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Role of the autonomic nervous system in tumorigenesis and metastasis

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Abbreviations: Ach, acetylcholine; Adrβ, adrenergic receptor; ANS, autonomic nervous system; BDNF, brain-derived eurotrophic factor; BMDC, bone marrow-derived cells; Chrm1, type 1 cholinergic muscarinic receptor; DCC, deleted in colorectal cancer; EGF, epidermal growth factor; Eph, Ephrin receptor; FGF2, fibroblast growth factor 2; G-CSF, granulocyte colony-stimulating factor; HPA, hypothalamic-pituitary-adrenal axis; MSC, mesenchymal stem cells; MDSC, myeloid cell-derived suppressor cells; NE, Norepinephrine; NGF, nerve growth factor; NT, neurotrophin; PIN, prostate intraepithelial neoplasia; PNI, perineural invasion; PNS, parasympathetic nervous system; Robo, slits-roundabout receptor; SAM, sympathetic-adrenal-medullary axis; SGZ, subgranular zone; SVZ, subventricular zone; SNS, sympathetic nervous system; TAM, tumor-associated macrophages; TEM, Tie-2-expressing monocytes; TGF, transforming growth factor; VEGF vascular endothelial growth factor.

Convergence of multiple stromal cell types is required to develop a tumorigenic niche that nurtures the initial development of cancer and its dissemination. Although the immune and vascular systems have been shown to have strong influences on cancer, a growing body of evidence points to a role of the nervous system in promoting cancer development. This review discusses past and current research that shows the intriguing role of autonomic nerves, aided by neurotrophic growth factors and axon cues, in creating a favorable environment for the promotion of tumor formation and metastasis.

Although the emergence of malignant cancer cells is the result of interplay between genetic and epigenetic alterations of epithelial cells, numerous studies have shown the influence of the tumorigenic microenvironment.[1] Indeed, a tumor seems to behave as an organ within which the microenvironment affects the gene expression and phenotype of cancer cells.[2,3] For example, teratocarcinoma cells can form tumors when implanted in the flank of 129/SV mice, but are unable to develop cancer when placed in the blastocyst of a pseudopregnant C57BL/6 mouse.[1,4] Conversely, implantation of normal mammary epithelial cells in an activated microenvironment induced through overexpression of different cytokines by fibroblasts is sufficient to induce the development of invasive carcinomas.[5-7] Cancer cells, in turn, recruit and corrupt normal cell types of the stroma, such as bone marrow-derived or endothelial cells, to support the initial phases of tumor formation and also promote tumor cell dissemination (**Fig. 1**). Recent studies have revealed that sympathetic and parasympathetic nerve fibers from the autonomic nervous system (ANS) infiltrate prostate or gastric tumors and contribute to the early stages of prostate cancer development, as well as tumor invasion and metastasis.[8-10]

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Activation of Neural Pathways During Tumor Development

Thirty years ago, J.G. Batsakis was the first to describe the presence of large nerves located in the vicinity of human epithelial carcinomas, such as head and neck, gastric, or prostate cancers.[11-13] These nerves were described as paths of metastatic spread through a process called perineural invasion (PNI), in which neoplastic cancer cells are able to invade and migrate in, around, and through the nerves. PNI is frequently associated with poor clinical outcomes. A striking illustration of this process was provided in a cohort of prostate cancer patients in whom the presence of PNI was correlated to poor prognosis compared with patients without pathological evidence of PNI.[14] Despite increasing clinical recognition of this pathological entity, the molecular and cellular mechanisms of PNI are not yet well understood. Previous studies have established connections between cancer and the nervous system.[15,16] *In vitro*, cancer–nerve interactions were imaged in cultures of sensory neurons from dorsal root ganglia that exhibit directional neurite outgrowth toward prostate cancer cells.[17] *In vivo*, the number of neurons per ganglia is increased in prostate cancer patients, suggesting that nerves play a role in tumor progression.[16]

The role of the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes in cancer

The findings described above complement further observations on the influence of social networks on health.[18] Social factors or stressors might predict health outcomes among cancer patients,[19] and epidemiological data show that psychological and social stress factors may be associated with cancer onset.[20]

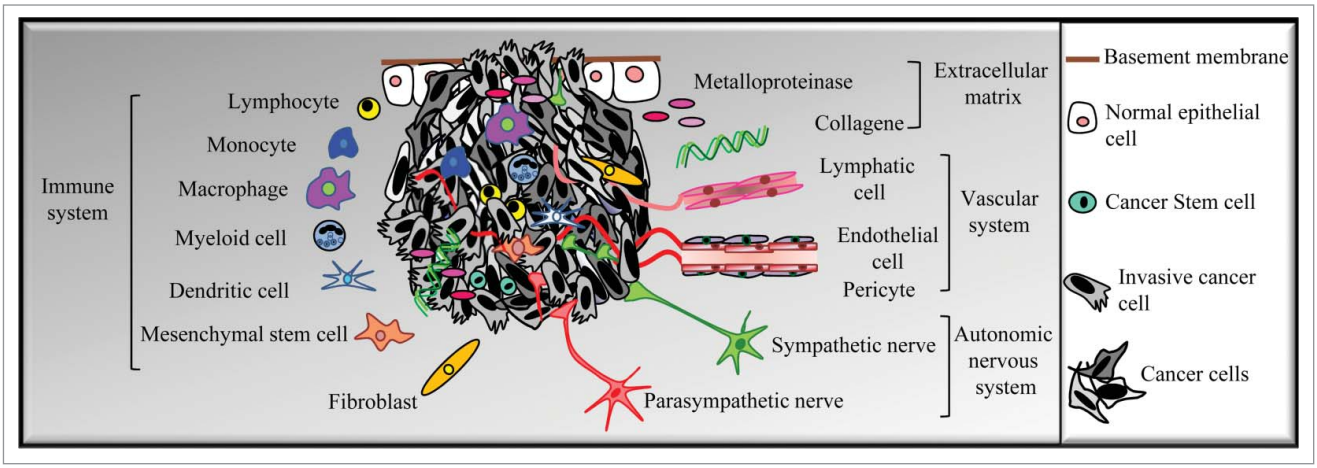

Figure 1. Tumor heterogeneity. Primary tumors contain different phenotypic profiles of cancer cells as a result of genetic or epigenetic changes. In addition, the tumor microenvironment—including bone marrow-derived cells (BMDCs) such as tumor-associated macrophages (TAM), myeloid cell-derived suppressor cells (MDSC), mesenchymal stem cells (MSC), or Tie2-expressing monocytes (TEM); fibroblasts; endothelial and lymphatic cells; extracellular matrix; and autonomic nerve fibers—further increases tumor heterogeneity by promoting the survival, proliferation, and dissemination of cancer cells. (Adapted from Magnon. Med Sci, 2013).

Similarly, studies performed decades ago on animal models revealed that the neural stimulation associated with chronic or prolonged stress promotes tumor growth and cancer cell dissemination and decreases survival.[21-25] The authors did not propose any mechanism but invoked that activation of the hypothalamic–pituitary–adrenal (HPA) axis might support the effect of stress on tumor incidence through the secretion of corticosteroids by the adrenal gland.[19,26] Glucocorticoids control growth and metabolism, suppress immune responses, and mediate the stress response to a variety of peripheral organs.[27] Activation of the HPA axis could play a role in termination of the stress response in cancer by altering the immunological control of cancer cells through loss or inactivation of T cells.[19] However, it was recently found that chronically stressed mice had increased numbers of neutrophils, monocytes, and lymphocytes in the blood as a result of activation of proliferation of hematopoietic stem cells in the bone marrow associated with an increased expression of adrenergic neurotransmitters.[28] Thus, it seems less likely that the HPA axis might control stress-induced tumor development through the immunosuppressive activity of corticosteroid hormones. Another possible explanation for tumor formation associated with stress might rely on the activation of the sympathetic nervous system (SNS) through the sympathetic–adrenal–medullary (SAM) axis, which controls the release of adrenergic neurotransmitters such as epinephrine or norepinephrine by the adrenals into the bloodstream in support of the fight-or-flight reflex. Involvement of adrenergic neurotransmitters in cancer has recently been revealed from studies monitoring tumor formation through pharmacological manipulations of the β-adrenergic signaling pathway.[29-31] Mice subjected to chronic stress conditions display an ovarian tumor burden associated with high blood levels of adrenergic neurotransmitters and increased expression of the vascular endothelial growth factor (VEGF) and metalloproteinases, leading to the development of abundant tumor vascularization.[29] Pharmacological blockade of β2 adrenergic receptors expressed on cancer cells leads to regulation of VEGF gene expression and cancer cell apoptosis.[29,30] The β-adrenergic signaling pathway is also able to regulate VEGF expression in adipose tissue and different cancer cell lines.[32,33] An intriguing study showed that putting animals in an enriched living environment increases expression of the gene encoding brain-derived neurotrophic factor (BDNF) in the hypothalamus of the mouse brain.[34] In turn, BDNF downregulates the production of leptin in adipocytes through activation of β-adrenergic receptors in white adipose tissue, leading to delayed tumor growth and increased survival. Taken together, these data suggest a key role for stress-related β-adrenergic signaling in the development of carcinoma, rather than the neuroendocrine regulation of cancer cell behavior via glucocorticoid release. This further raises the intriguing possibility that catecholamines might be able to bind different cell targets, depending on the type of cancer and leading to opposite activities. However, further research is needed to explain the divergent activity of the β-adrenergic signaling pathway in stress-mediated cancer.

The autonomic nervous system as a potential regulator of cancer

Activation of the sympathetic nervous system leads to the release of catecholamine neurotransmitters from the adrenal glands into the bloodstream through the SAM axis. Nevertheless, the uncertain role of the adrenal gland in controlling solid tumors[35] led us to consider an alternative hypothesis in which the sympathetic branch of the autonomic nervous system directly modulates cancer development through the local release of adrenergic neurotransmitters in peripheral tissues. Nerves partner with blood and lymphatic vessels throughout the body from development to adulthood.[36] Whereas tumor angiogenesis and lymphangiogenesis have been extensively explored,[37,38] the presence and

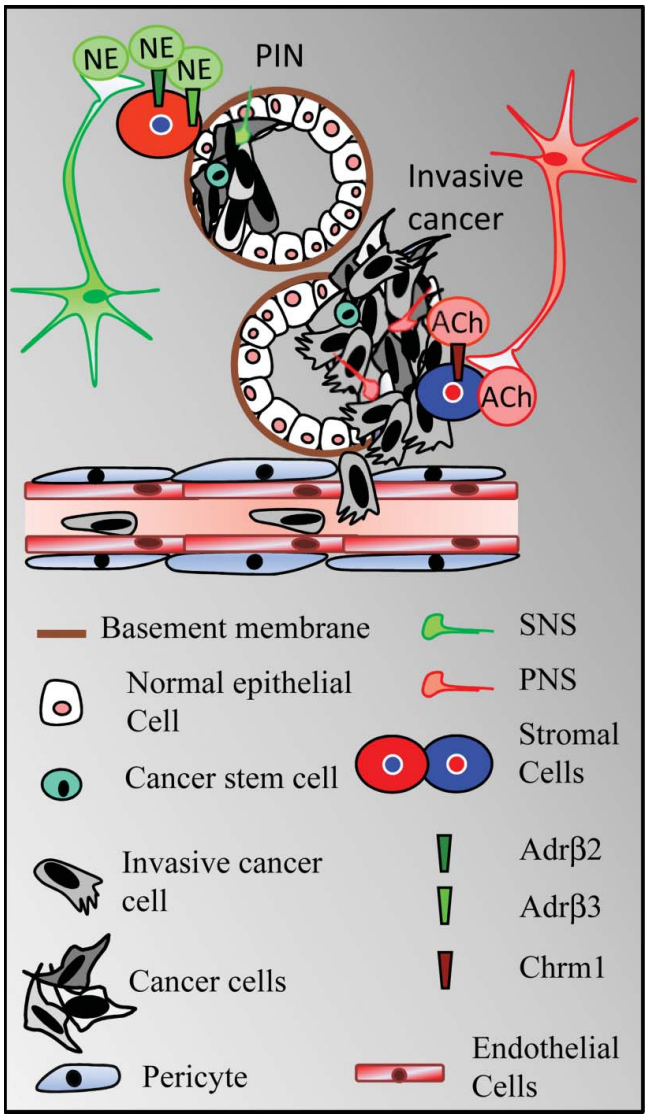

Figure 2. The autonomic nervous system contributes to tumor initiation and progression. Whereas the sympathetic nervous system (SNS) controls the early phases of tumor formation through activation of β2- and β3-adrenergic receptors (Adrβ2 et Adrβ3) expressed in the stroma, the parasympathetic nervous system (PNS) promotes tumor cell dissemination through activation of the type 1 muscarinic receptor (Chrm1) expressed in the tumor microenvironment. NE, Norepinephrine; Ach, Acetylcholine; PIN, prostate intraepithelial neoplasia. (Adapted from Magnon. Med Sci, 2013).

spreading of nerves into tumors has remained elusive. Recent studies indicated that autonomic adrenergic nerve fibers may infiltrate prostate adenocarcinoma and control malignant progression through the release of catecholamine neurotransmitters in the tumor microenvironment.[8] As summarized in **Figure 2**, chemical or surgical ablation of sympathetic adrenergic nerves prevents the formation of xenogeneic orthotopic or transgenic prostate tumors. Genetic depletion of β2- and β3-adrenergic receptors in the tumor microenvironment alters the transmission of adrenergic signals involved in the early phases of tumor development. Furthermore, the ANS is divided into 2 subsystems—the SNS and the parasympathetic nervous system (PNS)—that work in tandem in homeostasis. In cancer mouse models, parasympathetic cholinergic signaling has been identified as a key regulator of tumor invasion and metastatic spread by activation of the type 1 cholinergic muscarinic receptor (Chrm1) expressed in the stroma. Pharmacological and genetic approaches recapitulate the mechanism by which parasympathetic nerves in tumor tissues might be able to release acetylcholine that binds to Chrm1-expressing cell targets in the stroma. An additional blinded analysis of nerve densities in treatment-naïve patients with prostate adenocarcinoma revealed that sympathetic and parasympathetic nerve densities are significantly higher in tumors classified as high risk and that nerve density is associated with poor clinical outcome. Based on these data, both branches of the ANS have distinct but complementary functions in prostate tumor development, suggesting that tumor nerves might interact with different partners during the course of cancer.[8,9]

Neurotrophic Factors and Axon Guidance Molecules in Cancer

The formation of nerves, a process called neurogenesis, occurs throughout life in restricted neurogenic regions of the brain—the subgranular zone (SGZ) in the dentate gyrus of the hippocampus and the subventricular zone (SVZ) of the lateral ventricules.[39] This process is finely tuned and requires a variety of stimuli including neural growth factors, cytokines, neurotrophins, and axon guidance molecules for the activation of neural precursors within the neurogenic niche as well as for neuronal development and plasticity. For example, epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2) support the maintenance of adult neural stem cells *in vitro* and promote proliferation of neural precursors in the SVZ. The brain-derived neurotrophic factor also regulates neurogenesis in the brain.[40]

Similarly, a process of neurogenesis might occur in cancer as directional outgrowth of neurites from the dorsal root ganglia toward prostate cancer cells has been observed *in vitro*.[17] Indeed, cancer cells produce and release neurotrophic factors and axon guidance molecules that might be able to orchestrate axon outgrowth, pruning, and remodeling similar to the release of angiogenic growth factors to promote blood supply to tumors.[41-43] Conversely, the environment of the nerves surrounding tumors, which is particularly enriched in nerve-derived growth factors, promotes the survival and growth of cancer cells.[44,45] Additional clinical data support the potential processes of axonogenesis and neurogenesis in prostate tumors.[16] Cancer patients possess larger prostate ganglia associated with an increased number of neurons. These data suggest the secretion of soluble factors by cancer cells that might promote nerve sprouting or branching.[16] In support of these observations, nerve growth factor (NGF) has been identified in a variety of cancers, such as breast or prostate cancer, as a key regulator of tumor apoptosis, angiogenesis, and bone cancer pain.[46-48] Targeting NGF with sequestering antibodies prevents

nerve sprouting, angiogenesis, and tumor-induced pain.[46,48,49] BDNF has been identified in various carcinomas compared with healthy tissues, suggesting a specific role of BDNF in cancer development.[50-52] The neurotrophins (NT) family supports survival and proliferation of multiple cancers through deregulation of the PI3K/Akt and Ras/MEK/MAPK pathways.[53-55] Aberrant expression of FGF ligands and their cognate receptors leads to the activation of downstream pathways involved in cancer progression and tumor angiogenesis.[56] Although FGF determines neuronal survival and proliferation during development and adulthood, it has been also described as a pivotal regulator of neuronal migration, guidance, and synaptogenesis, suggesting a potential role in controlling nerve development in cancer.[57] Similarly, granulocyte colony-stimulating factor (G-CSF), the most commonly used hematopoietic stem cell mobilizer, acts as a bifunctional growth factor: it can stimulate the hematopoietic system while activating the nervous system. In mice, G-CSF elicits autonomic nerve survival, outgrowth, and spreading in prostate tumors, leading to tumor formation and dissemination.[58] Multiple functions of transforming growth factors (TGFs)/bone morphogenetic proteins have been described in the regulation of several life processes and in the tumor microenvironment.[59] The role of TGFs in neuronal development, such as the regulation of nerve survival or tissue repair, suggests further potential influences on tumor neurogenesis.[60]

In addition to these growth factors, axon guidance molecules have been revealed as intriguing partners in tumor progression.[61-63] The axons of developing neurons actively extend or retract under different circumstances in response to 4 families of guidance cues—netrins, slits, ephrins and semaphorins—that respectively bind UNC5 and deleted in colorectal cancer (DCC) receptors, slits-roundabout receptors (Robos), Ephrin receptors (Eph), and plexins or neuropilins.[64] In some instances, netrins determine axon outgrowth and provide guidance in the central nervous system as well as in vascular development, as nerves and vessels share cellular and molecular mechanisms to orchestrate the development of their reciprocal networks.[65-67] Also, netrins have been identified in peripheral organs and play a role in tumorigenesis by preventing cancer cell apoptosis. Controversial data preclude any definite conclusions on a potential direct effect of netrins on cancer cell migration;[61] however, their function in guidance of axons or vessels makes them attractive possible targets for inhibiting tumor angiogenesis and neurogenesis. In addition to their role in axon guidance that plays a role in vessel development, major vascular growth factors such as the vascular endothelial growth factor (VEGF) regulate development of the nervous system and increase neuronal plasticity during development and in the adult.[67] In the periphery, autonomic sympathetic axons follow arteries that release neurotrophic factors such as artemin and endothelin, which are necessary for axon outgrowth.[68,69] Conversely, the SNS regulates angiogenesis and arteriogenesis in hindlimb ischemic models.[70,71] This suggests an intricate interface between nerves and vessels that might support the development of both networks in cancer.

Perspectives: The Autonomic Nervous System as a Therapeutic Target

The finding that the autonomic nervous system promotes the development and progression of prostate or gastric cancer may open up neurogenesis as a frontier for cancer drug development.[8-10] Sympathetic nerve fibers play an intriguing role in helping tumors to grow and develop by interacting with β_2- and β_3-adrenergic receptors on stromal cells. In mice, a deficiency in β-adrenergic receptors impairs prostate cancer formation. These data are consistent with recent epidemiological reports that men with prostate adenocarcinoma who take non-selective β blockers have lower prostate cancer-specific mortality rates.[72,73] Additional clinical studies describe a similar activity of β blockers in melanoma or breast cancer patients,[74,75] indicating that adrenergic signaling might be involved in various types of cancer. Whereas existing β blockers primarily bind the β_1-adrenergic receptor, future drug development would aim to selectively target β_2- and β_3-adrenergic receptors.

In addition, inhibition of NGF or BDNF has been shown to impair cancer cell proliferation as well as tumor angiogenesis and growth.[46,49,76] Based on an intriguing parallel between neural and vascular development, VEGF and VEGFR have emerged as potent regulators of neurogenesis and neural plasticity, and may represent therapeutic targets for cancer. However, further research is needed to identify the mechanism by which tumor progression overcomes VEGF therapy.[77,78] Several FGFR tyrosine kinase inhibitors are in the early phases of clinical trials.[56] The high similarity between the kinase domains of FGFR, PDGFR, and VEGFR provides the advantage of possibly targeting both vessel and nerve development and overriding resistance to antiangiogenic drugs. Intervening in the TGFβ signaling pathway may have relevant effects in the stroma, leading to inhibition or reversal of changes in the microenvironment during tumor progression, and clinical trials have assessed the use of inhibitory antibodies or small molecule inhibitors targeting TGFs.[79]

In addition to the compelling evidence that autonomic nerves contribute to cancer progression through adrenergic or cholinergic signaling, this research raises questions over which mechanisms control cancer-related neurogenesis and, conversely, which biological systems or pathways might be regulated by the nervous system. Understanding the specific mechanisms of cancer–nerve interactions is pivotal to the development of novel cancer therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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