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Review Article

The autonomic nervous system and cancer

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A B S T R A C T

Recent data have demonstrated extensive autonomic nervous system (ANS) neural participation in malignant tumors and infiltration of nerve fibers in and around malignant tumors. ANS cybernetic imbalances deriving from central nervous system (CNS) stress are associated with poorer patient outcome and may play a key role in tumor expansion. The ANS modulates and can destabilize tissue stem cells, and it drives the expression of neurotransmitter receptors on tumor cells. Disruption of tumor innervation and pharmacological ANS blockade have abrogated cancer growth in preclinical models.

The present review interprets recent key findings with respect to the ANS and cancer. We highlight new data from animal models addressing specific cancers suggesting that unbalanced autonomic cybernetic control loops are associated with tissue instability which in turn promotes, (1) cancer stem cell based tumor initiation and growth, and (2) metastasis. We posit that identifying the sources of neural control loop dysregulation in specific tumors may reveal potential targets for antitumor therapy. Given the striking tumor regression results obtained with gastric vagotomy in gastric cancer models, and the effects of β-adrenergic blockade in pancreatic tumor models, it may be feasible to improve cancer outcomes with therapeutics targeted to the nervous system.

1. Introduction

The genesis of a malignant tumor represents a loss of control. Despite the fact that the nervous system is a superordinate control network, the prevalent dogma until quite recently was that it does not contribute to the loss of tissue control leading to cancer progression [1,2]. Histological and experimental evidence challenges this assumption, and it is now recognized that the nervous system densely infiltrates cancerous growths and is a tumor driver [3–7]. Experimental disruption of tumor innervation and pharmacological blockade in murine cancer models abrogate malignant tumors [8–10]. The nervous system has also been shown to modulate stem cells, the cell cycle, and gene expression [11,12]. This aligns with findings indicating that tumor initiation and expansion

is propelled by dysregulated stem cells and/or stem-like malignant cells [13].

Preclinical studies suggest that neuroanatomic linkages convey tumor signals to the brain which generates outgoing neural traffic along involuntary (autonomic) nerve fibers to elicit tumor initiation, growth and metastasis [14,15]. Although the study of tumor-neural interactions is still in its infancy, several landmark reports have unambiguously demonstrated that the nervous system is a major modulator of tumor growth and spread in pancreatic, prostate, and gastric cancer, which we discuss later in this review [6–8,10,16,17].

The present review highlights the concept that the loss of tissue stability leading to cancer can result from an imbalance of neural pathways. [18] These imbalances may be more fully contextualized and understood as positive versus negative feedback control loops which are the key concept contained within control theory or cybernetics. [19] Cybernetics, first articulated by Norbert Wiener in 1948, posits that feedback control loops govern the dynamics of organisms. [20] Hence in this review, we discuss the recently emerging and incompletely defined concept that disrupted neural control loops participate in promoting cancer, and we provide examples of specific tumor types in which excessive positive feedback destabilizes local tissue and helps drive tumor development. Based on current data we further suggest that delineation of the dynamics, structure, and tumor related changes of a neural cybernetic control system may help to **(1)** understand tumor initiation and expansion, and **(2)** identify potential opportunities for antitumor therapy.

2. Neural tissue and the tumor microenvironment

2.1. *Association between nerves and tumors in animal models*

Important approaches to understanding the neurally dependent behavior of tumors include the study in animal species of processes that involve nervous tissue and have relevance to tumorigenesis in humans [21–24]. Working with an invertebrate system, Scharr in 1945 and 1953 published intriguing reports showing that transection of the recurrent nerve in cockroaches resulted in the formation of malignant tumors in the organs innervated by this nerve [25,26]. This denervation clearly resulted in a loss of tissue homeostasis in this insect model [25]. It has long been known that epithelia, the tissue of origin for most cancers, are richly populated with autonomic and sensory nerve fibers, and hyperplastic skin exhibits an increased density of sensory fibers [5,27,28]. The nervous system variously regulates homeostasis of epithelia via control of stem and progenitor cells [8,29]. Pawlowski in 1967 reported on the induction of tumors in the denervated skin of the ears of rabbits [5]. Interestingly, denervation increased the rate of tumorigenesis in response to a topically applied carcinogen, indicating a disruption of local tissue homeostasis under neural control [5].

2.2. *Signaling dialog between nerve fibers and tumor cells*

Nerve fibers infiltrate growing tumors and nerve fibers and tumor cells stimulate each other via a number of pathways [12,30]. Neurally secreted neurotransmitters and growth factors act directly on tumor cells to promote tumor initiation and growth (Fig. 1) [6,7,31]. Nerve fibers have been identified in a range of solid tumor types, tumor cells secrete nerve growth factors, and tumors exhibit elevated levels of catecholamines and β-adrenergic receptors [4,7,32]. The microenvironment and associated nerve fibers appear to constitute a feedback loop that is dysregulated via positive feedback to an unstable state with uncontrolled growth and metastasis [14]. A number of tumor promoting molecules are upregulated by β-adrenergic signaling including transforming growth factor β (TGFB), vascular endothelial growth factor (VEGF), IL-6, matrix metalloproteinase 9 (MMP9), and PTGS2. Sympathetic β-adrenergic signaling can inhibit DNA damage repair and p53-associated apoptosis, and can stimulate in tumor cells several oncogenic signaling molecules including Src and HER-2 [33,34]. Shi et al. (2011) reported that β-adrenergic receptor levels correlated with Her-2 oncogene status in human breast
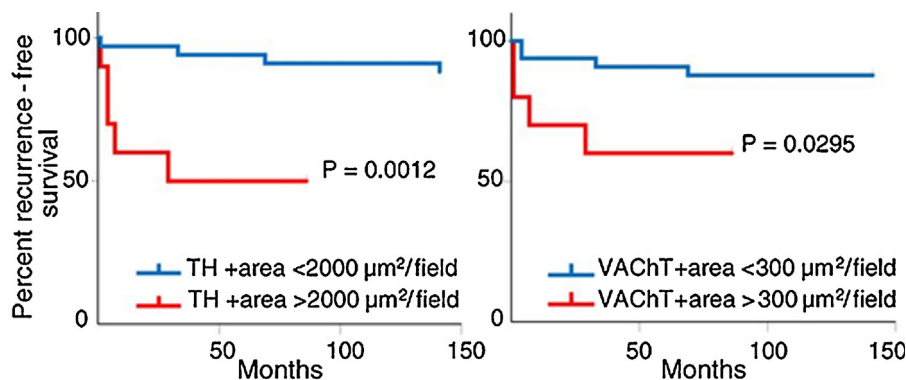
Fig. 1 – Tumor innervation density and recurrence free survival in human prostate cancer patients. Human prostate sections were probed for tyrosine hydroxylase (TH) to identify noradrenergic sympathetic fibers, and for vesicular acetylcholine transporter (VAChT), a marker of parasympathetic nerve fibers. Left Panel: Recurrence-free survival of patients with high (>2000 μm^2/field) and low (<2000 μm^2/field) adrenergic nerve densities. Right Panel: Recurrence-free survival of patients with high (>300 μm^2/field) and low (<300 μm^2/field) cholinergic nerve densities. From Magnon et al. [17]. Reprinted with permission from AAAS.

tumors [35]. Hence one mode of intervention may be to apply a β-adrenergic antagonist, such as propranolol to prevent excess positive feedback, i.e., excess sympathetic stimulation. This has been exploited in experimental cancers in preclinical models and has blocked tumor growth [3,36]. Moreover, disruption of neural innervation to tumors has blocked their growth or caused significant regression in mouse models of various cancer types [8–10].

3. The mammalian autonomic nervous system (ANS)

3.1. Organization and function of the ANS

The autonomic nervous system (ANS) both centrally, i.e., contained within the CNS, and peripherally, viz., peripheral nerve fibers, contains feedback control loops that orchestrate the functions of visceral organs, the skin, the heart, blood vessels, smooth muscle, secretory glands, and even stem cells in epithelia. The ANS innervates epithelial surfaces, blood vessels, the airways, intestines and urogenital organs and is largely under involuntary control. The ANS is comprised of efferent fibers that carry signals from the brain to the rest of the body, and afferent fibers, that convey sensory information from the periphery to the CNS [37,38]. The sympathetic branch of the ANS is generally regarded as efferent and excitatory, with the catecholamines epinephrine and norepinephrine as the main neurotransmitters [38]. Sympathetic activity varies according to innervation target and is in many visceral organs and tissues often nuanced and complex. The parasympathetic ANS is largely afferent and sensory, with acetylcholine as the primary neurotransmitter, but it also contains important afferent fibers which are inhibitory, and it should be noted the two primary parasympathetic trunks, the vagal nerves, contain sympathetic fibers [38,39]. A significant fraction of ANS fibers can secrete other chemical messengers and signaling peptides such as substance P.

3.2. ANS feedback loops (cybernetics)

Control theory was first developed in the context of engineering and mathematics and **(1)** addresses the behavior of closed loop dynamic systems that receive inputs, and **(2)** formalizes the primary factors that affect the stability of dynamic physiological systems via feedback (Fig. 2) [19]. Norbert Wiener defined cybernetics in 1948 as ''the scientific study of control and communication in the animal and the machine'' [20]. Systems vary in terms of stability with their output attaining a specific value or exhibiting oscillation. Negative feedback dampens the output of a cybernetic loop and leads to stability [40,41]. In a non-linear system the effects of positive feedback, which is destabilizing, can be substantial [42]. Data showing increased density of autonomic fibers in tumors and communication between tumor cells and nerve fibers is summarized in several excellent reviews [4,12,15,30]. The feedback between ANS fibers and tumor tissue appears to be mediated via tumor secreted nerve growth factors and by neurotransmitters that impact stem cells and tumor cells bearing muscarinic and β-adrenergic neurotransmitter receptors [4,8,43,44]. Accordingly, persistent ANS mediated β-adrenergic activation stimulated by signaling from the brain or runaway local signaling loops between nerves and tumor cells in the tumor microenvironment, i.e., sustained positive feedback, is hypothesized to disrupt tissue homeostasis [6,45]. Resultant instability in the stem cell compartment may trigger tissue hyperplasia or neoplasia, and may also promote the expansion of established tumors [7,27].

4. ANS imbalances

4.1. Animal models

Various investigators have hypothesized on the basis of recent data that a central ANS imbalance due to stress or other factors may cause chronic overactivity of one or both branches of the ANS, resultant abnormalities in visceral organ tissues, and
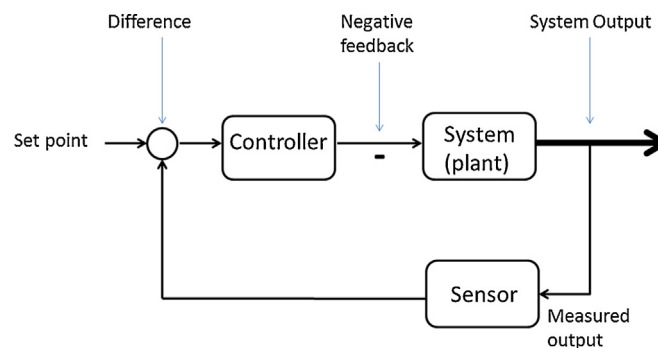
Fig. 2 – Diagrammatic representation of a negative feedback control (cybernetic) loop. The plant generates the system output, for example tissue growth or body temperature. The actual output is measured by a sensor and is compared to the set point value to yield the difference. The controller then adjusts the plant output by varying negative feedback so that the output converges to the set value. In the case of local tissue control parasympathetic fibers may have receptors that feed information to the CNS which then modulates parasympathetic output to adjust tissue status. In such a system positive feedback is destabilizing, and in the case of the autonomic nervous system activity of the sympathetic system represents positive feedback that would trigger a runaway loop.

cancer [12,16,30,36,39,46]. Physiologic stressors activate the sympathetic NS to release norepinephrine, i.e., β-adrenergic signaling, both systemically and within common metastatic target organs (Fig. 3) [14,36,45,47]. Sloan et al. (2010) found stress induced sympathetic activation in an orthotopic mouse model of breast cancer increased metastasis 30-fold, an effect that was blocked by the sympathetic β-adrenergic antagonist propranolol [36]. Shi et al. (2011) working with MC-7 human breast cancer cells, concluded that the β2-adrenergic (sympathetic NS) receptor and Her2 comprise a positive feedback loop [35]. The β2-adrenergic receptor (β2-AR) is a transmembrane G protein-coupled receptor (GPCRs), and was previously regarded as a short-term regulator of intermediary metabolism [35]. However, it has become apparent that β2 receptors participate in the long-term regulation of cell proliferation and differentiation in a variety of physiologic and pathophysiologic processes [35,48,49].

4.2.   Human patients

Autonomic dysfunction has been frequently observed in patients with advanced cancer [50–52]. For example, women with breast cancer that are depressed or experiencing stress, are more prone to tumors and their clinical course is worse [46,53]. Stone et al. (2012) assessed sympathetic and parasympathetic autonomic function by using cardiovascular measures and associated activities in185 patients with advanced cancer [50,54]. Cardiovascular reflex measures indicated a high incidence of autonomic dysfunction in these hospice care cancer patients [50,55]. Bruera et al. reported that patients with advanced breast cancer frequently exhibited cardiovascular autonomic insufficiency, were more likely to suffer chronic unexplained nausea, and that lower GI disturbances were present [56]. These patients were not malnourished and none of them had cardiovascular disease or were receiving drugs that
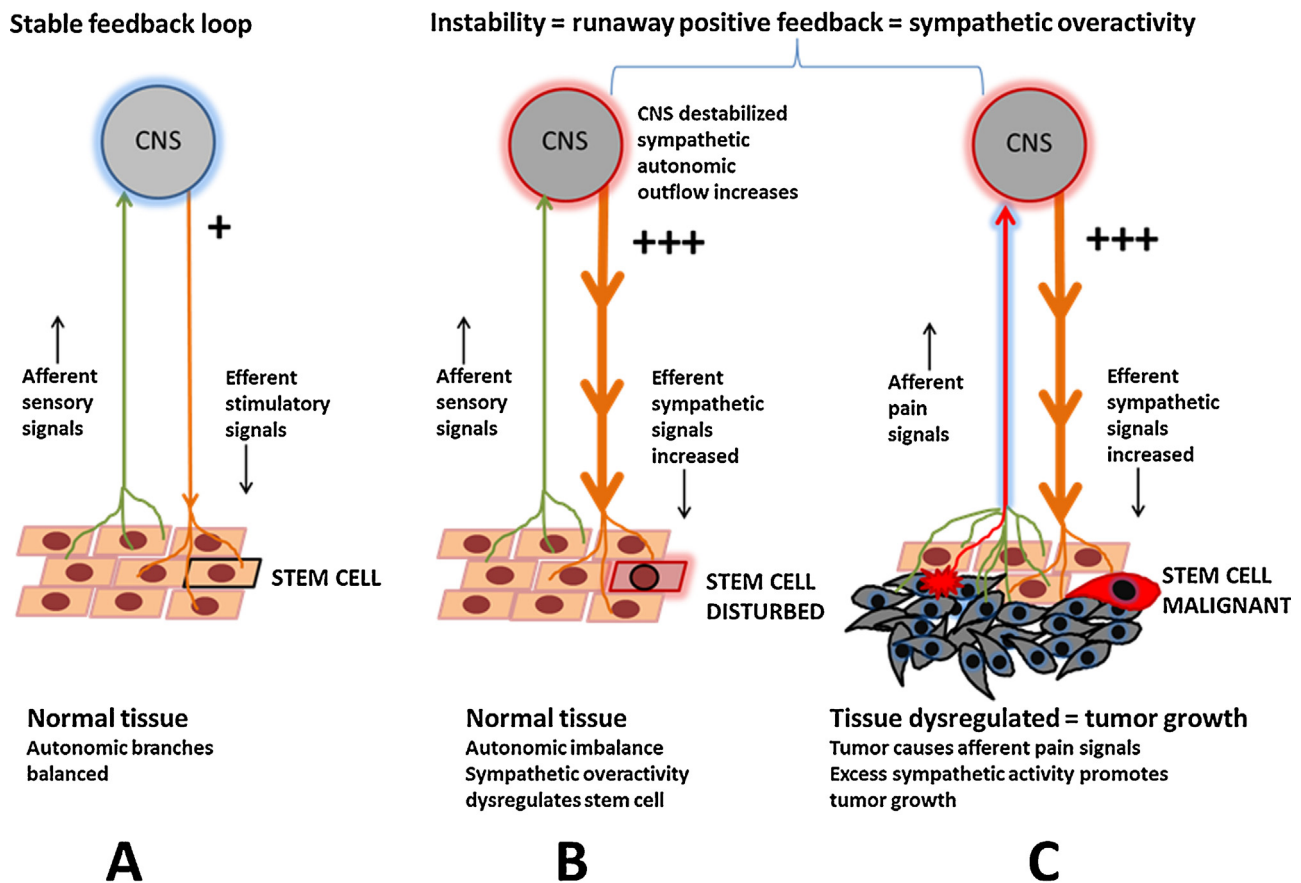

Fig. 3 – Possible autonomic imbalance manifested as sustained sympathetic outflow (positive feedback) leading to tumor progression.
(A) The figure depicts an autonomic cybernetic loop comprised of parasympathetic sensory nerve endings feeding signals to brainstem structures which then adjust ouput to the tissue of origin via sympathetic efferent nerves. The target tissue could for example be the prostate, and in panel A the system is stable. The stem/progenitor cells in the tissue are either quiescent or behaving normally, maintaining tissue homeostasis. (B) Here the CNS has become activated in a deleterious way, possibly due to stress, illness, damage, a response to maligant transformation in the target tissue, or other factors, and has generated sustained positive sympathetic stimulation to the target tissue. Excess sympathetic outflow is altering the tissue microenvironment and promoting malignant transformation of the stem cells(s). (C) Constant sympathetic stimulation is driving the development and growth of a tumor mass. The dysregulated stem cell is now a cancer stem-like cell and is propagating the tumor. The tumor has elicited the growth of neural fibers, and many are sensory in nature, causing pain signals to be conveyed to the brain.

could influence autonomic function. Bruera noted that some cancer patients with autonomic dysfunction die suddenly, speculating that autonomic failure is the cause [55,56]. Cancer cells often home to nerves and infiltrate those structures so one explanation may be that infiltration by tumor cells causes deterioration of the autonomic nerves [16]. An imbalance between the activity levels of sympathetic versus parasympathetic cardiovascular innervation can lead to sudden death [57,58]. The nausea and constipation seen in the esophageal cancer patient and other patients may implicate vagal afferent sensory fibers traveling from the periphery, quite possibly from the esophagus tumor site to the CNS [59,60]. Collectively the preceding human clinical observations and those acquired with preclinical models align with the concept of closed loop cybernetic ANS control [19,37]. Interestingly, open loop, i.e., continuous, positive brain stimulation has emerged as a way to restore aberrant neural activity, but often the stimulation is excessive and leads to side effects [61].

5. Autonomic neural control in pancreatic, prostate and gastric cancer

Both clinical observations and translational studies have provided consistent data for neural involvement in the natural history of several solid malignant tumor types [12,15,56,62]. The clinical and preclinical data is relatively developed for prostate, pancreatic and gastric tumors, and the host organs are heavily innervated by the ANS, so discussion will be limited to these three types and in this context seminal studies will be discussed [6,8,15].

5.1. Pancreatic cancer

Nervous system imbalances predisposing the pancreas to malignant tumor formation - The pancreas require balanced sympathetic (stimulatory) and parasympathetic (inhibitory) cybernetic control to maintain homeostasis [63]. ANS imbalances are associated with disorders that predispose to cancer, and two primary examples are diabetes and pancreatitis [64]. Diabetes is a risk factor for pancreatic cancer [65]. In diabetic patients autonomic dysfunction often develops with a disruption of normal sympathetic-parasympathetic responses, manifested as a constellation of symptoms [66]. El Newihi et al. (1988) found that exocrine pancreatic function was impaired in diabetics and in preclinical models with autonomic neuropathy [67]. Frokjaer et al. (2013) reported that MRI revealed microstructural changes of brain areas involved in visceral sensory processing and these changes were associated with autonomic dysfunction [68]. Patients with chronic pancreatitis have a 40% risk of developing pancreatic cancer, and chronic pancreatitis patients exhibit altered brain resting activity, reduced cortical thickness on anatomic MRI, and brain microstructural changes as detected by diffusion tensor MRI [15,64,69]. The CNS can trigger a fast response to pancreatitis in which autonomic efferents elicit a local inflammatory response, indicating bidirectional signaling and control [15].

Autonomic hyperactivity and pancreatic cancer - Sympathetic stimulation of inflammatory signaling in pancreatic tumors can promote tumor expansion and metastasis [15,33]. Persis-

tent neuropsychological stress in preclinical models elevates systemic catecholamines, which are secreted by post-ganglionic cells of the sympathetic nervous system and by the adrenal medulla [70,71]. These increased catecholamine levels accelerate pancreatic tumors [71]. Pancreatic tumors contain both sensory and sympathetic fibers and there is a clear increase in the density of CGRP fibers during tumor progression. [15,72,73] In human pancreatic cancer patients local hypertrophy of nerve trunks is observed along with increased pain [74]. The role of pain in the disruption of local neural control is unclear, although certainly pain input from the periphery via parasympathetics stresses the CNS causing sympathetic output further stimulating the pancreatic tumor [71]. The progression of pancreatic cancer in murine models as in the human disease is associated with sensory nerve infiltration and an escalation in pain indices [15,73,75,76].

β-Adrenergic receptors which are activated by noradrenaline and adrenaline released by sympathetic post-ganglionic fibers and by chromaffin cells in the adrenal medulla, cause a pronounced stimulation of cell proliferation and migration of human pancreatic cancer cells in vitro [32]. In a seminal study Al-Wadei et al. (2009) demonstrated that propanolol, a nonselective β-adrenergic receptor blocker has a marked inhibitory effect on pancreatic cancer in preclinical models [10]. These results suggest that sympathetic autonomic overactivity, i.e., sustained positive feedback, can alter local tissue balance and prompt pancreatic tumor expansion. This cybernetic neural control system involving central and peripheral neural elements is dysregulated leading to profound consequences. Interestingly, treatment of pancreatic duct epithelial cells in vitro with ethanol has been reported to increase the levels of intra-cellular cAMP, thus enhancing cell proliferation in response to β-adrenergic activation of cAMP related signaling cascades [77]. This is in essence is forcing positive feedback to escalate. It has been proposed that therapeutic intervention for pancreatic cancer should attempt to restore and maintain a balance between stimulatory and inhibitory neurotransmission [70].

5.2. Prostate cancer

Intact sympathetic nerves are critical for prostate tumor formation, and sympathectomy induces apoptosis and blocks tumor growth [9]. This suggests that cybernetic neural control plays an important part in the normal tissue homeostasis and the emergence of tumors in the prostate. In severely paralyzed mean the prostate gland tends to be notably small [78]. Both human and animal model prostate tumors exhibit a marked increase in sympathetic innervation (Fig. 4) [6,9]. The autonomic control system in the prostate appears to involve a network of sympathetic and parasympathetic fibers operating in a balanced, controlled manner [79,80]. This is not surprising as sympathetic and parasympathetic branches of the ANS frequently operate in a coordinated and quite nuanced manner to achieve homeostasis, for example in terms of cardiac function [81].

In what is regarded as a landmark paper, Magnon et al. (2015) reported that the two arms of the ANS have complementary roles in prostate tumor initiation and dissemination [6,17]. Through the use of prostate cancer xenograft and
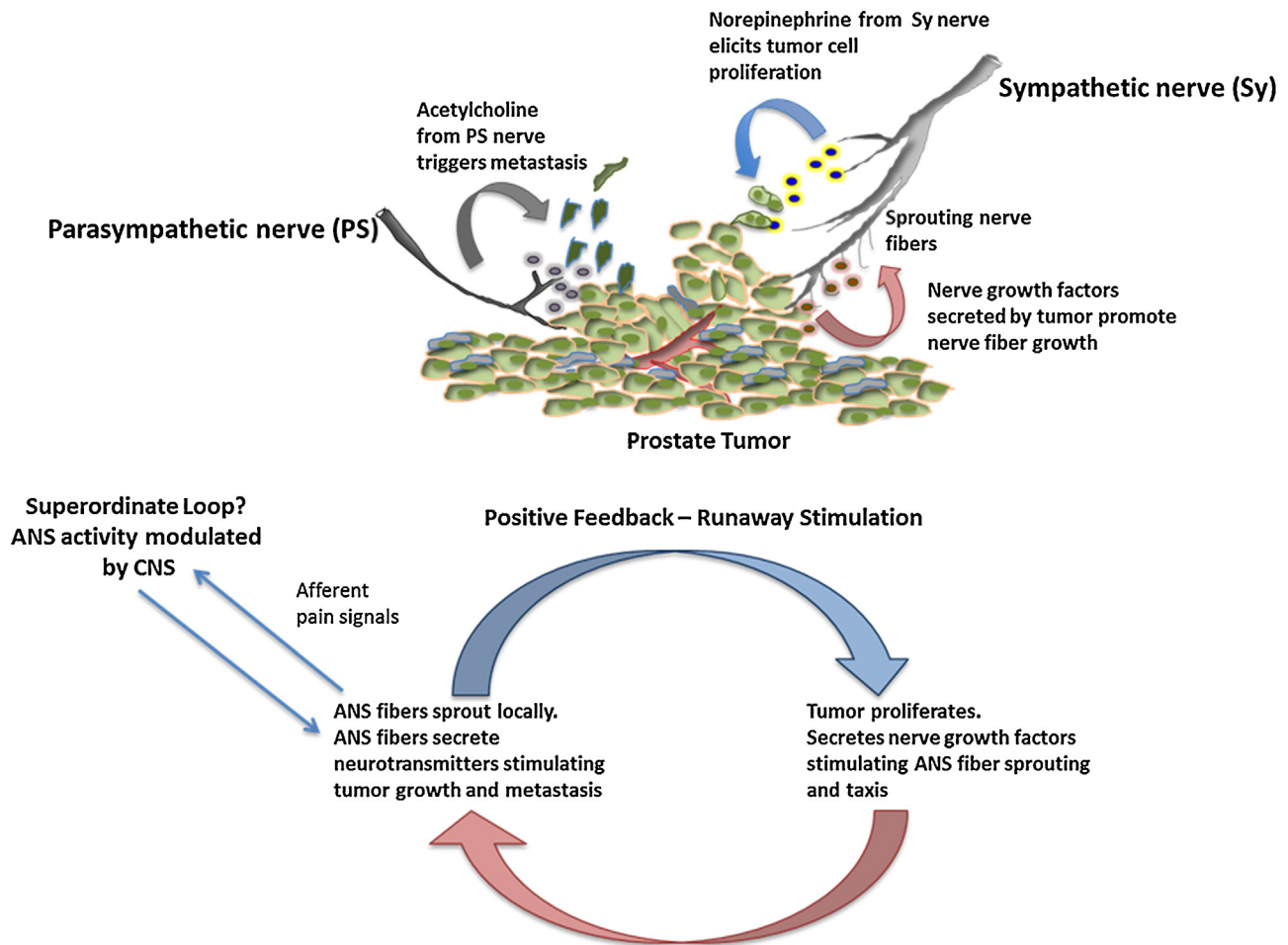
Fig. 4 – Positive feedback loop at the tumor nerve fiber level in prostate cancer. Sympathetic nerves secrete norepinephrine which engages β-adrenergic receptors on tumor cells and stimulates them to proliferate. Tumor cells secrete neurotrophic factors that elicit nerve fiber sprouting and taxis toward the tumor. Parasympathetic nerves secrete acetylcholine that activates muscarinic receptors on tumor cells stimulating epithelial to mesenchymal transition (EMT) and invasion and metastasis.

transgenic mouse models, the authors monitored tumor growth and progression by systematically modulating the sympathetic and parasympathetic nerves using pharmacologic and surgical ablative techniques [17]. These researchers concluded that the sympathetic nervous system promotes survival of cancer cells and initial tumor growth by releasing norepinephrine, which stimulates adrenergic β_2 and β_3 receptors found on the surface of the stromal cells, while the cholinergic fibers of the parasympathetic nervous system are responsible for the invasion and metastasis of malignant prostate tumor cells by releasing acetylcholine, which stimulates type 1 muscarinic receptors expressed on stromal cells (Fig. 4) [17]. To evaluate the relevance of these findings in human prostate cancer, the researchers analyzed densities of sympathetic and parasympathetic nerve fibers in prostatic adenocarcinoma specimens from 43 patients and found that aggressive cancers were associated with increased density of nerve fibers compared with less aggressive tumors. They suggested that long standing activation of mucosal afferents that have collaterals innervating the mucosal layer may induce stem cell proliferation and increase cancer risk [17].

5.3. Gastric cancer

The stomach wall is innervated by sympathetic fibers via the splanchnic nerves which supply gastric blood vessels and musculature and parasympathetic fibers from the medulla contained within the gastric branches of the vagi. All fibers are both sensory and motor [82,83]. The afferent fibers of the vagus nerve are the major neuroanatomical linkage between the stomach, the medulla, and the nucleus of the solitary tract in the hindbrain, where afferent input is integrated, to generate efferent output via the dorsal motor nucleus of the vagus (DMV) [83–85]. Gastric motility is controlled via an autonomic feedback loop, an example of a cybernetic control system. Parasympathetic satiety receptors send afferent impulses to the CNS which in turn activates parasympathetic and sympathetic efferents to modulate gastric motility and blood flow [83,86,87]. The stomach differs from other solid organs in that its autonomic innervation is mostly parasympathetic, and it is these cholinergic nerves that regulate gastric epithelial proliferation, unlike the prostate for example, in which the sympathetic fibers stimulate proliferation [8]. Vagotomy

decreases gastric mucosal thickness and cellular proliferation, and vagotomized patients have a 50% lower incidence of gastric cancer during the second decade after vagotomy [8,88]. Over twenty years ago Tatsuta and coworkers published a series of papers demonstrating that sympathetic antagonists as well as parasympathomimetic agents attenuated the progression of gastric and colon tumors in preclinical in vivo models [89–92].

In a widely regarded, transformative study, Zhao et al. (2014) found that in human subjects a higher density of vagal innervation is present in the lesser curvature of the stomach compared to the greater curvature [8]. Malignant gastric tumors arise more frequently in the lesser curvature of the stomach versus the greater curvature [8]. These authors found the same pattern in a genetic mouse model of malignant gastric tumors. Moreover, in human patients, gastric tumor stage reportedly correlated with both neural density, which was greater in more advanced tumors, and with activated Wnt levels [8]. This was mirrored in three discrete mouse gastric tumor models where bilateral or unilateral truncal gastric vagotomy markedly reduced tumor incidence and progression in denervated areas of the stomach. Denervation inhibited Wnt signaling and stem cell expansion, and in gastric organoid cultures, neurons stimulated growth via Wnt pathways activated by cholinergic signaling [8]. Pharmacological inhibition or genetic knockout of the muscarinic acetylcholine M3 receptor suppressed gastric tumorigenesis in mice. In aggregate these striking findings suggest that anti-cholinergic agents may have an important role in the therapy and possibly the prevention of gastric malignancy.

6.   Conclusions

Recently emerging data has shown that tumors are infiltrated by nerves and that there is bidirectional communication between nerve fibers and the tumors they innervate. Cybernetic control loops exist in the nervous system and also integrate the nervous system and tissue, and neural imbalances may lead to tumors. Evidence gathered from human patients and animal models involving nerve transection and pharmacologic neural blockage indicates that excess activity in either the sympathetic or parasympathetic branches of the ANS predisposes to tumors is associated with tumor growth and metastasis. In addition there has long been a perception that stress is associated with tumor recurrence and poorer outcome in breast cancer patients for example. Collectively these results have fueled the idea that the nervous system plays an important role in tumor initiation and expansion, and there is expanding interest and research directed at the neural–cancer link. It can be expected that pharmacologic and perhaps surgical interventions aimed at disrupting the dynamic between growing tumors and the nervous system will be incorporated into combined therapy clinical trials.

7.   Expert commentary

Control of a several major tumor types remains difficult with low survival rates in pancreatic and stomach cancer, and in metastasized prostate cancer, to name a few. Consequently, there is a pressing need to identify and understand all the elements that drive tumor progression that can be exploited to improve their clinical management. In this context, a developing perspective has addressed the physiological fact that the ANS is not a separate entity completely divorced from tumorigenesis, but rather is a superordinate control system and that is governed by multiple feedback loops involving sympathetic and parasympathetic signaling pathways which influence a myriad of functions related to tissue stability. Multiple reports clearly demonstrate that autonomic nerve fibers populate malignant tumors. Moreover in the host organs for pancreatic, prostate, and gastric tumors autonomic imbalance is associated with disorders that predispose to malignancy. For example the parasympathetic innervation of the pancreas triggers inflammation in that organ, resulting in pancreatitis, which if chronic, frequently leads to pancreatic cancer [31]. Importantly, several reports have demonstrated that surgical or pharmacologic interruption of tumor autonomic innervation resulted in abrogation of tumor progression [8,10].

In pancreatic, prostate, and gastric tumors cybernetic autonomic control systems regulating the host organs are aberrant, with excessive and sustained positive feedback driving tumor growth [9]. In each case the primary effector of instability, i.e., sympathetic or parasympathetic was identifiable. The identification of a neural role in a given tumor may provide a picture of the natural history of that tumor, and such data may suggest how the complete neural interaction operates and potential targets for intervention. Future general experiments in this context may be directed at determining how feedback loops between the tumor and local nerve fibers are affected by bidirectional signaling between the CNS and the tumor [14,35].

Experimental studies in animal models and human patients could reveal sites of instability, for example cortical stress pathways and neurotransmitters, subcortical and brain stem structures such as the area postrema, the medulla, and the nucleus of the solitary tract in the hindbrain, where afferent input is integrated to generate efferent output via the dorsal motor nucleus of the vagus (DMV) [53]. Moreover, parasympathetic afferents may stress cortical structures which then impact subcortical autonomic centers. Final sympathetic and parasympathetic pathways need to be identified along with relevant neurotransmitters and receptors such as α1, β1, and β2 adrenergic receptors and muscarinic receptors [93]. In addition the ANS secretes vasoactive intestinal polypeptide (VIP, and from the sympathetic branch neuropeptide Y) and from sensory nerves calcitonin gene-related peptide (CGRP) and tachykinins [94,95]. These peptides may serve as cotransmitters with acetylcholine and noradrenaline with interactions both at pre- and post-synaptic junctions [94,96,97]. Other autonomic transmitters may include GABA, 5-HT, ATP, and dopamine [98–100].

Ultimately what is needed is further characterization of the role of nerve fibers in specific tumors, the neurotransmitters involved. Ideally, some form of quantification of neural participation in specific tumors and the Integration of experimental data as graded values and components of a cybernetic framework may eventually provide a basis for mathematically weighting the contribution of each element

and pathway of the cybernetic tissue/organ control system in the context of tumor biology, in effect an approach akin to that employed in mathematical systems biology. Notwithstanding, the immediate more attainable goal should be to identify potential therapeutic targets and opportunities along with possible combination therapies to in effect reset the neural control system to help induce tumor regression, curtail metastasis, and enhance treatment and durability of response. This is a realistic aim given the striking results obtained with gastric vagotomy in gastric cancer models, and the effects of β-adrenergic blockade in pancreatic tumor models.

We fully expect that a role of the nervous system will be uncovered in more cancer types and that clinical trials involving nerve transection and pharmacologic modulation of ANS activity in cancer patients will expand. Moreover, the realization that the central nervous system plays a key part in the balance and function of the ANS, and thus may influence the expansion of tumors in patients. It has long been observed that psychological stress and depression may be associated with a poorer outcome in cancer, for example in breast tumor patients. Hence, an emerging body of newer data and perspectives highlighting the importance of the nervous system in cancer may prompt investigations and possibly interventions to modulate stress factors in cancer patients. In aggregate these trends may be expected to foster the development of new combination therapies for the clinical management of solid tumors.

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