine the role of nerves in a somatic cancer [50]. This study examined the role of cutaneous nerves in a model of spontaneous BCC produced by genetic deletion of *PTCH1,* a suppressor of hedgehog signaling. Tumors develop predominantly in touch domes and bulge regions of hair follicles, but not in the interfollicular epidermis. Similar to the gastric cancer report, these experiments utilize within animal controls by unilateral denervation of the back skin. Unlike the gastric model study, the dorsal cutaneous nerves contain mostly sensory and a few sympathetic fibers.

A recent study of pancreas cancer further supports the role of sensory innervation in tumorigenesis [11]. In a GEMM of PDAC, sensory denervation of the pancreas was achieved by ablation of **TRP**V1 (transient receptor potential cation channel subfamily V member 1) positive fibers using neonatal capsaicin treatment. This treatment is sensory neuron specific with no known effects on sympathetic and parasympathetic fibers [53, 54]. In this GEMM, a Kras gain-of-function mutation and deletion of p53 is targeted to the pancreas, resulting in tumors in >95% of mice within 4 months. Capsaicin-mediated denervation of the pancreas was found to correlate with increased survival; mice with the greatest sensory neuron loss also had little or no pancreas pathology as measured by histological assessment up to 19 months of age. Denervation decreased tumorigenesis and slowed disease progression as measured by staging of pancreatic intraepithelial neoplasias (**PanINs**).

In all of these cancer models, early denervation was the most effective in delaying disease progression; in the prostate and gastric models, later intervention did not prevent development of tumors, slow growth or reduce the extent of metastasis. However, it should be noted that evidence was provided suggesting gastric denervation combined with chemotherapeutic treatment is superior to chemotherapy alone for slowing advanced disease [49].

Direct vs. indirect effects of denervation

Nerves, like the vasculature, lymphatics and innate immune system, are just one component of the incipient tumor microenvironment. Thus, the effect of denervation could actually be direct or indirect. Sensory and autonomic nerve fibers are known to modulate proliferation and maintenance of their target structures. Moreover, decades of research have shown intimate interactions between the PNS and immune cells [55-58], which are known contributors to the development of cancer via their role in inflammation. Thus, denervation of either sensory or autonomic nerve fibers may initiate a cascade of events that indirectly regulate cancer progression. Evidence for indirect effects comes from the prostate cancer study and experiments utilizing β2 and β3 adrenergic receptor knockout mice. These receptors bind NE, which is released from sympathetic fibers that were the target of the initial ablation studies. The prostate study combined adrenergic receptor gene deletion with xenografts of multiple cancer cell lines. In all cases, the loss of noradrenergic signaling correlated with a decrease in tumor growth. In these experiments, gene deletion was global within all host tissue, without affecting the xenograft (receptor expression may or may not be present in these cancer cells). Therefore, there was no signaling defect between sympathetic fibers that release NE and the tumor itself, strongly indicating that the effect of the loss of β adrenergic receptor signaling must be on other host cells within the tumor microenvironment. In wild type animals, adrenergic receptors would be expressed in the vasculature, immune cells and other peripheral nerves including sensory fibers. It should be noted, however, that co-culture of neurons with cancer cell lines can accelerate proliferation, suggesting a possible direct effect on tumorigenesis [48].

In the gastric cancer model [49], the effect of denervation was proposed to be direct based on the fact that the VN contains parasympathetic fibers that release acetylcholine, and that the muscarinic acetylcholine receptor (**mAchR**) type 1 was upregulated in tumors. A caveat to this conclusion is that the VN is primarily sensory, with preganglionic parasympathetic fibers making up only 10-20% of the axons. The effect of the loss of sensory fibers was not considered in this paper. A direct effect is also suggested in the basal cell carcinoma (**BCC**) study; mRNA for the three hedgehog ligands is present in dorsal root ganglia (**DRG**) [50], the location of sensory neuron cell bodies that project to the skin. In the BCC study, the authors hypothesized that the loss of sensory-derived signaling molecules inhibiting the hedgehog pathway was the driving factor for tumorigenesis. A direct role of peripheral nerves in cutaneous epithelial cell homeostasis comes from the Merkel cell literature that shows progressive loss of Merkel cells following denervation [59, 60]. Epidermally-derived tumors such as BCC are also lined with Merkel cells. In the *PTCH1* model, five weeks after denervation, mice not only had significantly fewer Merkel cells, but also had significantly fewer tumor cells compared to the sham-lesioned contralateral side. This observation led to the suggestion that denervation may not only be a potential therapeutic tool for BCC, but for Merkel cell tumors as well [50]. However, it has been suggested that although Merkel cell tumors exhibit a phenotype similar to native Merkel cells, they actually arise from skin stem cells (which would still be influenced by cutaneous innervation) [61]. The potential for nerves directly regulating the turnover of cutaneous stem cells does not rule out additional indirect roles for the nerves, including interactions with the immune system. There is a rich literature addressing the link between the nervous and immune systems, and recent studies

have shown cutaneous afferents are needed for coordination of T-cell and dendritic cell response to an immune challenge [62]. Thus, it is possible that nerve ablation had an indirect effect on BCC to the extent that inflammation is thought to play a role in this type of cancer [63]. However, the effect of ablation on tumorigenesis in the mouse BCC model differentially protected discrete areas of the skin (touch dome and bulge) and not other regions (interfollicular epidermis) that share a common immune milieu making it difficult to envision a role for the immune system.

Studies of the role of nerves in PDAC were motivated by two observations. The first is that chronic **pancreatitis**, a condition that is a risk factor for PDAC [64-66], is known to be driven by **neurogenic inflammation**, a pathological collaboration between the pancreas and the sensory nervous system [67-69]. The second is that in the PDAC GEMM, high dose dexamethasone (a potent anti-inflammatory) can slow or block tumorigenesis [70]. These observations suggest that for PDAC, denervation of the pancreas would be efficacious by dampening inflammation driven by neural-immune interactions. That nerves regulate cancer through interactions with the immune system is supported by the observation that in early stages of PDAC tumor progression, before cancer is present, inflammatory changes can be detected in the nerves and spinal cord innervating the pancreas [11]. In pancreatitis, both acute and chronic, studies have shown that neural inflammation can feed back onto the pancreas, increasing the release of inflammatory modulators from peptidergic sensory terminals [68, 69]. Thus, the most parsimonious explanation for the role of nerves in pancreatic cancer is through interactions with the immune system, although it does not rule out direct mechanisms [71].

Signaling pathways affected by denervation

Both gastric and prostate cancer studies invoke mechanisms in which cancer related signaling processes are initiated by the release of neurotransmitters, including NE and Ach, from the autonomic nervous system. Both studies report links to proliferation via cholinergic receptor signaling, specifically type 1 and type 3 muscarinic receptors, respectively [48, 49]. In the gastric cancer model, linkage is suggested between a down-regulation of WNT signaling, a pathway invoked in multiple cancers [72-74] and the expression of type 3 muscarinic receptors in a subset of gastric epithelial cells that express the Lrg5 G-protein-coupled receptor. In the BCC model, the cancer signaling pathway regulated by nerves is distinct from that of visceral cancers with dependence on the ability of nerves to regulate hedgehog signaling. In the PDAC model, the proposed signaling pathways are those that regulate inflammation through coordinated cytokine and chemokine production. In both chronic pancreatitis and PDAC, the inflamed pancreas produces significantly greater amounts of inflammatory factors that not only enhance release of immunomodulatory peptides, but also induce upregulation of receptors (e.g., TRP channels) that further sensitize primary afferents, causing additional release of pro-inflammatory molecules and generating a catastrophic feed-forward loop. Interestingly, at the PanIN-to-cancer transition the pancreas also exhibits a massive spike in neurotrophic growth factor receptor expression that may allow a negative synergy in the nerve-immune-tumor interaction [3, 10, 75].

Concluding Remarks

Neuromodulatory chemicals influence both the initiation and progression of cancer. It is widely accepted that many chemicals are risk factors for developing cancer. Indeed, alcohol, nicotine, and others can induce plasticity in multiple tissues including nerves. Neurogenic inflammation and other changes in the microenvironment create a setting conducive to tumorigenesis. Interestingly, stress alone can lead to neurochemical changes that promote tumorigenesis and cell proliferation. However, there are instances in which use of neuromodulators such as inhibitors of adrenergic signaling seem to create an anti-tumor environment. Thus, the current evidence suggests these neuroactive agents may be influencing the probability of developing cancer through their neuromodulatory effects. Furthermore, the preclinical studies detailed in this review begin to examine mechanisms that could explain the prominent role nerves and neuroactive molecules have in determining the disease trajectory for multiple cancers.

There are a number of observations that are common to the main studies of denervation and cancer summarized in Table 1. One is that regardless of the GEMM model, denervation can slow or halt disease progression. This is remarkable since in these models the development of cancer in the absence of intervention is almost guaranteed. And while there are other examples in GEMM models in which chemical treatments can slow disease progression (e.g. via high dose steroids or anti-IL6 therapies [70, 76]), the studies reviewed here are the first to demonstrate that removal of nerves from the tumor microenvironment is sufficient to alter disease trajectory. While exciting, the utility of denervation as a treatment for cancer is diminished by the realization that its most efficacious impact on disease progression occurred early in the disease process or even before precancerous lesions developed. Thus, for most patients who are diagnosed with cancer, it is unlikely significant benefits would be obtained by denervation with respect to primary tumor growth, although for some cancers it could slow metastasis (e.g. prostate or pancreas). One cohort for which denervation could potentially be valuable would be patients that, because of genotype, are at high risk for developing a particular cancer (e.g., familial chronic pancreatitis patients).

The mechanism by which denervation alters cancer development is only hinted at by these studies. In addition to direct damage to targeted nerves, loss of neural input is likely to impact the functional properties of unaffected nerves that arrive at the target via a different anatomical pathway (Fig. 1) or that survive chemical ablation. Surviving fibers will be functioning in a novel environment, producing an imbalance in neural signaling locally and at the level of the CNS. This potential cascade of pathological events adds complexity to nerve-cancer interactions that future studies will need to address. These complications will be further multiplied if other cell types in the tumor microenvironment (e.g. immune cells) act as intermediaries in this process. Even with the complexity of the nerve-cancer interactions, a positive interpretation of the GEMM studies is that genetic manipulations that cause tumor production require communication with other cell types (i.e., neural) and that in their absence, disease progression is blocked. With ongoing development of tools that allow ‘molecular surgery’ on specific populations of neurons in the PNS (e.g., neurotoxins that are population specific), it may be possible to remove key co-conspirators before real damage is done.

Acknowledgments

Support provided by T32-NS086749 (JLS), R01-CA177857 (BMD), K08-DK088945 and Cancer Prevention Institute of Texas (ADR).

Glossary

Term	full name	pertinent information
AA	arachidonic acid	AA is an unsaturated fatty acid present in phospholipid membranes. Upon release, AA and its metabolites have been shown to activate TRP channels.
Ach	acetylcholine	Ach is the primary neurotransmitter released by motor neurons to activate muscles; Ach is also a neurotransmitter employed by the autonomic and sensory nervous systems.
Artn	artemin	Growth factor expressed by neurons and some cancer cells
BCC	basal cell carcinoma	Abnormal uncontrolled growths or lesions originating from basal cells of the skin epidermis
BDNF	brain-derived neurotrophic growth factor	Growth factor expressed by neurons and some cancer cells
Cancer		Disease in which abnormal cells divide without control; can invade other tissues (e.g. blood, lymph, nerves)
CG	celiac ganglion	Abdominal ganglion that contains axons of sensory neurons and cell bodies of sympathetic neurons that innervate the stomach and pancreas
CNS	central nervous system	Complex of nerve tissues comprised of the brain and spinal cord
CGRP	calcitonin gene related peptide	Peptide released by sensory neurons; functions as a vasodilator and contributes to neurogenic inflammation
DRG	dorsal root ganglia	Clusters of the cell bodies of spinal sensory neurons
ET-R	endothelin receptor	G-protein coupled receptor that elevates intracellular calcium and modulates vasoconstriction
GDNF	glial cell-line derived growth factor	Growth factor expressed by neurons and some cancer cells
Ganglia		Cluster of nerve cell bodies
GEMM	genetically engineered mouse model	Mice with genomes that have been engineered to model aspects of human diseases
GFRα1	GDNF receptor alpha 1	GPI-linked receptor that binds GDNF and Nrtn; mediates activation of the tyrosine receptor kinase RET
GFRα2	GDNF receptor alpha 2	GPI-linked receptor that binds Nrtn; mediates activation of the tyrosine receptor kinase RET; expressed by neurons and cancer cells
GFRα3	GDNF receptor alpha 3	GPI-linked receptor that binds Artn; mediates activation of the tyrosine receptor kinase RET; expressed by neurons and cancer cells
IL-6	Interleukin-6	Pro-inflammatory cytokine
IMG	inferior mesenteric ganglion	Prevertebral ganglia located where the inferior mesenteric artery branches from the abdominal

Term	full name	pertinent information
		aorta. Contains the sympathetic neurons that innervate the prostate
mAchR	muscarinic acetylcholine receptor	G-protein coupled receptor activated by acetylcholine; classically regulates signaling in the autonomic nervous system
metastasis		Refers to the development of malignant growths at sites distant from the primary site of cancer
nAchR	nicotinic acetylcholine receptor	Ion channel expressed by neurons and some cancer cells; implicated in motor function
NE	norepinephrine	Stress hormone and neurotransmitter involved in homeostasis of bodily functions (e.g. vascular, glucose, gastrointestinal)
NE-R	norepinephrine receptor	Adrenergic G-protein coupled receptors that bind by NE; activation typically stimulates skeletal muscle (e.g. “flight or fight” response).
neurogenic inflammation		Neuronal release of small molecules that can contribute to inflammation, e.g., substance P, calcitonin gene related peptide, glutamate, cholecystokinin and ATP. Effects can be on blood vessels, other neurons and immune cells to establish inflammatory milieu.
neuropathic pain		Pain that results from direct damage to the nervous system
NG	nodose ganglia	Ganglia located anterior to the internal jugular vein that contain sensory and parasympathetic cell bodies of the vagus nerve
NGF	nerve growth factor	Growth factor expressed by neurons and some cancer cells
NK-R	neurokinin receptor	G-protein coupled receptor involved in nociception
NPY	neuropeptide Y	Peptide released from sensory neurons that functions as a vasoconstrictor
Nrtn	neurturin	Growth factor expressed by neurons and some cancer cells
P2X	ionotropic purinergic receptor	Ion channel activated by ATP; implicated in modulating nociception, cardiac function, vascular tone and micturition
P2Y	metabotropic purinergic receptor	G-protein coupled receptor activated by ATP and its metabolites; implicated in multiple cellular functions including nociception, cytokine secretion, proliferation and apoptosis
pancreatitis		A complex inflammatory disease with multiple etiologies including both genetic and environmental (internal and external) components. Resulting pathology has a common histological presentation including edema, vasodilation, invasion of immune cells and varying degrees of breakdown in the barriers of the different tissue compartments within the pancreas
PanIN	pancreatic intraepithelial neoplasia	Precancerous lesions in the ductal structures of the pancreas composed of columnar or cuboidal cells
PAR2	protease activated receptor 2	G-protein coupled receptor that modulates inflammatory responses
PDAC	pancreatic ductal adenocarcinoma	Most common form of pancreas cancer; tumor derived from epithelial cells that line the pancreatic ducts and ductules

Term	full name	pertinent information
PG	paravertebral ganglia	Ganglia alongside the spinal column that contain sympathetic neuron cell bodies
PNI	perineural invasion	Refers to when cancer cells invade the nerves; cells may invade all layers (endoneurium, perinerium, and/or epineurium) within the nerve
PNS	peripheral nervous system	Consists of nerves and ganglia outside the brain and spinal cord; primary subdivisions include somatosensory and autonomic nervous systems.
SN	splanchnic nerve	Visceral nerve of autonomic and sensory fibers connecting the spinal cord and abdominal organs
SP	substance P	Peptide released from sensory neurons; can act as a modulator of neurogenic inflammation
TrkA	tropomyosin receptor kinase A	Tyrosine receptor kinase activated by NGF; expressed by neurons and cancer cells
TrkB	tropomyosin receptor kinase B	Tyrosine receptor kinase activated by BDNF; expressed by neurons and cancer cells
TRP	transient receptor potential family	Family of ionotropic receptors (ion channels) expressed on neurons; can influence nociceptive tone
VN	vagus nerve	Parasympathetic and sensory fibers arising from neurons of the nodose ganglion; have peripheral synapses on intrinsic neurons within organs
xenograft		Transplantation of cancer cells into animals to model aspects of human disease

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Outstanding Questions Box

Are different components of the nervous system critical for development of different tumor types?

Are there other cell types (e.g. immune) involved in nerve-tumor interactions?

Does dysregulated nerve-nerve communication contribute to cancer pathology?

Is inflammation only pro-tumorigenic or does it contribute to anti-cancer conditions?

Are there molecules in nerve-tumor signaling that can be used as biomarkers?

Can we improve prognosis by modulating signaling of molecules identified as participants in nerve-tumor signaling?

Trends Box

The peripheral nervous system is necessary for homeostasis of target tissues.

Two-way communication between the nervous system and target tissues engages multiple signaling pathways.

The peripheral nervous system is a critical part of the tumor microenvironment and plays a role in tumor initiation and metastasis.

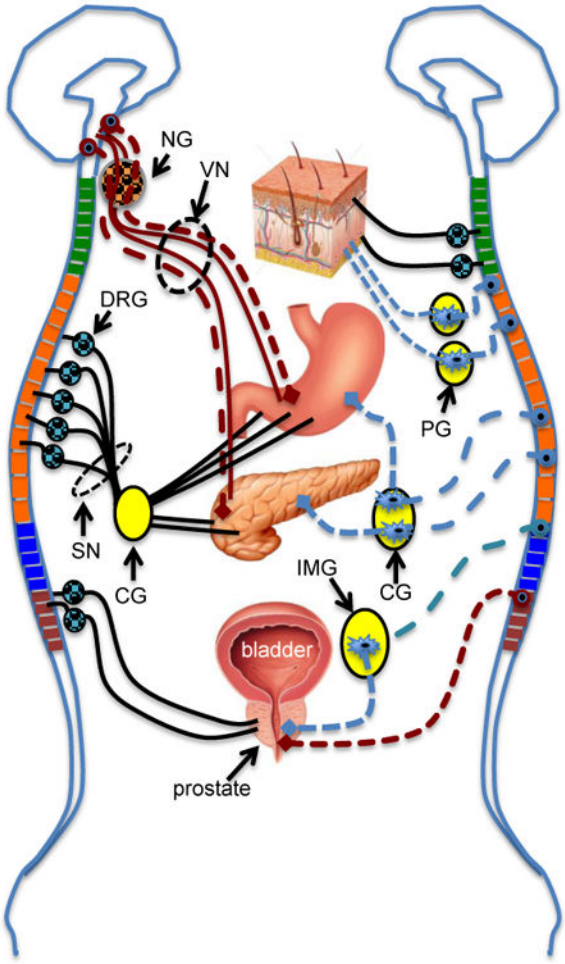

Figure 1.

Peripheral tissues including skin, stomach, pancreas and prostate are innervated by sensory neurons of the dorsal root ganglia (DRG; solid black lines). Thoracic and abdominal organs also receive sensory input from primary afferents whose cells bodies are located in the nodose ganglion (**NG**; solid red lines) and travel in the vagus nerve (VN). Sensory innervation from DRG to the stomach and pancreas travels with sympathetic preganglionic axons (right side of diagram) in the greater splanchnic nerve (**SN**) and pass through the celiac ganglion (**CG**) before reaching their target organ. The VN also contains parasympathetic preganglionic axons (dashed red lines) whose cell bodies are located in the brainstem. These axons synapse on parasympathetic postganglionic neurons (not shown) in the organ wall. Sympathetic innervation arises from sympathetic preganglionic neurons (blue dashed lines, right side of diagram) whose cell bodies are in the spinal cord at T1-L2 vertebral levels. Axons from these neurons innervate sympathetic postganglionic neurons in paravertebral ganglia (**PG**) located alongside the vertebral column or prevertebral ganglia found near the organ. Prevertebral ganglia include the CG, that innervates the stomach and pancreas, and the inferior mesenteric ganglion (**IMG**) that innervates the prostate. Preganglionic parasympathetic axons innervating the prostate (dashed red lines) arise from neurons located at sacral spinal cord levels and travel via pelvic SN to synapse on

postganglionic parasympathetic neurons near the base of the bladder (not shown). Skin receives both sensory and sympathetic postganglionic input from appropriate spinal levels, but no parasympathetic input.

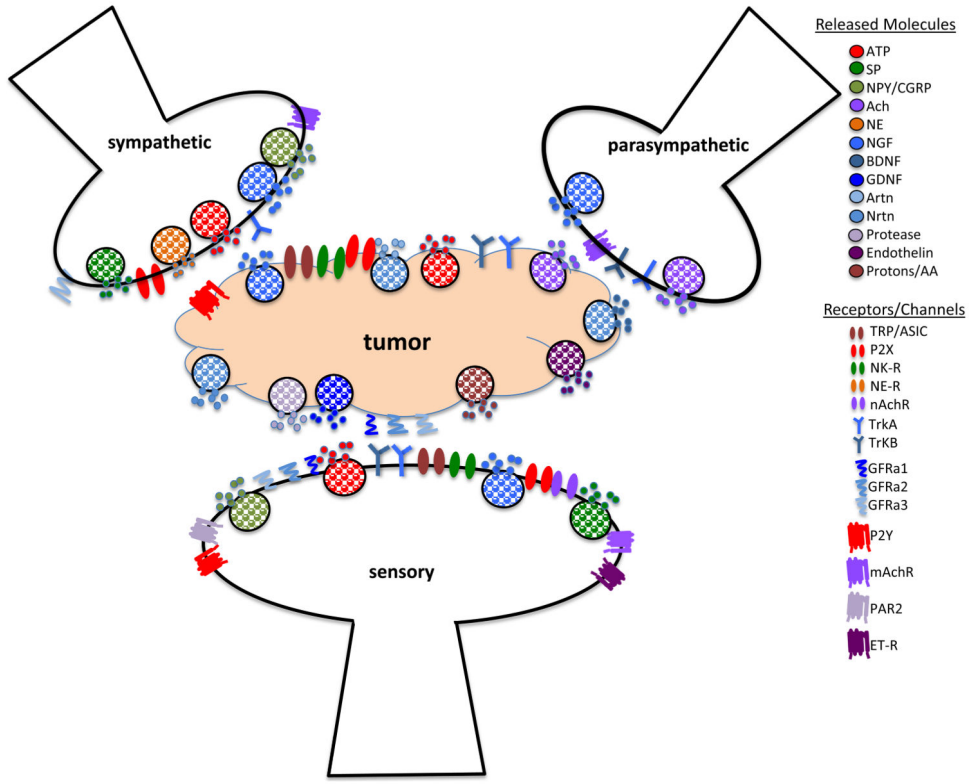

Figure 2.

Two-way chemical communication exists between cancer cells and the peripheral nervous system. Tumors release molecules that also are made by neurons including neurotransmitters and neurotrophic growth factors (e.g. **Artn**, **NGF, GDNF, BDNF, Nrtn**). Tumors also have receptors that respond to molecules released by nerves and, in an autocrine fashion, to molecules released by the tumor itself. Neurons have receptors that allow them to respond to molecules released by other neurons and glia and these interactions are likely amplified in the tumor environment. “Released Molecules” are color coded to match their respective “Receptor/Channel”. SP, substance P; **NPY**, neuropeptide Y; **CGRP**, calcitonin gene related peptide; **Ach**, acetylcholine; NE, norepinephrine, NGF, nerve growth factor, BDNF, brain-derived neurotrophic growth factor; GDNF, glial cell-line derived growth factor; Artn, artemin; Nrtn, neurturin; **AA**, arachidonic acid; TRP, transient receptor potential family (e.g. TRPV1, TRPA1); **P2X**, ionotropic purinergic receptor; **NK-R**, neurokinin receptor (for SP); **NE-R**, norepinephine receptor (e.g., beta 2/3 adrenergic receptor), nAchR, nicotinic acetylcholine receptor; **TrkA**, tropomyosin receptor kinase A; **TrkB**, tropomyosin receptor kinase B; **GFRα1**, GDNF receptor alpha 1 (binds GDNF and Nrtn); **GFRα2**, GDNF receptor alpha 2 (binds Nrtn and GDNF); **GFRα3**, GDNF receptor alpha 3 (binds Artn); **P2Y**, metabotropic purinergic receptor; mAchR, muscarinic acetylcholine receptor; **PAR2**, protease activated receptor 2; **ET-R**, endothelin receptor.

Table 1

Studies that have examined the effect of neural ablation on cancer development and progression

Tumor Type	Ref.	Models Employed			Neural Ablation		Nerves Affected by Treatment			Age of Effective Intervention			Outcomes		
		GEMM	Xeno	Chem	Surg	Chem	Symp	Para	Sensory	Neonate	Juvenile	Adult	Reduced precancer lesions	Reduced tumor growth	Reduced metastasis
Prostate	[48]	✓	✓		✓	✓	✓	(✓)	✓	✓	✓		✓	✓	✓
Stomach	[49]	✓		✓	✓	✓		✓	✓			✓	✓	✓	✓
PDAC	[11]	✓				✓			✓	✓			✓	✓	ND
BCC	[50]	✓			✓		(✓)		✓		✓		ND	✓	ND

Parentheses indicate small or minor effects on this population of neurons. ND, not determined. PDAC, pancreatic ductal adenocarcinoma; BCC; basal cell carcinoma; GEMM, genetically engineered mouse model; Xeno, xenograft cancer model; Chem, chemically induced cancer; Surg, surgical ablation; Chem, chemical ablation; Symp, postganglionic sympathetic nerves; Para, postganglionic parasympathetic nerves.