Received: 5 July 2021 | Revised: 27 July 2021 | Accepted: 4 August 2021

DOI: 10.1096/fba.2021-00080

FASEB BioAdvances WILEY

REVIEW

The nervous system: Orchestra conductor in cancer, regeneration, inflammation and immunity

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Funding information
This work was supported by the University of Newcastle, Australia.

This article is part of the Neuroscience of Cancer, Regeneration, and Immunity special collection.

Abstract

Although the role of nerves in stimulating cellular growth and dissemination has long been described in tissue regeneration studies, until recently a similar trophic role of nerves in disease was not well recognized. However, recent studies in oncology have demonstrated that the growth and dissemination of cancers also requires the infiltration of nerves in the tumor microenvironment. Nerves generate various neurosignaling pathways, which orchestrate cancer initiation, progression, and metastases. Similarly, nerves are increasingly implicated for their regulatory functions in immunity and inflammation. This orchestrator role of nerves in cellular and molecular interactions during regeneration, cancer, immunity, and inflammation offers new possibilities for targeting or enhancing neurosignaling in human health and diseases.

KEYWORDS

cancer, immunity, inflammation, nerves, nervous system, regeneration

1 | INTRODUCTION

The peripheral nervous system (PNS) comprises nerves outside of the central nervous system (CNS), including selected cranial nerves, spinal roots, sensory and autonomic ganglia, somatic nerves, and neuromuscular junctions. The role of the PNS has been thought to be restricted to several basic functions, including control of voluntary striated muscles, conveyance of nonvisual sensory information to the CNS, and autonomic function regulation. Peripheral nerves have also been well characterized in injury and disease. Traditionally, peripheral nerve dysfunction includes peripheral neuropathies, peripheral nerve injuries, and neuromuscular disorders, such as amyotrophic lateral sclerosis, muscular dystrophy, myasthenia gravis, and spinal muscular atrophy.

In recent years, the field of cancer neuroscience has emerged and has highlighted the role of nerves beyond traditional peripheral nerve diseases and to a variety of other organ systems.[1,2] Nerves are emerging as promoters of cancer growth and dissemination and although their mechanisms of action need to be fully elucidated, nerves appear to stimulate various signaling pathways in cancer cells and other cellular components of the tumor microenvironment (TME).[1,3] Apart from tumor cells and stromal cells, immune cells are a major component in the TME and also interact with nerves and tumor innervation, which should now be considered a hallmark of cancer.[3] More broadly, nerves are increasingly described for their regulatory functions in immunity and inflammation. Diseases from inflammatory bowel disease[4] to endometriosis[5] have posited neural etiologies, at least in

part. Interestingly, the role of nerves in stimulating cellular growth and dissemination has long been associated with animal regeneration, where nerves are necessary for the reconstitution of lost body parts,[6] and the recent extension of the concept of nerve dependence from regeneration to cancer and immunity is an important milestone.[7]

In this review, we aim to offer a perspective about exoneural biology, the role of nerves outside the nervous system in health and disease. We will first highlight the current knowledge about nerve dependence in regeneration and the emerging role of nerves in both cancer and immunity. The striking similarities in nerve activities between cancer, regeneration, and immunity emphasize the trophic impact of nerves and suggest that targeting nerves and neurosignaling is a promising therapeutic approach for the treatment of various human diseases.

2 | DEPENDENCE OF REGENERATION ON NERVES

2.1 | The role of nerves in regeneration

Nerve involvement in limb regeneration was initially discovered in the salamander, which has the remarkable property to regenerate appendages (limbs and tail) after amputation. Starting with the formation of a cellular bud, called the blastema, regeneration of limb and tail occurs in only a few weeks and requires the infiltration of nerves into the blastema. Denervation of the stump prevents the formation and growth of the blastema, and in the absence of nerves, instead of regeneration a simple wound healing takes place. Nerve dependence in regeneration was first reported in the middle of the 19th century[6] in the context of salamander limb regeneration and was later shown to also apply to tissues other than appendages and to other species. In regeneration of the amphibian lens, neural retina, and the forebrain, regeneration can only occur in the presence of olfactory nerve projections.[8] In the fish, fin and barbel regeneration also requires innervation for the creation of a regenerative blastema and the progressive reconstitution of a fully functional structure.[8-10] In mammals, nerves are required for heart regeneration through the stimulation of stem cell growth,[11] and in digit tip regeneration (the remnant of limb regeneration in amphibians), denervation also blocks regeneration.[12,13]

2.2 | The molecular bases for nerve dependence in regeneration

The understanding of nerve involvement in regeneration at the molecular level largely remains to be elucidated. On the one hand, blastema cells produce neurotrophic factors that attract nerves in the regenerative structure, and on the other hand, nerve liberate various mitogenic factors and neurotransmitters that stimulate neurosignaling in blastema cells. Neuregulin and nerve growth factor (NGF) have been shown to facilitate innervation during heart regeneration[11] and in digit tip regeneration, a Wnt-mediated mechanism, is necessary to attract nerves that promote blastema cell growth.[13] Immune cells, and in particular macrophages, may also contribute to the attraction of nerves to the blastema. Macrophages secrete neurotrophic factors that can stimulate nerve outgrowth,[14] and this mechanism seems to be at play in regeneration.[15] Importantly, growing nerves have been shown to secrete a series of growth factors and neurotransmitters through nerve endings. Transferrin,[16] substance P,[17] fibroblast growth factors (FGFs) and bone morphogenetic protein-2 (BMP2),[18] platelet-derived growth factor (PDGF) and oncostatin,[19] as well as the morphogenetic factor nAG (a determinant of proximodistal position)[20,21] have all been shown to be released by nerve endings during regeneration and actively stimulate the growth of the regenerate. Nerves also induce the overexpression of histone deacetylase 1 (HDAC1) that contributes to the proliferation of regenerative cells.[22] Denervation causes the deprivation of the above listed nerve-released molecules and that results in the impairment or strong reduction in regenerative capacities. Of note, it is likely that this list of trophic factors released by nerves is not exhaustive, with other molecular players likely yet to be discovered. Importantly, the cellular complexity of nerves should be taken into account in the molecular mechanisms of nerve dependence. Indeed, peripheral nerves are not only made of neurons but also include supportive Schwann cells, which are also involved in the stimulatory impact of nerves in regeneration by directly producing and releasing trophic factors such as PDGF.[19-21]

2.3 | Nerves as a source of stem/progenitor cells

Aside from the release of molecules by nerve endings in the blastema cells, an important mechanism of nerve dependence in regeneration has recently been discovered. In digit tip regeneration and skin repair, peripheral nerves provide a reservoir of mesenchymal precursor cells that directly contribute to regeneration.[23] Neural crest–derived mesenchymal precursor cells in the endoneurium are able to migrate to the blastema and later evolve into progenitors of nonneural cells, contributing to the growth and differentiation of the blastema, and in particular the formation of bones.[23] Similarly, neural

crest–derived nerve mesenchymal cells contributed to the dermis during skin wound healing.[23] These findings support a model where peripheral nerves directly contribute precursor cells to promote repair and regeneration of injured tissues.

Together, not only nerves stimulate regeneration through paracrine-based molecular interactions but also they can provide a source of precursor cells that directly contribute to regeneration. This dual function of nerves places them in a central role as orchestrator for the cellular and molecular interactions played during regeneration and, as we will describe in the next section, there are strong similarities between the role and mechanism of action of nerves in regeneration and cancer (Figure 1).

3 | THE ROLE OF NERVES IN CANCER

3.1 | The importance of nerves in cancer

Previous studies have pointed to the expression and involvement of neurotrophic growth factors, such as NGF[24] and other neurotrophins,[25] as well as neurotransmitter signaling[26] in tumor growth. Perineural invasion (the invasion of nerves by cancer cells) has been known for several years,[27] but the role of nerves in tumorigenesis was not acknowledged until more recently. Nerve dependence in regeneration was basically ignored by the cancer community despite demonstrations, made as early as the 1950s, that denervation can lead to a slow down or even

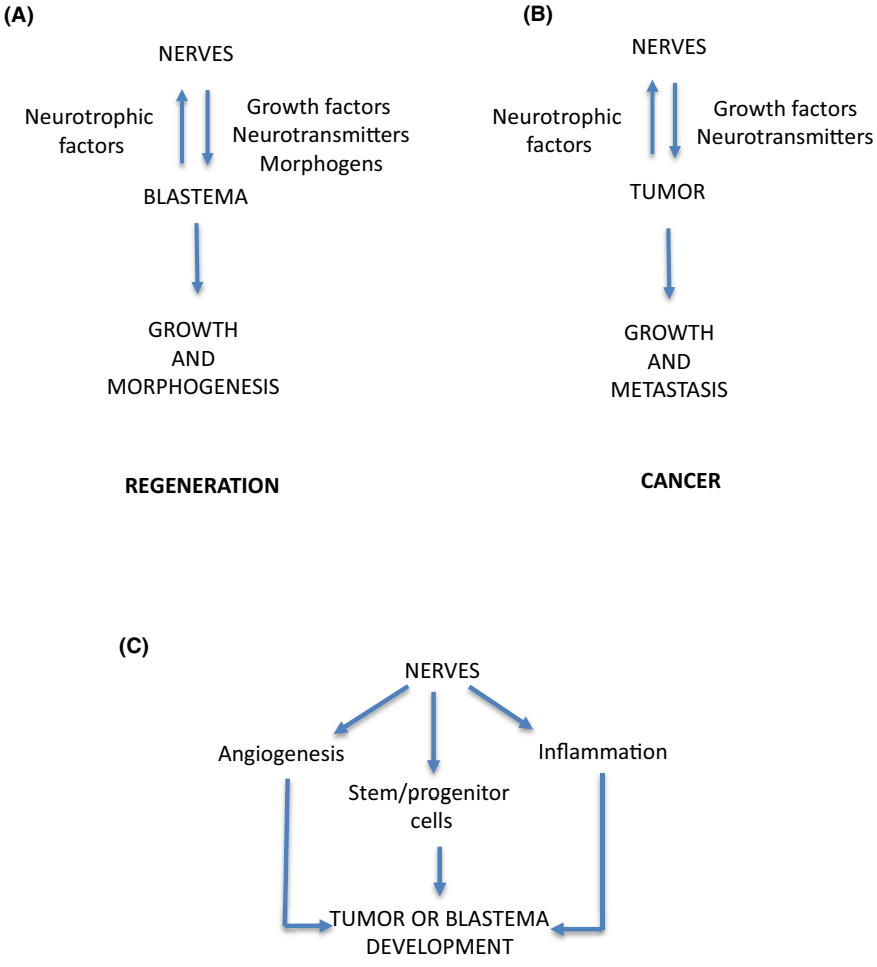

FIGURE 1 The orchestrating role of nerves in regeneration versus cancer. (A) In regeneration, the outgrowth of new nerves in the blastema is stimulated by the production and release of neurotrophic factors from blastema cells. In return, nerves liberate growth factors, neurotransmitters and morphogens in the blastema, leading to the stimulation of blastema growth and morphogenesis to reconstitute the missing structure. (B) In cancer, the outgrowth of new nerves in the tumor microenvironment is stimulated by the release of neurotrophic factors from tumor cells. In return, nerves liberate neurotransmitters and growth factors in the tumor microenvironment and that leads to the stimulation of tumor growth and metastasis. (C) In both regeneration and cancer, the release of neurotransmitters and growth factors by nerve endings stimulate not only the proliferation of stem and progenitor cells, but also there is an impact of nerves in the stimulation of angiogenesis and inflammation, further fueling the development of the blastema and the tumor, respectively

the arrest of tumor growth in cervical cancer,[28] pheochromocytoma[29] and transplanted tumors in the mouse.[30] However, cancer research on the role of nerves accelerated in 2013 when the impact of denervation on the development of prostate cancer was reported.[31] The authors found that denervation of sympathetic (adrenergic) and parasympathetic (cholinergic) nerves reduced both tumor progression and the formation of metastases in the mouse. Beta-adrenergic and cholinergic signaling in tumor cells, presumably activated by the liberation of noradrenaline and acetylcholine from sympathetic and parasympathetic nerves, respectively, resulted in the stimulation of beta-adrenergic and cholinergic receptors and ultimately led to prostate tumor growth and dissemination.[31] In a separate study, sympathetic nerves were also shown to be the inducers of an angio-metabolic switch, through the release of noradrenaline, resulting in the vascularization of prostate tumors, thus promoting overall tumor growth and dissemination.[32] Interestingly, this nerve dependence in prostate cancer provided an explanation for the long-observed fact that men with spinal cord injuries had a lower incidence of prostate cancer,[33] as spinal cord injury induces a functional denervation, and the crucial importance of neural signaling in prostate cancer is now acknowledged.[34] Preventing the infiltration of sympathetic and parasympathetic nerves in the prostate, or targeting their respective signaling pathways, is now being evaluated in clinical trials with beta-blockers (antagonists of beta-adrenergic receptors).[34] Existing epidemiological studies had suggested that the use of beta-blockers could reduce mortality in prostate cancer.[35] Interestingly, the clinical ramifications of the role of nerves in cancer go beyond treatment, as nerves could also be used to identify life-threatening prostate cancers (that require aggressive therapeutic interventions) from indolent prostate cancers (that only require active surveillance). Nerve infiltration is indeed higher in high-risk prostate cancer compared with low-risk prostate cancer[31] and perineural invasion, which is associated with nerve infiltration, has recently been shown to be an independent predictor of metastatic progression in prostate cancer.[36] In addition, as nerve trunks in the prostate can be observed by using magnetic resonance imaging (MRI), nerve density determined by MRI could be a noninvasive way to identify aggressive prostate cancers at the time of diagnosis.[37] Thus, in clinical terms, nerve involvement could be used for the establishment of cancer prognosis, to predict patient outcome, and in the treatment for preventing or interfering with neurosignaling. As will be described below, it is also likely that these findings and clinical ramifications in prostate cancer can be extended to other, if not all, human tumors.

After prostate cancer, the stimulatory impact of nerves in tumorigenesis was reported in gastric cancer. In gastric cancer, based on surgical and chemical denervation, the vagal nerve was shown to be necessary for tumor initiation and progression.[38] Denervation experiments, as well as the use of inhibitors or molecular targeting against cholinergic signaling, demonstrated the role of parasympathetic nerves in the promotion of gastric cancer.[38,39] Interestingly, a feedforward loop has been demonstrated in which gastric tumor cells produce and release NGF to promote tumor innervation and in return, cholinergic signaling activates proliferation and dissemination of gastric cancer stem cells though Yap- and Wnt-mediated pathways.[39]

In basal cell carcinoma of the skin, surgical ablation of sensory nerves in hair follicles suppresses tumor formation, and sensory nerves stimulate stem cell proliferation through a mechanism involving the activation of nerve-derived hedgehog signaling.[40] Importantly, this demonstrated that the stimulatory role of nerves in cancer is not limited to autonomic nerves (sympathetic and parasympathetic) but that sensory nerves are also involved.

Pancreatic cancer development appears to be under a balanced neural influence where sensory[41,42] and sympathetic nerves[43] stimulate the growth of pancreatic cancer cells, through neurokinin receptor and beta-adrenergic signaling, respectively, whereas parasympathetic nerves suppress cancer growth through cholinergic signaling.[44] In the regulation of cardiac activity, a positive versus negative type of regulation by sympathetic versus parasympathetic nerves is well established,[45] and the same principle of opposing neural effects may also be applicable in cancer progression. Of note, both nerve density and nerve size are increased in pancreatic cancer, and these changes may be of interest as prognostic biomarkers.[46]

In breast cancer, a differential impact of sympathetic versus parasympathetic innervation is also at play. Using genetic manipulation in the mouse, breast cancer growth and progression were accelerated following stimulation of sympathetic nerves in breast tumors but were reduced following stimulation of parasympathetic nerves.[47] There was also an increased sympathetic and decreased parasympathetic nerve density in tumors associated with poor clinical outcomes and correlated with higher expression of immune checkpoint molecules.[47] These data demonstrate that similarly to pancreatic cancer, different nerve types may have a differential, and possibly opposite, impact on breast tumor development; whether this is applicable to other cancer types will need to be clarified.

Although brain cancer occurs in the CNS, the impact of neurons on brain cancer development has been shown. Neuronal cells have been shown to promote glioma growth through the liberation of synaptic protein neuroligin-3 (NLGN3) that stimulates glioma cell proliferation through a PI3K-mTOR signaling pathway.[48]

NLGN3 release is stimulated by neural activity[48] and can be targeted in animal models to decrease the development of glioma cells.[49] The release of other proteins, such as pleiotrophin from neural cells, can promote glioma cell invasion[50] and in return, glioma cells can also impact neuron activity.[51] One mechanism that ties brain cancer and synaptic signaling is dependent on the presence of driver mutations in the PI3K gene, drawing an important connection between the genomic instability of cancer and activation of neural signals.[52] These studies in brain cancer extend the demonstration that neuronal cells and neuromolecules are essential in cancer and could be targeted in future treatments.

3.2 | The brain as a possible source of tumor progenitor cells

A recent study has identified that some neural progenitor cells produced in the subventricular zone—a neurogenic area of the brain—can cross the blood–brain barrier and egress into the circulation.[53] These cells can then infiltrate and reside in the prostate tumor where they generate new adrenergic neurons that contribute to the stimulation of prostate cancer growth and dissemination.[53] This new paradigm, by which the brain is a source of progenitor cells that participate in tumor progression, is similar to recent discoveries in the field of regeneration pointing to peripheral nerves as a source of mesenchymal stem and progenitor cells that participate in the outgrowth of the regenerate.[23]

3.3 | The role of nerves in cancer immunity and inflammation

The cross talk between nerves and immune cells is thought to be involved in cancer immunity and inflammation. Neuroimmune interactions, from the nervous to the immune systems and vice versa are well established,[54] and their impact in cancer progression has been reviewed.[55] Not only various neurosignaling, and in particular adrenergic signaling, are necessary for the generation of immune cells from the bone marrow,[56] but also the infiltration and activation of immune cells in the TME can be driven by adrenergic signaling and contribute to metastasis.[26] The interaction between innervation and inflammation is also illustrated by the fact that the vagus nerve modulates memory T cells, resulting in the inhibition of myeloid-derived suppressor cells growth in the spleen, and the promotion of cancer progression through suppression of cytotoxic T cells.[57] Together, in terms of neuroimmune interactions in cancer, it seems that only the tip of the iceberg has been explored to date, and the coming years should see a considerable expansion of this field of research.

Overall, the role of nerves in cancer and the resulting therapeutic ramifications are emerging, with striking similarities between the regulatory impact of nerves in regeneration and cancer (Figure 1). It should be noted that there are also differences in the role of nerves in regeneration versus cancer, as a balance between stimulatory and inhibitory neural effects has never been described in regeneration. Whether dual roles of nerves in regeneration have not been described because they do not exist or because it has been missed until now remains to be elucidated. In any case, the concept of nerve dependence in regeneration has now been extended to cancer and beyond the cancers described above, innervation of the TME is reported in an increasing number of malignancies, such as in thyroid (58) and esophageal (59) cancer.

4 | THE ROLE OF NERVES IN INFLAMMATION AND IMMUNITY

4.1 | Neuroimmunology

Neuroimmunology has primarily focused on the CNS and associated neuroinflammatory disorders, such as multiple sclerosis, as well as the role for neuroimmune interactions in neurodegenerative and neuropsychiatric diseases.[58] Neuroimmune interactions in the CNS can have both deleterious effects and a role in normal brain development and recovery from trauma. Multiple sclerosis is a classic example of deleterious effects of aberrant immune activation, in which T lymphocytes and other inflammatory mediators attack the myelin sheath in the CNS.[59] Neuroimmune interactions in the CNS extend to microglia and the complement system, with roles in neurodegenerative disorders, including Alzheimer's disease.[60] More recently, the study of neuroimmune interactions related to the PNS has come to the fore.[61]

4.2 | Cross talk between peripheral neurons and immune cells

As opposed to oncology, research on the gastrointestinal (GI) tract has long acknowledged a role of neurons, including those of the enteric nervous system (ENS), in selected gastroenterological diseases, such as inflammatory bowel disease (IBD), and serves to illustrate general principles relevant to peripheral neuroimmunology.[4] The GI tract is characterized by a dense, complex network of nerves and neurons that coordinate gut physiological functions.[62] In addition, the GI tract is replete with a variety of immune

cells that interact with nerves and neurons. Neuroimmune cross talk in the gut is critical to maintenance of normal physiology and homeostasis as well as being involved in a variety of gut perturbations including infection, food allergy, and IBD.[63]

In the gut, ENS neurons and neurites are entangled and communicate with immune cells including macrophages. One premise for gut physiology is that both immune cells and neurons sense danger and communicate with each other. The PNS and immune systems serve as sentinels for dangerous pathogens, noxious agents, and other stimuli. Figure 2 illustrates a simple, pragmatic view of homeostasis and disrupted biology. Figure 2A shows a homeostatic gut with tolerogenic communication between neurons and immune cells. We designate the tolerogenic state by notations, I_0 or N_0. When neurons and/or immune cells receive an inflammatory stimulus, they convert to an inflammatory state we depict as I_1 or N_1. If the inflammatory stimulus is brief or inconsequential, neurons and immune cells can revert back to baseline and homeostasis. But otherwise, initial remodeling and disease initiation commence. As disease progresses, immune cells have a large role in driving inflammation and disease progression and can recruit additional neurons into the disease state as in Figure 2B. As disease progresses further and may be treated with, for example, anti-TNFα agents, immune cells are brought back to the I_0 state, but if the enteric neuron aberration is not resolved, neurons could bring the immune cells back to the activated state I_1 as shown in Figure 2C. Activation of neural anti-inflammatory pathways could have potential for treating IBD that is refractory to other, primarily immune, treatments.

ENS neurons that influence gut immune cells include intrinsic primary afferent neurons, vasoactive intestinal peptide neurons that project to the mucosa and cholinergic neurons that influence macrophages in the external muscle layers.[62] Canonical enteric neuropeptides, such as calcitonin gene-related peptide, and neurotransmitter pathways, including cholinergic, influence immune cells with anti-inflammatory potential.[61] Acetylcholine is an important neurotransmitter for communication between extrinsic/intrinsic neurons and ENS to immune cells. The muscarinic GPCRs and nicotinic ligand gated ion channels are expressed in varying patterns across the subsets of neurons and immune cells enabling specific signaling. It is expressed on multiple neuronal types and particularly on peripheral nerves including the ENS. A number of preclinical studies have confirmed the therapeutic potential of targeting alpha 7 nicotinic acetylcholine receptor-mediated anti-inflammatory effects through modulation of proinflammatory cytokines.[64] Alone or in combination, neuropeptide and/or neurotransmitter modulation may restore neuroimmune homeostasis with potential anti-inflammatory benefit for IBD.

Outside of the GI system, neuroimmune cross talk has a wide-ranging role in the maintenance of the tolerogenic state, as well as a factor in variety of diseases. The role of the PNS and immune systems as sentinels for dangerous signals is common with barrier tissues, including the skin, replete with immune cells, nociceptors, and sensory neurons that serve to detect a variety of danger alerts. Innate lymphoid cells and the PNS communicate and determine the state of resident immune cells, including macrophages, and fibroblasts.[65] In fact, neuroimmune interactions appear to play a fundamental role in psoriasis, a chronic inflammatory skin disease, including dysfunction of nociceptive neurons.[66] Neuroimmune interactions in disease are not limited to the skin and the GI system. For example, the PNS plays an important role in the pathophysiology of endometriosis, a chronic debilitating condition.[67] Sensory nerves that surround and innervate endometriotic lesions not only drive the chronic and debilitating pain associated with endometriosis but also contribute to a pro-growth phenotype by secreting neurotrophic factors and interacting with surrounding immune cells.

5 | CONCLUSION: EMERGING CLINICAL TRANSLATION

The role of the nervous system in health and disease is expanding, and the emerging exploration of the neuroscience

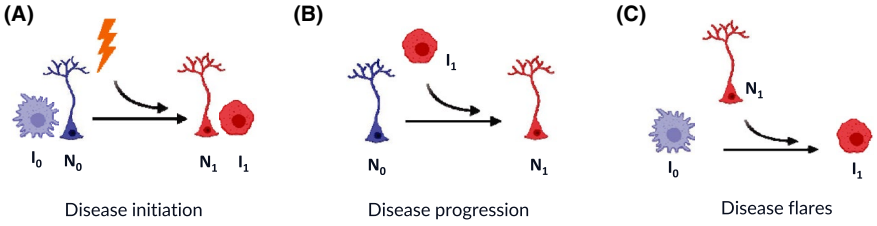

FIGURE 2 The role of neuroimmune crosstalk in maintenance of homeostasis and diseased states in inflammatory disorders. (A) Disease initiation: neurons and immune cells sense danger together or independently. (B) Disease progression: inflammatory immune cells convert neurons to inflamed state. (C) Disease flares: inflamed neurons convert immune cells to inflamed state. I_0, tolerogenic immune cell. N_0, tolerogenic neuron. I_1, diseased immune cell. N_1, diseased neuron

of human diseases opens a new frontier in biomedicine. From regeneration to cancer, immunity and beyond, a better understanding of the role played by the nervous system as the orchestra conductor of cellular and tissular growth and differentiation should delineate new avenues for the management of human health and diseases.

Therapeutic translation of cancer neuroscience is already emerging with the targeting of adrenergic and cholinergic neurosignaling in the TME, proven to be effective in reducing tumor progression in vivo,[31,38,43,44] but the existing experimental and clinical evidence now need to be tested in clinical trials. Some clinical trials have already been completed, and more are on the way about the use of beta-blockers to target adrenergic signaling in cancer. In breast cancer, β-blockers reduced the biomarkers of metastasis in a phase II randomized trial[68] and inhibited cancer progression with reduced patient mortality.[69] It should also be noted that, at this stage, the reported neurosignaling activities in cancer are mostly adrenergic and cholinergic, but the potential role of other neurosignaling pathways should not be underestimated. For instance, dopamine receptor D2 is correlated with gastric cancer prognosis[70] and repositioning dopamine D2 receptor agonists can enhance chemotherapy and treat bone metastatic tumors[71]; therefore, dopamine and its signaling also appear as valid targets in cancer. Aside from impairing neurosignaling, another promising approach is to target neurotrophic growth factors to prevent tumor innervation.[72] Blocking antibodies against NGF[24] and other neurotrophic growth factors,[25] or pharmacological inhibitors of their tyrosine kinase receptors Trk[39,43,44] have been demonstrated to inhibit tumor progression, and the effect of antineurotrophic growth factor strategies also extends to the inhibition of cancer-induced pain.[73] Pain is a serious issue in oncology, and the perspective of targeting simultaneously cancer progression and cancer pain by targeting neurotrophic growth factors and their signaling pathways is particularly attractive.

Aside from therapeutics, the other promising area for cancer neuroscience is tumor prognosis. Determining the outcome of the tumor at the time of diagnosis is increasingly important for treatment choice and patient segmentation, and as nerve infiltration in the TME is associated with tumor aggressiveness,[31,46,74,75] the assessment of nerve density may become part of routine clinicopathological analyses in oncology, as well as increasing utility through imaging, particularly in prostate cancer.[37] Similarly, neurotrophic growth factors and their receptors are overexpressed in human tumors,[76-79] and they could also be of value in cancer clinicopathology. Of note, the expression of neurotrophic growth factors has been shown to be associated with cancer prognosis in dogs and therefore the value of quantifying neurotrophic growth factors in clinicopathology may also be applicable to veterinary oncology.[80]

In conclusion, clinical translation currently emerging in the fields of cancer neuroscience and exoneural biology is likely to pave the way for further clinical developments in immunity, inflammation, cancer, and regenerative medicine. Moreover, the nervous system, and particularly the brain, is the integration center of cognition, emotions, and social interactions. The deciphering of the psychological mechanisms involved in physical health has already been pioneered,[81] and it can be anticipated that the recent developments of neuroscience that we have described here may also lead to a better understanding of the contribution of neurophysiological, cognitive, and social inputs in human health and diseases.

ACKNOWLEDEGMENTS

We gratefully acknowledge robust discussions with Grazia Piizzi leading to the concepts shown in Figure 2.

CONFLICT OF INTEREST

Pearl S. Huang and John A. Wagner are employees of Cygnal Therapeutics and may own stock and/or stock options. Hubert Hondermarck is a member of the Scientific Advisory Board of Cygnal Therapeutics.

AUTHOR CONTRIBUTIONS

All authors collaborated on the paper and offered substantive revisions and approval of the final version.

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How to cite this article: Hondermarck H, Huang PS, Wagner JA. The nervous system: Orchestra conductor in cancer, regeneration, inflammation and immunity. *FASEB BioAdvances*. 2021;3:944–952. https://doi.org/10.1096/fba.2021-00080