

Role of the nervous system in cancer metastasis (Review)

SHA LI¹, YANLAI SUN^{2,3} and DONGWEI GAO¹

¹Department of Radiation Oncology, Lanzhou General Hospital of PLA, Lanzhou, Gansu 730050;

²Department of Gastrointestinal Tumor Surgery, Shandong Cancer Hospital, Jinan, 250117; ³Institute of Oncology, Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan 250021, P.R. China

Received August 9, 2012; Accepted October 17, 2012

DOI: 10.3892/ol.2013.1168

"SYMPATHIC" Nerves

Abstract. The notion that tumors lack innervation was proposed several years ago. However, nerve fibers are irregularly found in some tumor tissues. Their terminals interaction with cancer cells are considered to be neuro-neoplastic synapses. Moreover, neural-related factors, which are important players in the development and activity of the nervous system, have been found in cancer cells. Thus, they establish a direct connection between the nervous system and tumor cells. They modulate the process of metastasis, including degradation of base membranes, cancer cell invasion, migration, extravasation and colonization. Peripheral nerve invasion provides another pathway for the spread of cancer cells when blood and lymphatic metastases are absent, which is based on the interactions between the microenvironments of nerve fibers and tumor cells. The nervous system also modulates angiogenesis, the tumor microenvironment, bone marrow, immune functions and inflammatory pathways to influence metastases. Denervation of the tumor has been reported to enhance cancer metastasis. Stress, social isolation and other emotional factors may increase distant metastasis through releasing hormones from the brain, the hypothalamic-pituitary-adrenal axis and autonomic nervous system. Disruption of circadian rhythms will also promote cancer metastasis through direct and indirect actions of the nervous system. Therefore, the nervous system plays an important role in cancer metastasis.

5. The nervous system modulates angiogenesis and micro-environments in tumors to affect metastasis
6. Nervous system interacts with immune function and inflammation to influence cancer metastasis
7. Interactions between bone marrow and nervous system: implication for cancer metastasis
8. Cancer as an independent organ is being recognized and should not be isolated from the nervous system
9. Clinical and biological implications for the role of the nervous system in cancer metastasis
10. Conclusions

1. Introduction

Since the 1970s, it has been generally accepted in the field of pathology that tumors lack innervation (1). However, the nervous system is a superordinate structure in the body and controls the functions and activities of virtually all other tissues and organs. Cancer tissues are not isolated structures within organisms, therefore they should also interact with the neural system. This speculation has been testified from clinical, epidemiological and experimental studies.

One the one hand, neural functions and tissues exert important functions on cancer initiation and development. Firstly, psychological and behavioral factors, such as chronic stress, depression and social isolation, are considered to contribute to the initiation and progression of certain types of cancer (2-6). Stress is inevitable in human life. The brain is the key organ of the response to stress (7). In the whole brain, activation of the hypothalamic-pituitary-adrenal axis (HPA) plays an important role in the response (2,7). Thus, acting on certain areas in the brain has been reported to influence the growth and development of cancer (8-10). Secondly, the peripheral nervous system is also involved in cancer. 6-Hydroxydopamine was shown to influence the growth rate of certain tumors (11) and induce neuronal changes on the sympathetic nervous system to augment the growth of neuroblastoma (12), suggesting that an intact functional sympathetic nervous system is necessary for certain tumors. Peripheral nerve fibers were found to innervate some tumors (13-16). Neurons of dorsal root ganglia interact with cancer cells (17-19). Denervation of a tumor also alters the behavior of tumor growth (20-22). Peripheral nerve invasion (PNI) induced by cancer is an independent factor for poor prognosis in some cancer patients (23-26).

Contents

1. Introduction
2. Search strategies and selection criteria
3. Connection, communication and interaction between the neural system and cancer cells
4. Nerve invasion is another route for cancer cell dissemination

Correspondence to: Dr Dongwei Gao, Department of Radiation Oncology, Lanzhou General Hospital of PLA, 333 Southern Binhe Road, Lanzhou, Gansu 730050, P.R. China
E-mail: gdw3152007@hotmail.com

Key words: nervous system, cancer metastasis

On the other hand, cancer also has remote effects on neural tissues (27-29). These facts indicate that there is a bidirectional correlation between the nervous system and cancer and challenge the traditional view that cancers lack innervation. Therefore, the role of the nervous system in cancer is gaining attention in cancer research (5, 29-31). Recently, the study by Sloan *et al* (32) study further showed that stress increases distant metastases but has little effect on primary tumor growth, prompting our interest in investigating the role of the nervous system in cancer metastasis.

It is well known that metastasis is the major cause of mortality from solid carcinomas. Despite great advances in metastasis research, the prognosis remains extremely poor. The formation of metastasis is a complex and sequential process, involving four basic steps: i) departure from the primary tumor, ii) survival in the circulatory system, iii) breaching of endothelium and basement membrane of target organs, and iv) establishment of a colony of metastatic cells (33). In these steps, immune functions, inflammation, organic microenvironments and bone marrow are involved (34-40), all of which are directly or indirectly regulated by the nervous system. Thus, cancer metastasis may also establish connections with the nervous system through these pathophysiological changes and functional organs. Therefore, the nervous system may play an essential role in cancer metastasis. To gain a more comprehensive understanding of the role of the nervous system in cancer metastasis, we reviewed English-language literature on this topic and analyzed how the nervous system exerts its functions in cancer metastasis.

2. Search strategies and selection criteria

The literature-based review was conducted by searching for keywords in Pubmed and Google Scholar using the search terms: 'cancer', 'tumor', 'neoplasm', 'malignant', 'metastasis', 'spread pathway', 'stress', 'depression', 'cancer-related neural disease', 'immune', 'inflammation', 'neuroendocrine', 'hypothalamic-pituitary-adrenal axis', 'innervation', 'nervous system', 'neurotransmitters', 'neurotrophic factors', 'semaphorins', 'psychoneuroimmunology', 'sympathetic', 'vagal' and 'vagus'. Only papers published in English prior to March 2012 and focusing on the association between the nervous system and cancer metastasis were included.

3. Connection, communication and interaction between the neural system and cancer cells

The nervous system is formed of the central and peripheral nervous systems, which modulate the functions of the whole body through two main methods. The first is that they have a direct connection through a specific structure of classical or non-classical synapses. The other is that they interact with each other through humoral modulations. If the two methods are also found in cancer, the connection between the nervous system and cancer will be established.

Classical and non-classical synapse structures are the elements by which neurons innervate other tissues. Several lines of evidence also support the existence of these anatomical structures in tumor tissues. Nerve fibers have been found in certain tumor tissues, which may be due to

i) the possibility of nerve fiber innervation vessels in cancer tissues, ii) the persistence of pre-existing nerves, or nerves becoming included within the cancer owing to the invasive character of its growth, iii) nerve endings growing into cancer tissue, or iv) an integral part of the cancerous growth (41). The first possibility was excluded in the study by Mitchell *et al* (42). Although the second possibility exists and often leads to cancer pain, this type of nerve fiber is surrounded by cancer tissues and hardly exerts any function on cancer cells. The latter two were also observed in previous studies. Nerve fibers in central tumor areas were observed by Seifert *et al* (13,14,43) using a transmission electron microscope. These nerve fibers in tumor tissues were irregularly distributed and had abnormal morphologies, which indicated that occurrences of these abnormal nerve fibers were accompanied with tumor tissues but not the pre-existing nerve fibers in corresponding normal tissues (44). Experimental studies showed that rectal cancer cells stimulated neurogenesis when they were cocultured with neuroepithelial cells (18). Thus, denervation by resection, capsaicin or vagotomy slows tumor growth (20-22) and promotes cancer progression and metastasis (45-47). These facts indicate that neuro-neoplastic synapses may exist between nerve fibers and tumor cells (48,49), and that neurogenesis, like angiogenesis, is also a trait of cancer cells (18,48,50,51). Thus, in primary and pre-metastatic organs, cancer cells actively establish connections with nerve fibers and receive signals from the nervous system.

Although the above studies indicated that tumor tissues were innervated, others do not support this theory (42,52,53). However, humoral modulation is the alternative means for the neural system to modulate other organs, which is also found in cancer. The axes of the systems of the HPA and autonomic nervous system (ANS) are typical pathways of humoral modulation through releasing hormones and neurotransmitters to bind corresponding receptors in other tissues to modulate functions of various tissues, including cancer. Thus, making lesions in these areas have significant effects on the behavior of cancer growth and metastasis. For example, Pollak *et al* (54) showed that hypophysectomy inhibited metastatic behavior in murine osteosarcoma. Function of the pineal gland and effect of spatial disorientation had an important influence on metastasis (55). These effects were mainly via humoral modulators, including neurotransmitters and neuropeptides, neurotrophic factors, semaphorins and other axon growth factors. These modulators of neural development and maintenance have been found to exert essential functions in cancer growth and development, and have been studied and reviewed by numerous authors (56-95). Cancer cells also express these molecules and their receptors. For example, breast cancer cells can express β -endorphin (96), and transplantation of β -endorphin neurons into the hypothalamus inhibit the growth and metastasis of mammary carcinoma (97). Cancer cells also promote neurite formation through generating neurotrophic factors and axon growth molecules (98). Thus, they will establish a connection with the nervous system through humoral modulation.

Thus, the existence of neuro-neoplastic synapses and receptors of neural markers in cancer cells provides a substantial basis for communication between neurons and cancer cells. Recent studies have shown that the nervous system influences the process of cancer metastasis through nerve endings and

humoral modulations (32,40,44-47,58,67,75-79,85,97,98). For cancer cells to form metastases in ectopic sites, they must depart from the primary tumor and conquer the barriers of primary tissue inhibition. Proteolytic enzymes can help tumor cells escape from primary cancer; i.e. by degrading the surrounding normal tissues. In this process, the overexpression of matrix metalloproteinases (MMPs) in tumor cells is one of the most sustained events (99,100); this may be induced by stress, neural-related factors and neurotransmitters. For example, Wu *et al* (101) reported that stress due to social isolation enhanced invasion and metastasis of colon cancer cells through increasing proteolytic proteases. Yang *et al* (102) also found that stress modulates levels of MMPs through activation of the HPA and sympathetic-adrenal medullary (SAM) axes. Heregulin- β 1 and nerve growth factor, as essential factors in the normal development of the nervous system, mediate the activation of MMP-9 and MMP-2 to promote invasion of breast cancer cells (103) and pancreatic cancer cells (104,105). Neurotrophins also promote invasion by enhancing the production of basement membrane-degradative enzymes (106). Norepinephrine (NE) and γ -aminobutyric acid as classical neurotransmitters upregulate the expression of MMPs in nasopharyngeal cancer cells (107) and cancer cells of the prostate (108). Anoikis, a form of apoptosis, results from loss of cell-matrix interactions and acts as a physiological barrier to metastasis (109). Tropomyosin receptor kinase B (TrkB), a receptor of brain-derived neurotrophic factor (BDNF), induces cancer metastasis by suppression of anoikis (110-112). Migration of cancer cells is a prerequisite for metastasis. Axon-guidance molecules, such as slits, semaphorins and netrins, can navigate or inhibit migration of cancer cells (77,85,113-117). The neurotransmitter/receptor system is also involved in cancer cell migration (118). NE, a classical neurotransmitter, has a stimulatory effect on the migration of colon carcinoma cells (119) and breast cancer cells (120). A similar role was also reported for dopamine and neuropeptides, including met-enkephalin, substance P and bombesin (120). γ -aminobutyric acid as an inhibitory neurotransmitter in the brain inhibits the migratory activity of colon carcinoma cells (121). Although these substances are also expressed in other organs (122) and tumor cells, inhibition of the activity of corresponding neurons can reverse their effects on cancer cells. For example, β -blockers acting on the ANS inhibit the migration of cancer cells induced by NE (119). Chemokines exerting important effects on neurogenesis and brain development (123,124) are also important modulators of cancer metastasis (125-127). In the process of cancer cell migration through the blood system, 99.9% of cancer cells are killed, which is called metastatic inefficiency (128). Mechanical forces including shear stress contribute to this inefficiency (129,130) while the shear force is mainly due to vasomotor changes. Nerve endings and receptors of neuropeptides are distributed in vascular walls (131). Based on the anatomical structures, the nervous system modulates the vascular functions, leading to changes in vascular dilation and constriction that can produce mechanical forces. Vascular permeability is important for cancer cell extravasation and colonization. Neuropeptides increase vascular permeability (132,133) to promote cancer cell extravasation and colonization. Thus, the process of cancer cell departure from the primary tumor,

invasion, migration, cancer cell inefficiency, extravasation and colonization are associated with the nervous system.

Therefore, the connections between the neural system and cancer through synapse, non-synapse or humoral modulation make it possible to establish reciprocal interactions and communications between cancers and neurons.

4. Nerve invasion is another route for cancer cell dissemination

Tumor dissemination from primary cancer is the first step in the formation of metastatic tumors at distant sites. Three major routes are considered to be involved in the spread of tumor cells: lymphatic vessels, blood vessels and serosal surfaces (130). The route of cancer cells along nerve fibers has been a forgotten pathway (134). Recently, PNI has been found in certain types of malignancies and identified to be another pathway for cancer cell dissemination, particularly in the absence of lymphatic or hematogenous metastasis (26). Although PNI has not been considered as a routine test in pathological reports, it has been identified as a key pathological feature in tumors and is used to predict clinical outcomes in many cancers (18,23-26,135-143).

It remains unknown what drives cancer cells to migrate along nerve fibers. In addition, since PNI has been accepted as an emerging route for cancer cell dissemination, PNI requires further definition. For the past 40 years, the predominant theory regarding the pathogenesis of PNI is that distributed tumor cells have the privilege of a low-resistance plane in the neural sheaths, which serves as a conduit for their migration. However, recent studies have shown that reciprocal signaling interactions between tumor cells and nerves may contribute to PNI. To explore these interactions, it is necessary to clarify the process of neurite formation. It has been shown that neurotrophic factors (NGF) and axonal guidance molecules are vital for axonal growth (144-149). These molecules and their corresponding receptors are also found in tumor cells (61,64,84,86,115), which provide the possibility for cancer cells to bind to the neurite (150). In addition, stromal cells, extracellular matrix and their releasing factors are also involved in the process of axonal formation (151), and are also important for tumor cell migration. Thus, these tumor cells spreading along neural fibers may acquire the ability to respond to proinvasive signals within the peripheral nerve milieu and become neurotrophic. It is known that nerve fibers are composed of three layers, the epineurium, perineurium and endoneurium, from the outside to the inside. According to the definition of Liebig *et al*, when tumor cells are found within any of the three layers of the nerve sheath or tumor foci outside of the nerve with involvement of 33% of the nerve's circumference, PNI may be diagnosed (26). This definition provides a new concept in the study of cancer cell dissemination.

5. The nervous system modulates angiogenesis and microenvironments in tumors and affects metastasis

Angiogenesis is vital for the development of metastasis (152-154). Vascular endothelial growth factor (VEGF) plays an important role in the process of angiogenesis. Several

reports have demonstrated that psychological factors influence tumor angiogenesis in certain types of cancer through regulating of VEGF level. Chronic stress is common in cancer patients and often causes depression and bad moods. It has been reported that chronic stress mediates the vascularization of intraperitoneal metastasis and enhances tumor angiogenesis in the xenograft models of ovarian cancer via increasing VEGF expression (155,156). SNS can be activated in stressed animals (155) and may release neurotransmitters. These neurotransmitters, such as NE, dopamine and bradykinin, have been reported to induce or suppress VEGF expression (132,158-161). Thus, the possible mechanism for chronic stress to enhance tumor angiogenesis may be that neurotransmitters released by activated SNS regulate VEGF expression to promote angiogenesis, which is also applicable to social isolation. It was reported that a perceived lack of social isolation was associated with elevated intratumoral NE in ovarian carcinoma patients. The elevated NE levels were correlated with high grade and advanced stage tumor (162) and indicated metastasis, which may be due to that NE induce VEGF expression and thus lead to stimulate angiogenesis (158). Other neural-related factors also have important effects on tumor angiogenesis. Axon growth molecules such as neuropilins and semaphorins can promote or inhibit angiogenesis (63,86,163-166). A neuropeptide, calcitonin gene-related peptide (CGRP), can facilitate tumor-associated angiogenesis (167). Although it is expressed by other tissues, this experiment testifies that it is derived from neuronal systems. Neuropeptide Y also promotes angiogenesis through regulation of VEGF (168). Circadian rhythm is a basic regulator of normal physiology. Its disruption can also accelerate tumor growth through a Wnt signaling pathway (169), a critical pathway to regulate angiogenesis (170,171). Thus, the neural system is capable of modulating the process of angiogenesis. Moreover, neurogenesis also exists as a trait of certain types of cancer. Cancer cells also express these neural-related factors and their receptors. In fact, there are common molecules between angiogenesis and neurogenesis (172-174), indicating that they may occur in concert in tumors and collectively exert functions on cancer metastasis (175).

The microenvironment regulates not only the growth of primary cancer but also the formation of metastasis, which is formed mainly of stromal cells and signal molecules. On the one hand, these cells and molecules have a direct or indirect correlation with the nervous system (73). Within the tumor microenvironment, stromal cells express β -adrenergic receptors that may be activated by neurotransmitters from local sympathetic nerve fibers and circulating blood. Macrophages in tumor microenvironments are important players in cancer metastasis, and are the key targets of β -adrenergic regulation in several cancer contexts (73). Certain molecules produced and released by neural tissues are the important origins of signals in the tumor microenvironment (176). However, stromal and tumor cells produce neural-related factors to stimulate neurite formation, receive nervous signals and act on the nervous system. Thus, cancer cells are able to take advantage of the factors produced by the nerve fibers to generate a positive microenvironment for cell survival and proliferation in the primary site and secondary organ. Therefore, the microenvironments and neural system establish a feedback loop. They

also collectively contribute to the growth of primary cancer and the secondary tumor.

6. Nervous system interacts with immune function and inflammation to influence cancer metastasis

The immune system has been identified to play a vital role in cancer metastasis (35,177,178). The association between the immune system and the nervous system has been widely studied and reviewed by many neurobiologists and immunologists (179,180). Several pathways are involved in the interaction between them. Among them, the neuroendocrine and neuronal pathways are the most significant, and are involved in the control of the humoral and cellular immune responses including the immunosuppressive effect, immunosurveillance and immunoenhancement. However, the immune system also influences the central nervous system. The bidirectional neural-immune interactions mainly occur through the neural and immune signal molecules including hormones, neurotransmitters, neuropeptides, cytokines or their receptors, all of which have been demonstrated to contribute to the process of metastasis (181-183). Thus, the neural system modulates cancer metastasis through the immune system. For example, mood disorders, such as stress and depression, inhibit the immune system by decreasing cytotoxic T-cell and natural killer (NK) cells involved in innate immunity that can surveil for cancer metastasis (2). Therefore, stress enhances tumor metastasis via suppression of the immune system (184,185). It also has been identified that mood and relevant immunological status, along with important biological prognostic variables may contribute to the notable outcome variance in early-stage breast cancer (186). Circadian rhythm modulates the immune system by conveying timing information. Circadian disruption may lead to vulnerability to infection and other diseases, including cancer (187,188). Therefore, the nervous system and its psychological or behavioral factors modulate metastasis through immune molecules, cells and effects (189).

The immune effect can induce an inflammatory response. However, unlike the association between the nervous system and immune system, the role of the nervous system in inflammation has only recently been described. It was also found that as well as controlling heart rate and other vital functions in real time, the nervous system reflexively regulates the inflammatory response (190,191). The vagus nerve, the arc of the reflex and neural-related factors such as netrin-1 and neuropeptides, are all involved in the control of inflammation (131,192-200). Thus, the nervous system modulation of cancer development via inflammatory responses has been recognized. Inflammation has been thought to be a driving force for cancer metastasis (36). The inflammatory cells and pathways are the players in cancer metastasis. These players are reported to be influenced by the nervous system. Macrophages are key players not only for inflammation but also metastasis, and are regulated by neuromediators (196,198). Stress has been demonstrated to increase the level of IL-6 (201), which is a proinflammatory factor and plays an important role in cancer metastasis. NE and β -adrenergic receptors that can be induced by stress also regulate IL-6 (202,203). The transcription factor NF- κ B is a significant inflammatory factor that has been identified to play a role in cancer development and metas-

tasis (183,204). The neuronal guidance molecule netrin-1 is a direct transcriptional target of NF- κ B and demonstrates upregulation under inflammatory conditions (205). Therefore, the nervous system modulates cancer metastasis through immunity and inflammation.

7. Interactions between bone marrow and nervous system: implication for cancer metastasis

A recent discovery revealed the mechanism of bone marrow recruiting disseminated tumor cells (206). Moreover, it also plays an important role in sustaining tumor angiogenesis (207), microenvironment (208,209) and formation of the pre-niche for cancer cells arriving in pre-metastatic organs (210,211). Bone marrow recruits disseminated tumor cells by a recently discovered mechanism (206). It has been found that bone marrow can be innervated by the nervous system, including the ANS and noradrenergic sympathetic nerve fibers (212-216). Preprotachykinin-I (PPT-I) peptides, a family of neuropeptides released by the ANS, are hematopoietic modulators and are highly expressed in cancer cells, which may explain the early integration of cancer cells in the bone marrow (217,218). Progenitor cells of bone marrow may contribute to tumor vascularization (207,219,220). The neurotransmitter dopamine regulates the process of mobilization of endothelial progenitor cells from bone marrow to tumor (221). Stromal cells of the bone marrow are an important source of tumor microenvironments (222), including formation of the pre-metastatic niche in metastatic organs. For example, tumor macrophages, which are derived from bone marrow, contribute to metastasis (223-225). During migration, they are navigated by the nervous system (226-228). Bone marrow stem cells play an important role in the repair of tissue injury, and are also thought to contribute to neurogenesis in cancer (50). They migrate from bone marrow to a terminal, then lodge and mature in the terminal under the control of the nervous system (228,229). Therefore, the role of bone marrow in cancer metastasis is modulated by the nervous system.

8. Cancer as an independent organ is being recognized and should not be isolated from the nervous system

As cancer is formed of cancer cells and their surrounding tissues, and there are interactions between tumor cells and their micro- and macroenvironment, cancer is now being considered as a new organ or an independent structure in the body (230). Egeblad *et al* (231) considered tumors to be independent from other organs in the whole organism. This cancer organ is comprised of tumor cells, extracellular matrix, stromal cells and vessels. Although these components are abnormal, they can be organized into a new organ in a pathophysiological manner, which further exchanges and interacts with other organs. Thus, metastasis is viewed to be a result of the interactions between the tumor and the rest of the body. Mareel *et al* (232) viewed cancer as an ecosystem inside a living organism. The ecosystem comprises the primary tumor, lymph node and distant metastasis, bone marrow, blood and lymph circulation. The five elements constitute a vicious circle and interact with each other, finally leading to an influence on the whole system. Egeblad *et al* and Mareel *et al* had different views on cancer but shared

the understanding that cancer is an independent system from other organ systems of the body. In this system, the components exchange information and communicate with other systems. However, these two views do not refer to the nerve system. It is well known that the constitutive elements of organs as well as microecosystems are all under the control of nervous system. In the process of metastasis, these elements exchange information with the nervous system. More importantly, the role of the neural system cannot be replaced by other systems. As a central system, it processes and stores information released by cancer cells. In clinical phenomena of cancer metastasis, metastatic tumors still resemble their primary cancers even after decades of dormancy. Comparisons between primary tumors and matched metastasis reveals similarities both at cancer cell and stromal levels, which may be modulated by the neural system.

9. Clinical and biological implications for the role of nervous system in cancer metastasis

From the above findings, we can conclude that the neural system has an important influence on cancer metastasis. Stress, depression and social isolation as psychological factors have been reported to promote distant metastasis, which is due to them suppressing immune functions (185), promoting angiogenesis, activating macrophages and releasing proinflammatory factors, such as IL-6 (201) and TNF- α (101) and acting on the HPA and ANS (3,233) to release neurotransmitters (234). Circadian rhythm also influences distant metastasis through modulation of angiogenesis (235), the HPA and the immune system (187,236,237). The brain modulates cancer development including cancer metastasis through the vagus nerve (45). It has significant biological and clinical relevance.

Firstly, stress is a common phenomenon and prompts cancer metastasis, indicating that suppressing stress and modulating mood will be helpful for cancer patients (234,238). Thus, psychologically effective interventions on individuals with a variety of cancers can be resistant to cancer progression and improve clinical outcome for advanced cancer patients (239). Secondly, PNI offers another pathway for the spread of cancer cells. Determining the mechanism of PNI may provide additional options for the prevention and treatment of metastasis by inhibiting the pathway. Thirdly, neoangiogenesis and neurogenesis may exert their effects in concert on cancer metastasis. Inhibition of neoangiogenesis alone has little and even reverse effects on treating metastasis (240). For example, VEGF inhibitors have been reported to have no value in metastatic breast cancer (241) and even enhance metastasis in animal studies (240,242). Establishing the common molecules between the two types of genesis in cancer tissues and identify them as new targets is likely to aid in treating cancer metastasis. Fourthly, modulating the activities of the nervous system has an important influence on cancer metastasis. The brain is able to show functional or pathological changes when other organs in the whole organism are affected by cancer. The monitoring of these changes in the brain may be a new diagnostic approach to detect tumorigenesis and cancer recurrence. The vagus nerve is central in the response to extrinsic and intrinsic stressors and receiving the signals of the brain and other visceral organs, including cancer. Thus, inhibition of the activity of the vagus

nerve is another strategy to prevent cancer metastasis (243-245). For example, β -blockers are being considered to be a novel adjuvant to existing therapeutic strategies in clinical oncology (73). Finally, as important modulators in the nervous system and cancer, neurotrophic factors, neuropilins, axonal guidance molecules, neurotransmitters and their receptors are being considered to exploit new drugs to be used to treat metastasis (78,82,111,165,234,246-250).

The study of metastasis is multifaceted (251). Numerous investigators have devoted themselves to metastasis from their own profession. Although their studies have made great advances, a number of questions remain to be addressed. The connection between the neural system and cancer that we propose in this review is not based on analogy of the association between the nervous system and the immune system but on current studies. The aim of this review was to aid individuals to gain a deeper understanding of cancer metastasis to a certain extent. Although it may not produce major breakthroughs in cancer metastasis, the role of the nervous system in cancer metastasis should not be neglected.

10. Conclusions

In conclusion, the possible existing synapses in tumor cells and neural-related factors, such as neurotrophic factors and neurotransmitters, make it possible to establish direct connections between the nervous system and cancer. PNI offers another pathway for cancer cell distribution. On an anatomical basis, the nervous system is involved in the processes of metastasis, including tumor cell growth, proliferation, angiogenesis, apoptosis, departure from primary cancer, migration, extravasation and colonization, metastatic inefficiency, and modulators of cancer metastasis such as immunity, inflammation and bone marrow. Therefore, the nervous system plays an important role in cancer metastasis. Understanding its mechanism has important implications for exploring the biology of metastasis and the management of cancer metastasis.

References

- Willis RA: The Spread of Tumors in the Human Body. 3rd edition. Butterworths, London, 1973.
- Reiche EM, Nunes SO and Morimoto HK: Stress, depression, the immune system, and cancer. *Lancet Oncol* 5: 617-625, 2004.
- Lutgendorf SK and Sood AK: Biobehavioral factors and cancer progression: physiological pathways and mechanisms. *Psychosom Med* 73: 724-730, 2011.
- Thaker PH and Sood AK: Neuroendocrine influences on cancer biology. *Semin Cancer Biol* 18: 164-170, 2008.
- Armaiz-Pena GN, Lutgendorf SK, Cole SW and Sood AK: Neuroendocrine modulation of cancer progression. *Brain Behav Immun* 23: 10-15, 2009.
- Williams JB, Pang D, Delgado B, Kocherginsky M, Tretiakova M, Krausz T, Pan D, He J, McClintock MK and Conzen SD: A model of gene-environment interaction reveals altered mammary gland gene expression and increased tumor growth following social isolation. *Cancer Prev Res (Phila)* 2: 850-861, 2009.
- McEwen BS: Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev* 87: 873-904, 2007.
- Toh YC: Inhibitory effect of hypothalamic lesions on liver tumor induction by N-2-fluorenylacetic acid in male rats. *Cancer Res* 38: 42-51, 1978.
- Karasek M and Pawlikowski M: Pineal gland, melatonin and cancer. *NEL Review. Neuro Endocrinol Lett* 20: 139-144, 1999.
- Bruni JE and Montemurro DG: Effect of hypothalamic lesions on the genesis of spontaneous mammary gland tumors in the mouse. *Cancer Res* 31: 854-863, 1971.
- Chelmicka-Szorc E and Arnason BG: Effect of 6-hydroxydopamine on tumor growth. *Cancer Res* 36: 2382-2384, 1976.
- Chelmicka-Szorc E and Arnason BG: Modulatory effect of the sympathetic nervous system on neuroblastoma tumor growth. *Cancer Res* 38: 1374-1375, 1978.
- Seifert P and Spitznas M: Tumours may be innervated. *Virchows Arch* 438: 228-231, 2001.
- Seifert P, Benedic M and Effert P: Nerve fibers in tumors of the human urinary bladder. *Virchows Arch* 440: 291-297, 2002.
- Lu SH, Zhou Y, Que HP and Liu SJ: Peptidergic innervation of human esophageal and cardiac carcinoma. *World J Gastroenterol* 9: 399-403, 2003.
- Liang YJ, Zhou P, Wongba W, Guardiola J, Walker J and Yu J: Pulmonary innervation, inflammation and carcinogenesis. *Sheng Li Xue Bao* 62: 191-195, 2010.
- Li JH, Ma QY, Shen SG and Hu HT: Stimulation of dorsal root ganglion neurons activity by pancreatic cancer cell lines. *Cell Biol Int* 32: 1530-1535, 2008.
- Albo D, Akay CL, Marshall CL, Wilks JA, Verstovsek G, Liu H, Agarwal N, Berger DH and Ayala GE: Neurogenesis in colorectal cancer is a marker of aggressive tumor behavior and poor outcomes. *Cancer* 117: 4834-4845, 2011.
- Ayala GE, Wheeler TM, Shine HD, Schmelz M, Frolov A, Chakraborty S and Rowley D: In vitro dorsal root ganglia and human prostate cell line interaction: redefining perineural invasion in prostate cancer. *Prostate* 49: 213-223, 2001.
- Batkin S, Piette LH and Wildman E: Effect of muscle denervation on growth of transplanted tumor in mice. *Proc Natl Acad Sci USA* 67: 1521-1527, 1970.
- Papageorgiou A, Trontzos C, Kallistratos H, Kokkas B, Grigoriadis N and Grammaticos P: Slowing growth and histology changes in Lewis lung carcinoma implanted in a partly denervated muscle. *Cancer Invest* 21: 869-872, 2003.
- Romeo HE, Colombo LL, Esquifino AI, Rosenstein RE, Chuluyan HE and Cardinali DP: Slower growth of tumours in sympathetically denervated murine skin. *J Auton Nerv Syst* 32: 159-164, 1991.
- Peng J, Sheng W, Huang D, Venook AP, Xu Y, Guan Z and Cai S: Perineural invasion in pT3N0 rectal cancer: the incidence and its prognostic effect. *Cancer* 117: 1415-1421, 2011.
- Feng FY, Qian Y, Stenmark MH, Halverson S, Blas K, Vance S, Sandler HM and Hamstra DA: Perineural invasion predicts increased recurrence, metastasis, and death from prostate cancer following treatment with dose-escalated radiation therapy. *Int J Radiat Oncol Biol Phys* 81: e361-e367, 2011.
- Poeschl EM, Pollheimer MJ, Kornprat P, Lindtner RA, Schlemmer A, Rehak P, Vieth M and Langner C: Perineural invasion: correlation with aggressive phenotype and independent prognostic variable in both colon and rectum cancer. *J Clin Oncol* 28: e358-e360, e361-e362, 2010.
- Liebig C, Ayala G, Wilks JA, Berger DH and Albo D: Perineural invasion in cancer: a review of the literature. *Cancer* 115: 3379-3391, 2009.
- Khasraw M and Posner JB: Neurological complications of systemic cancer. *Lancet Neurol* 9: 1214-1227, 2010.
- Toothaker TB and Rubin M: Paraneoplastic neurological syndromes: a review. *Neurologist* 15: 21-33, 2009.
- Mravec B, Gidron Y and Hulin I: Neurobiology of cancer: Interactions between nervous, endocrine and immune systems as a base for monitoring and modulating the tumorigenesis by the brain. *Semin Cancer Biol* 18: 150-163, 2008.
- Entschladen F, Palm D, Niggemann B and Zaenker KS: The cancer's nervous tooth: Considering the neuronal crosstalk within tumors. *Semin Cancer Biol* 18: 171-175, 2008.
- Ondicova K and Mravec B: Role of nervous system in cancer aetiopathogenesis. *Lancet Oncol* 11: 596-601, 2010.
- Sloan EK, Priceman SJ, Cox BF, Yu S, Pimentel MA, Tangkanangnukul V, Arevalo JM, Morizono K, Karanikolas BD, Wu L, Sood AK and Cole SW: The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res* 70: 7042-7052, 2010.
- Gupta GP and Massague J: Cancer metastasis: building a framework. *Cell* 127: 679-695, 2006.
- de Visser KE, Eichten A and Coussens LM: Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer* 6: 24-37, 2006.

35. DeNardo DG, Johansson M and Coussens LM: Immune cells as mediators of solid tumor metastasis. *Cancer Metastasis Rev* 27: 11-18, 2008.
36. Wu Y and Zhou BP: Inflammation: a driving force speeds cancer metastasis. *Cell Cycle* 8: 3267-3273, 2009.
37. Solinas G, Marchesi F, Garlanda C, Mantovani A and Allavena P: Inflammation-mediated promotion of invasion and metastasis. *Cancer Metastasis Rev* 29: 243-248, 2010.
38. Nguyen DX, Bos PD and Massague J: Metastasis: from dissemination to organ-specific colonization. *Nat Rev Cancer* 9: 274-284, 2009.
39. Sung SY, Hsieh CL, Wu D, Chung LW and Johnstone PA: Tumor microenvironment promotes cancer progression, metastasis, and therapeutic resistance. *Curr Probl Cancer* 31: 36-100, 2007.
40. Calorini L and Bianchini F: Environmental control of invasiveness and metastatic dissemination of tumor cells: the role of tumor cell-host cell interactions. *Cell Commun Signal* 8: 24, 2010.
41. Shapiro DM and Warren S: Cancer innervation. *Cancer Res* 9: 707-711, 1949.
42. Mitchell BS, Schumacher U, Stauber VV and Kaiserling E: Are breast tumours innervated? Immunohistological investigations using antibodies against the neuronal marker protein gene product 9.5 (PGP 9.5) in benign and malignant breast lesions. *Eur J Cancer* 30A: 1100-1103, 1994.
43. Seifert P and Spitznas M: Axons in human choroidal melanoma suggest the participation of nerves in the control of these tumors. *Am J Ophthalmol* 133: 711-713, 2002.
44. Feng F, Yang J, Tong L, Yuan S, Tian Y, Hong L, Wang W and Zhang H: Substance P immunoreactive nerve fibres are related to gastric cancer differentiation status and could promote proliferation and migration of gastric cancer cells. *Cell Biol Int* 35: 623-629, 2011.
45. Gidron Y, Perry H and Glennie M: Does the vagus nerve inform the brain about preclinical tumours and modulate them? *Lancet Oncol* 6: 245-248, 2005.
46. Erin N, Boyer PJ, Bonneau RH, Clawson GA and Welch DR: Capsaicin-mediated denervation of sensory neurons promotes mammary tumor metastasis to lung and heart. *Anticancer Res* 24: 1003-1009, 2004.
47. Erin N, Akdas BG, Harms JF and Clawson GA: Vagotomy enhances experimental metastases of 4THMpc breast cancer cells and alters substance P level. *Regul Pept* 151: 35-42, 2008.
48. Palm D and Entschladen F: Neoneurogenesis and the neuro-neoplastic synapse. *Prog Exp Tumor Res* 39: 91-98, 2007.
49. Zanker KS: The neuro-neoplastic synapse: does it exist? *Prog Exp Tumor Res* 39: 154-161, 2007.
50. Varner JA: Stem cells and neurogenesis in tumors. *Prog Exp Tumor Res* 39: 122-129, 2007.
51. Ayala GE, Dai H, Powell M, Li R, Ding Y, Wheeler TM, Shine D, Kadmon D, Thompson T, Miles BJ, Ittmann MM and Rowley D: Cancer-related axonogenesis and neurogenesis in prostate cancer. *Clin Cancer Res* 14: 7593-7603, 2008.
52. Mitchell BS, Schumacher U and Kaiserling E: Are tumours innervated? Immunohistological investigations using antibodies against the neuronal marker protein gene product 9.5 (PGP 9.5) in benign, malignant and experimental tumours. *Tumour Biol* 15: 269-274, 1994.
53. Terada T and Matsunaga Y: S-100-positive nerve fibers in hepatocellular carcinoma and intrahepatic cholangiocarcinoma: an immunohistochemical study. *Pathol Int* 51: 89-93, 2001.
54. Pollak M, Sem AW, Richard M, Tetenes E and Bell R: Inhibition of metastatic behavior of murine osteosarcoma by hypophysectomy. *J Natl Cancer Inst* 84: 966-971, 1992.
55. Giraldo T, Perissin L, Zorzet S, Rapozzi V and Rodani MG: Metastasis and neuroendocrine system in stressed mice. *Int J Neurosci* 74: 265-278, 1994.
56. Marchetti B, Spinola PG, Pelletier G and Labrie F: A potential role for catecholamines in the development and progression of carcinogen-induced mammary tumors: hormonal control of beta-adrenergic receptors and correlation with tumor growth. *J Steroid Biochem Mol Biol* 38: 307-320, 1991.
57. Fava G, Marucci L, Glaser S, Francis H, De Morrow S, Benedetti A, Alvaro D, Venter J, Meininger C, Patel T, Taffetani S, Marzioni M, Summers R, Reichenbach R and Alpini G: Gamma-Aminobutyric acid inhibits cholangiocarcinoma growth by cyclic AMP-dependent regulation of the protein kinase A/extracellular signal-regulated kinase 1/2 pathway. *Cancer Res* 65: 11437-11446, 2005.
58. Al-Wadei HA, Plummer HK III and Schuller HM: Nicotine stimulates pancreatic cancer xenografts by systemic increase in stress neurotransmitters and suppression of the inhibitory neurotransmitter gamma-aminobutyric acid. *Carcinogenesis* 30: 506-511, 2009.
59. Yamanaka Y, Mammoto T, Kirita T, Mukai M, Mashimo T, Sugimura M, Kishi Y and Nakamura H: Epinephrine inhibits invasion of oral squamous carcinoma cells by modulating intracellular cAMP. *Cancer Lett* 176: 143-148, 2002.
60. Wang T, Huang W and Chen F: Baclofen, a GABAB receptor agonist, inhibits human hepatocellular carcinoma cell growth in vitro and in vivo. *Life Sci* 82: 536-541, 2008.
61. Ellis LM: The role of neuropilins in cancer. *Mol Cancer Ther* 5: 1099-1107, 2006.
62. Rizzolio S and Tamagnone L: Multifaceted role of neuropilins in cancer. *Curr Med Chem* 18: 3563-3575, 2011.
63. Kreuter M, Bielenberg D, Hida Y, Hida K and Klagsbrun M: Role of neuropilins and semaphorins in angiogenesis and cancer. *Ann Hematol* 81 (Suppl 2): S74, 2002.
64. Chedotal A, Kerjan G and Moreau-Fauvarque C: The brain within the tumor: new roles for axon guidance molecules in cancers. *Cell Death Differ* 12: 1044-1056, 2005.
65. Nakagawara A: Trk receptor tyrosine kinases: a bridge between cancer and neural development. *Cancer Lett* 169: 107-114, 2001.
66. Wong HP, Ho JW, Koo MW, Yu L, Wu WK, Lam EK, Tai EK, Ko JK, Shin VY, Chu KM and Cho CH: Effects of adrenaline in human colon adenocarcinoma HT-29 cells. *Life Sci* 88: 1108-1112, 2011.
67. Marin YE and Chen S: Involvement of metabotropic glutamate receptor 1, a G protein coupled receptor, in melanoma development. *J Mol Med (Berl)* 82: 735-749, 2004.
68. Castro-Rivera E, Ran S, Brekken RA and Minna JD: Semaphorin 3B inhibits the phosphatidylinositol 3-kinase/Akt pathway through neuropilin-1 in lung and breast cancer cells. *Cancer Res* 68: 8295-8303, 2008.
69. Kigel B, Varshavsky A, Kessler O and Neufeld G: Successful inhibition of tumor development by specific class-3 semaphorins is associated with expression of appropriate semaphorin receptors by tumor cells. *PLoS One* 3: e3287, 2008.
70. Pisick E, Jagadeesh S and Salgia R: Receptor tyrosine kinases and inhibitors in lung cancer. *Scientific World Journal* 4: 589-604, 2004.
71. Muller JM: Potential inhibition of the neuro-neoplastic interactions: the clue of a GPCR-targeted therapy. *Prog Exp Tumor Res* 39: 130-153, 2007.
72. Fitzgerald PJ: Is norepinephrine an etiological factor in some types of cancer? *Int J Cancer* 124: 257-263, 2009.
73. Cole SW and Sood AK: Molecular pathways: beta-adrenergic signaling pathways in cancer. *Clin Cancer Res* 18: 1201-1206, 2011.
74. Al-Wadei HA, Plummer HK III, Ullah MF, Unger B, Brody JR and Schuller HM: Social stress promotes and gamma-aminobutyric acid inhibits tumor growth in mouse models of non-small cell lung cancer. *Cancer Prev Res (Phila)* 5: 189-196, 2012.
75. Casazza A, Kigel B, Maione F, Capparuccia L, Kessler O, Giraudo E, Mazzone M, Neufeld G and Tamagnone L: Tumour growth inhibition and anti-metastatic activity of a mutated furin-resistant Semaphorin 3E isoform. *EMBO Mol Med* 4: 234-250, 2012.
76. Erin N, Zhao W, Bylander J, Chase G and Clawson G: Capsaicin-induced inactivation of sensory neurons promotes a more aggressive gene expression phenotype in breast cancer cells. *Breast Cancer Res Treat* 99: 351-364, 2006.
77. Nasarre P, Potiron V, Drabkin H and Roche J: Guidance molecules in lung cancer. *Cell Adh Migr* 4: 130-145, 2010.
78. Weick A and Augustin HG: Double attack on tumors by targeting with guidance molecules. *Arterioscler Thromb Vasc Biol* 31: 721-722, 2011.
79. Bernet A and Fitamant J: Netrin-1 and its receptors in tumour growth promotion. *Expert Opin Ther Targets* 12: 995-1007, 2008.
80. Schuller HM and Al-Wadei HA: Neurotransmitter receptors as central regulators of pancreatic cancer. *Future Oncol* 6: 221-228, 2010.
81. Novotny A, Ryberg K, Heiman UJ, Nilsson L, Khorram-Manesh A, Nordgren S, Delbro DS and Nylund G: Is acetylcholine a signaling molecule for human colon cancer progression? *Scand J Gastroenterol* 46: 446-455, 2011.
82. Al-Wadei HA, Al-Wadei MH and Schuller HM: Cooperative regulation of non-small cell lung carcinoma by nicotinic and beta-adrenergic receptors: a novel target for intervention. *PLoS One* 7: e29915, 2012.

83. Al-Wadei HA, Ullah MF and Al-Wadei M: GABA (γ -aminobutyric acid), a non-protein amino acid counters the β -adrenergic cascade-activated oncogenic signaling in pancreatic cancer: a review of experimental evidence. *Mol Nutr Food Res* 55: 1745-1758, 2011.
84. Neufeld G, Shraga-Heled N, Lange T, Guttman-Raviv N, Herzog Y and Kessler O: Semaphorins in cancer. *Front Biosci* 10: 751-760, 2005.
85. Rizzolio S and Tamagnone L: Semaphorin signals on the road to cancer invasion and metastasis. *Cell Adh Migr* 1: 62-68, 2007.
86. Chen C, Li M, Chai H, Yang H, Fisher WE and Yao Q: Roles of neuropilins in neuronal development, angiogenesis, and cancers. *World J Surg* 29: 271-275, 2005.
87. Baba T, Kariya M, Higuchi T, Mandai M, Matsumura N, Kondoh E, Miyaniishi M, Fukuhara K, Takakura K and Fujii S: Neuropilin-1 promotes unlimited growth of ovarian cancer by evading contact inhibition. *Gynecol Oncol* 105: 703-711, 2007.
88. Warrington RJ and Lewis KE: Natural antibodies against nerve growth factor inhibit in vitro prostate cancer cell metastasis. *Cancer Immunol Immunother* 60: 187-195, 2011.
89. Arakawa H: Netrin-1 and its receptors in tumorigenesis. *Nat Rev Cancer* 4: 978-987, 2004.
90. Kalariti N, Pissimissis N and Koutsilieris M: The glutamatergic system outside the CNS and in cancer biology. *Expert Opin Investig Drugs* 14: 1487-1496, 2005.
91. Watanabe M, Maemura K, Oki K, Shiraiishi N, Shibayama Y and Katsu K: Gamma-aminobutyric acid (GABA) and cell proliferation: focus on cancer cells. *Histol Histopathol* 21: 1135-1141, 2006.
92. Chang HJ, Yoo BC, Lim SB, Jeong SY, Kim WH and Park JG: Metabotropic glutamate receptor 4 expression in colorectal carcinoma and its prognostic significance. *Clin Cancer Res* 11: 3288-3295, 2005.
93. Park SY, Lee SA, Han IH, Yoo BC, Lee SH, Park JY, Cha IH, Kim J and Choi SW: Clinical significance of metabotropic glutamate receptor 5 expression in oral squamous cell carcinoma. *Oncol Rep* 17: 81-87, 2007.
94. Palma C: Tachykinins and their receptors in human malignancies. *Curr Drug Targets* 7: 1043-1052, 2006.
95. Ruscica M, Dozio E, Motta M and Magni P: Relevance of the neuropeptide Y system in the biology of cancer progression. *Curr Top Med Chem* 7: 1682-1691, 2007.
96. Chatikhine VA, Delpech B, Duval C, Chauzy C, D'Aniou J and Chevrier A: Expression of beta-endorphin in human breast cancer and adenofibromas. *Ann NY Acad Sci* 680: 473-475, 1993.
97. Sarkar DK, Zhang C, Murugan S, Dokur M, Boyadjieva NI, Ortiguera M, Reuhl KR and Mojtehdzadeh S: Transplantation of beta-endorphin neurons into the hypothalamus promotes immune function and restricts the growth and metastasis of mammary carcinoma. *Cancer Res* 71: 6282-6291, 2011.
98. Mancino M, Ametller E, Gascon P and Almendro V: The neuronal influence on tumor progression. *Biochim Biophys Acta* 1816: 105-118, 2011.
99. MacDougall JR and Matrisian LM: Contributions of tumor and stromal matrix metalloproteinases to tumor progression, invasion and metastasis. *Cancer Metastasis Rev* 14: 351-362, 1995.
100. Deryugina EI and Quigley JP: Matrix metalloproteinases and tumor metastasis. *Cancer Metastasis Rev* 25: 9-34, 2006.
101. Wu W, Yamaura T, Murakami K, Ogasawara M, Hayashi K, Murata J and Saiki I: Involvement of TNF- α in enhancement of invasion and metastasis of colon 26-L5 carcinoma cells in mice by social isolation stress. *Oncol Res* 11: 461-469, 1999.
102. Yang EV, Bane CM, MacCallum RC, Kiecolt-Glaser JK, Malarkey WB and Glaser R: Stress-related modulation of matrix metalloproteinase expression. *J Neuroimmunol* 133: 144-150, 2002.
103. Yao J, Xiong S, Klos K, Nguyen N, Grijalva R, Li P and Yu D: Multiple signaling pathways involved in activation of matrix metalloproteinase-9 (MMP-9) by heregulin-beta1 in human breast cancer cells. *Oncogene* 20: 8066-8074, 2001.
104. Okada Y, Eibl G, Guha S, Duffy JP, Reber HA and Hines OJ: Nerve growth factor stimulates MMP-2 expression and activity and increases invasion by human pancreatic cancer cells. *Clin Exp Metastasis* 21: 285-292, 2004.
105. Okada Y, Eibl G, Duffy JP, Reber HA and Hines OJ: Glial cell-derived neurotrophic factor upregulates the expression and activation of matrix metalloproteinase-9 in human pancreatic cancer. *Surgery* 134: 293-299, 2003.
106. Menter DG, Herrmann JL and Nicolson GL: The role of trophic factors and autocrine/paracrine growth factors in brain metastasis. *Clin and Exp Metastasis* 13: 67-88, 1995.
107. Yang EV, Sood AK, Chen M, Li Y, Eubank TD, Marsh CB, Jewell S, Flavahan NA, Morrison C, Yeh PE, Lemeshow S and Glaser R: Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. *Cancer Res* 66: 10357-10364, 2006.
108. Azuma H, Inamoto T, Sakamoto T, Kiyama S, Ubai T, Shinohara Y, Maemura K, Tsuji M, Segawa N, Masuda H, Takahara K, Katsuoka Y and Watanabe M: Gamma-aminobutyric acid as a promoting factor of cancer metastasis; induction of matrix metalloproteinase production is potentially its underlying mechanism. *Cancer Res* 63: 8090-8096, 2003.
109. Simpson CD, Anyiwe K and Schimmer AD: Anoikis resistance and tumor metastasis. *Cancer Lett* 272: 177-185, 2008.
110. Douma S, Van Laar T, Zevenhoven J, Meuwissen R, Van Garderen E and Peeper DS: Suppression of anoikis and induction of metastasis by the neurotrophic receptor TrkB. *Nature* 430: 1034-1039, 2004.
111. Geiger TR and Peeper DS: The neurotrophic receptor TrkB in anoikis resistance and metastasis: a perspective. *Cancer Res* 65: 7033-7036, 2005.
112. Geiger TR and Peeper DS: Critical role for TrkB kinase function in anoikis suppression, tumorigenesis, and metastasis. *Cancer Res* 67: 6221-6229, 2007.
113. Strizzi L, Bianco C, Raafat A, Abdallah W, Chang C, Raafat D, Hirota M, Hamada S, Sun Y, Normanno N, Callahan R, Hinck L and Salomon D: Netrin-1 regulates invasion and migration of mouse mammary epithelial cells overexpressing Cripto-1 in vitro and in vivo. *J Cell Sci* 118: 4633-4643, 2005.
114. Christensen C, Ambartsumian N, Gilestro G, Thomsen B, Comoglio P, Tamagnone L, Guldberg P and Lukanidin E: Proteolytic processing converts the repelling signal Sema3E into an inducer of invasive growth and lung metastasis. *Cancer Res* 65: 6167-6177, 2005.
115. Kruger RP, Aurandt J and Guan KL: Semaphorins command cells to move. *Nat Rev Mol Cell Biol* 6: 789-800, 2005.
116. Kim HK, Zhang H, Li H, Wu TT, Swisher S, He D, Wu L, Xu J, Elmetts CA, Athar M, Xu XC and Xu H: Slit2 inhibits growth and metastasis of fibrosarcoma and squamous cell carcinoma. *Neoplasia* 10: 1411-1420, 2008.
117. Casazza A, Finisguerra V, Capparuccia L, Camperi A, Swiercz JM, Rizzolio S, Rolny C, Christensen C, Bertotti A, Sarotto I, Risio M, Trusolino L, Weitz J, Schneider M, Mazzone M, Comoglio PM and Tamagnone L: Sema3E-Plexin D1 signaling drives human cancer cell invasiveness and metastatic spreading in mice. *J Clin Invest* 120: 2684-2698, 2010.
118. Entschladen F, Lang K, Drell TL, Joseph J and Zaenker KS: Neurotransmitters are regulators for the migration of tumor cells and leukocytes. *Cancer Immunol Immunother* 51: 467-482, 2002.
119. Masur K, Niggemann B, Zanker KS and Entschladen F: Norepinephrine-induced migration of SW 480 colon carcinoma cells is inhibited by beta-blockers. *Cancer Res* 61: 2866-2869, 2001.
120. Drell TT, Joseph J, Lang K, Niggemann B, Zaenker KS and Entschladen F: Effects of neurotransmitters on the chemokinesis and chemotaxis of MDA-MB-468 human breast carcinoma cells. *Breast Cancer Res Treat* 80: 63-70, 2003.
121. Joseph J, Niggemann B, Zaenker KS and Entschladen F: The neurotransmitter gamma-aminobutyric acid is an inhibitory regulator for the migration of SW 480 colon carcinoma cells. *Cancer Res* 62: 6467-6469, 2002.
122. Watanabe M, Maemura K, Kanbara K, Tamayama T and Hayasaka H: GABA and GABA receptors in the central nervous system and other organs. *Int Rev Cytol* 213: 1-47, 2002.
123. Miller RJ, Rostene W, Apartis E, Banisadr G, Biber K, Milligan ED, White FA and Zhang J: Chemokine action in the nervous system. *J Neurosci* 28: 11792-11795, 2008.
124. Zhang N and Oppenheim JJ: Crosstalk between chemokines and neuronal receptors bridges immune and nervous systems. *J Leukoc Biol* 78: 1210-1214, 2005.
125. Muller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, McClanahan T, Murphy E, Yuan W, Wagner SN, Barrera JL, Mohar A, Verastegui E and Zlotnik A: Involvement of chemokine receptors in breast cancer metastasis. *Nature* 410: 50-56, 2001.
126. Balkwill F: Cancer and the chemokine network. *Nat Rev Cancer* 4: 540-550, 2004.

127. Singh S, Sadanandam A and Singh RK: Chemokines in tumor angiogenesis and metastasis. *Cancer Metastasis Rev* 26: 453-467, 2007.
128. Weiss L: Cancer cell traffic from the lungs to the liver: an example of metastatic inefficiency. *Int J Cancer* 25: 385-392, 1980.
129. Weiss L: Deformation-driven, lethal damage to cancer cells. Its contribution to metastatic inefficiency. *Cell Biophys* 18: 73-79, 1991.
130. Bacac M and Stamenkovic I: Metastatic cancer cell. *Annu Rev Pathol* 3:221-247, 2008.
131. Brain SD: Sensory neuropeptides: their role in inflammation and wound healing. *Immunopharmacology* 37: 133-152, 1997.
132. Ishihara K, Kamata M, Hayashi I, Yamashina S and Majima M: Roles of bradykinin in vascular permeability and angiogenesis in solid tumor. *Int Immunopharmacol* 2: 499-509, 2002.
133. O'Connor TM, O'Connell J, O'Brien DJ, Goode T, Bredin CP and Shanahan F: The role of substance P in inflammatory disease. *J Cell Physiol* 201: 167-180, 2004.
134. Marchesi F, Piemonti L, Mantovani A and Allavena P: Molecular mechanisms of perineural invasion, a forgotten pathway of dissemination and metastasis. *Cytokine Growth Factor Rev* 21: 77-82, 2010.
135. Jhaveri M, Coit D, Brennan M, Qin LX, Gonen M, Klimstra D, Tang L, Kelsen DP and Shah MA: Perineural invasion after preoperative chemotherapy predicts poor survival in patients with locally advanced gastric cancer: gene expression analysis with pathologic validation. *Am J Clin Oncol* 32: 356-362, 2009.
136. Bilici A, Seker M, Ustaalioglu BB, Kefeli U, Yildirim E, Yavuzer D, Aydin FM, Salepci T, Oncel M and Gumus M: Prognostic significance of perineural invasion in patients with gastric cancer who underwent curative resection. *Ann Surg Oncol* 17: 2037-2044, 2010.
137. Ceyhan GO, Liebl F, Maak M, Schuster T, Becker K, Langer R, Demir IE, Hartel M, Friess H and Rosenberg R: The severity of neural invasion is a crucial prognostic factor in rectal cancer independent of neoadjuvant radiochemotherapy. *Ann Surg* 252: 797-804, 2010.
138. Binmadi NO and Basile JR: Perineural invasion in oral squamous cell carcinoma: a discussion of significance and review of the literature. *Oral Oncol* 47: 1005-1010, 2011.
139. Tai SK, Li WY, Chu PY, Chang SY, Tsai TL, Wang YF and Huang JL: Risks and clinical implications of perineural invasion in T1-2 oral tongue squamous cell carcinoma. *Head Neck* 34: 994-1001, 2011.
140. Miller ME, Palla B, Chen Q, Elashoff DA, Abemayor E, St John JM and Lai CK: A novel classification system for perineural invasion in noncutaneous head and neck squamous cell carcinoma: histologic subcategories and patient outcomes. *Am J Otolaryngol* 33: 212-215, 2012.
141. Hibi T, Mori T, Fukuma M, Yamazaki K, Hashiguchi A, Yamada T, Tanabe M, Aiura K, Kawakami T, Ogiwara A, Kosuge T, Kitajima M, Kitagawa Y and Sakamoto M: Synuclein-gamma is closely involved in perineural invasion and distant metastasis in mouse models and is a novel prognostic factor in pancreatic cancer. *Clin Cancer Res* 15: 2864-2871, 2009.
142. Karak SG, Quatrano N, Buckley J and Ricci AJ: Prevalence and significance of perineural invasion in invasive breast carcinoma. *Conn Med* 74: 17-21, 2010.
143. Meinel A, Fischer U, Bilek K, Hentschel B and Horn LC: Morphological parameters associated with perineural invasion (PNI) in carcinoma of the cervix uteri. *Int J Surg Pathol* 19: 159-163, 2011.
144. Bixby JL and Harris WA: Molecular mechanisms of axon growth and guidance. *Annu Rev Cell Biol* 7: 117-159, 1991.
145. Goldberg JL: How does an axon grow? *Genes Dev* 17: 941-958, 2003.
146. Pasterkamp RJ, Peschon JJ, Spriggs MK and Kolodkin AL: Semaphorin 7A promotes axon outgrowth through integrins and MAPKs. *Nature* 424: 398-405, 2003.
147. Chilton JK: Molecular mechanisms of axon guidance. *Dev Biol* 292: 13-24, 2006.
148. Winckler B: BDNF instructs the kinase LKB1 to grow an axon. *Cell* 129: 459-460, 2007.
149. Artigiani S, Comoglio PM and Tamagnone L: Plexins, semaphorins, and scatter factor receptors: a common root for cell guidance signals? *J Neurosci* 19: 477-482, 1999.
150. Iwahashi N, Nagasaka T, Tezel G, Iwashita T, Asai N, Murakumo Y, Kiuchi K, Sakata K, Nimura Y and Takahashi M: Expression of glial cell line-derived neurotrophic factor correlates with perineural invasion of bile duct carcinoma. *Cancer* 94: 167-174, 2002.
151. Tomaselli KJ, Reichardt LF and Bixby JL: Distinct molecular interactions mediate neuronal process outgrowth on non-neuronal cell surfaces and extracellular matrices. *J Cell Biol* 103: 2659-2672, 1986.
152. Folkman J: Role of angiogenesis in tumor growth and metastasis. *Semin Oncol* 29: 15-18, 2002.
153. Hillen F and Griffioen AW: Tumour vascularization: sprouting angiogenesis and beyond. *Cancer Metastasis Rev* 26: 489-502, 2007.
154. Weis SM and Cheresh DA: Tumor angiogenesis: molecular pathways and therapeutic targets. *Nat Med* 17: 1359-1370, 2011.
155. Lutgendorf SK, Cole S, Costanzo E, Bradley S, Coffin J, Jabbari S, Rainwater K, Ritchie JM, Yang M and Sood AK: Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. *Clin Cancer Res* 9: 4514-4521, 2003.
156. Thaker PH, Han LY, Kamat AA, Arevalo JM, Takahashi R, Lu C, Jennings NB, Armaiz-Pena G, Bankson JA, Ravoori M, Merritt WM, Lin YG, Mangala LS, Kim TJ, Coleman RL, Landen CN, Li Y, Felix E, Sanguino AM, Newman RA, Lloyd M, Gershenson DM, Kundra V, Lopez-Berestein G, Lutgendorf SK, Cole SW and Sood AK: Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med* 12: 939-944, 2006.
157. Tilan J and Kitlinska J: Sympathetic neurotransmitters and tumor angiogenesis - link between stress and cancer progression. *J Oncol* 539706, 2010.
158. Park SY, Kang JH, Jeong KJ, Lee J, Han JW, Choi WS, Kim YK, Kang J, Park CG and Lee HY: Norepinephrine induces VEGF expression and angiogenesis by a hypoxia-inducible factor-1 α protein-dependent mechanism. *Int J Cancer* 128: 2306-2316, 2011.
159. Chakraborty D, Sarkar C, Basu B, Dasgupta PS and Basu S: Catecholamines regulate tumor angiogenesis. *Cancer Res* 69: 3727-3730, 2009.
160. Chakraborty D, Sarkar C, Mitra RB, Banerjee S, Dasgupta PS and Basu S: Depleted dopamine in gastric cancer tissues: dopamine treatment retards growth of gastric cancer by inhibiting angiogenesis. *Clin Cancer Res* 10: 4349-4356, 2004.
161. Basu S, Nagy JA, Pal S, Vasile E, Eckelhoefer IA, Bliss VS, Manseau EJ, Dasgupta PS, Dvorak HF and Mukhopadhyay D: The neurotransmitter dopamine inhibits angiogenesis induced by vascular permeability factor/vascular endothelial growth factor. *Nat Med* 7: 569-574, 2001.
162. Lutgendorf SK, DeGeest K, Dahmouch L, Farley D, Penedo F, Bender D, Goodheart M, Buckers TE, Mendez L, Krueger G, Clevenger L, Lubaroff DM, Sood AK and Cole SW: Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. *Brain Behav Immun* 25: 250-255, 2011.
163. Basile JR, Castilho RM, Williams VP and Gutkind JS: Semaphorin 4D provides a link between axon guidance processes and tumor-induced angiogenesis. *Proc Natl Acad Sci USA* 103: 9017-9022, 2006.
164. Kigel B, Rabinowicz N, Varshavsky A, Kessler O and Neufeld G: Plexin-A4 promotes tumor progression and tumor angiogenesis by enhancement of VEGF and bFGF signaling. *Blood* 118: 4285-4296, 2011.
165. Casazza A, Fu X, Johansson I, Capparuccia L, Andersson F, Giustacchini A, Squadrito ML, Venneri MA, Mazzone M, Larsson E, Carmeliet P, De Palma M, Naldini L, Tamagnone L and Rolny C: Systemic and targeted delivery of semaphorin 3A inhibits tumor angiogenesis and progression in mouse tumor models. *Arterioscler Thromb Vasc Biol* 31: 741-749, 2011.
166. Sakurai A, Doci C and Gutkind JS: Semaphorin signaling in angiogenesis, lymphangiogenesis and cancer. *Cell Res* 22: 23-32, 2012.
167. Toda M, Suzuki T, Hosono K, Hayashi I, Hashiba S, Onuma Y, Amano H, Kurihara Y, Kurihara H, Okamoto H, Hoka S and Majima M: Neuronal system-dependent facilitation of tumor angiogenesis and tumor growth by calcitonin gene-related peptide. *Proc Natl Acad Sci USA* 105: 13550-13555, 2008.

168. Lee EW, Michalkiewicz M, Kitlinska J, Kalezić I, Switalska H, Yoo P, Sangkharat A, Ji H, Li L, Michalkiewicz T, Ljubisavljevic M, Johansson H, Grant DS and Zukowska Z: Neuropeptide Y induces ischemic angiogenesis and restores function of ischemic skeletal muscles. *J Clin Invest* 111: 1853-1862, 2003.
169. Filipinski E and Levi F: Circadian disruption in experimental cancer processes. *Integr Cancer Ther* 8: 298-302, 2009.
170. Goodwin AM and D'Amore PA: Wnt signaling in the vasculature. *Angiogenesis* 5: 1-9, 2002.
171. Masckauchan TN and Kitajewski J: Wnt/Frizzled signaling in the vasculature: new angiogenic factors in sight. *Physiology (Bethesda)* 21: 181-188, 2006.
172. Adams RH and Eichmann A: Axon guidance molecules in vascular patterning. *Cold Spring Harb Perspect Biol* 2: a1875, 2010.
173. Melani M and Weinstein BM: Common factors regulating patterning of the nervous and vascular systems. *Annu Rev Cell Dev Biol* 26: 639-665, 2010.
174. Carmeliet P and Tessier-Lavigne M: Common mechanisms of nerve and blood vessel wiring. *Nature* 436: 193-200, 2005.
175. Entschladen F, Palm D, Drell TT, Lang K and Zaenker KS: Connecting a tumor to the environment. *Curr Pharm Des* 13: 3440-3444, 2007.
176. Capparuccia L and Tamagnone L: Semaphorin signaling in cancer cells and in cells of the tumor microenvironment - two sides of a coin. *J Cell Sci* 122: 1723-1736, 2009.
177. Schirmacher V, Fogel M, Russmann E, Bosslet K, Altevogt P and Beck L: Antigenic variation in cancer metastasis: immune escape versus immune control. *Cancer Metastasis Rev* 1: 241-274, 1982.
178. Tan W, Zhang W, Strasner A, Grivennikov S, Cheng JQ, Hoffman RM and Karin M: Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signalling. *Nature* 470: 548-553, 2011.
179. Rabin BS, Cohen S, Ganguli R, Lysle DT and Cunnick JE: Bidirectional interaction between the central nervous system and the immune system. *Crit Rev Immunol* 9: 279-312, 1989.
180. Steinman L: Connections between the immune system and the nervous system. *Proc Natl Acad Sci USA* 90: 7912-7914, 1993.
181. Grivennikov SI, Greten FR and Karin M: Immunity, inflammation, and cancer. *Cell* 140: 883-899, 2010.
182. Lin WW and Karin M: A cytokine-mediated link between innate immunity, inflammation, and cancer. *J Clin Invest* 117: 1175-1183, 2007.
183. Karin M and Greten FR: NF-kappaB: linking inflammation and immunity to cancer development and progression. *Nat Rev Immunol* 5: 749-759, 2005.
184. Ben-Eliyahu S, Yirmiya R, Liebeskind JC, Taylor AN and Gale RP: Stress increases metastatic spread of a mammary tumor in rats: evidence for mediation by the immune system. *Brain Behav Immun* 5: 193-205, 1991.
185. Ben-Eliyahu S, Page GG, Yirmiya R and Shakh G: Evidence that stress and surgical interventions promote tumor development by suppressing natural killer cell activity. *Int J Cancer* 80: 880-888, 1999.
186. Levy SM, Herberman RB, Lippman M, D'Angelo T and Lee J: Immunological and psychosocial predictors of disease recurrence in patients with early-stage breast cancer. *Behav Med* 17: 67-75, 1991.
187. Logan RW and Sarkar DK: Circadian nature of immune function. *Mol Cell Endocrinol* 349: 82-90, 2012.
188. Rana S and Mahmood S: Circadian rhythm and its role in malignancy. *J Circadian Rhythms* 8: 3, 2010.
189. Kiecolt-Glaser JK and Glaser R: Psychoneuroimmunology and cancer: fact or fiction? *Eur J Cancer* 35: 1603-1607, 1999.
190. Tracey KJ: The inflammatory reflex. *Nature* 420: 853-859, 2002.
191. Libert C: Inflammation: A nervous connection. *Nature* 421: 328-329, 2003.
192. Rosas-Ballina M and Tracey KJ: Cholinergic control of inflammation. *J Intern Med* 265: 663-679, 2009.
193. Rosenberger P, Schwab JM, Mirakaj V, Masekowsky E, Mager A, Morote-Garcia JC, Unertl K and Eltzschig HK: Hypoxia-inducible factor-dependent induction of netrin-1 dampens inflammation caused by hypoxia. *Nat Immunol* 10: 195-202, 2009.
194. Tracey KJ: Reflex control of immunity. *Nat Rev Immunol* 9: 418-428, 2009.
195. Van Der Zanden EP, Boeckstaens GE and de Jonge WJ: The vagus nerve as a modulator of intestinal inflammation. *Neurogastroenterol Motil* 21: 6-17, 2009.
196. Ley S, Weigert A and Brune B: Neuromediators in inflammation - a macrophage/nerve connection. *Immunobiology* 215: 674-684, 2010.
197. Meregnani J, Clarencon D, Vivier M, Peinnequin A, Mouret C, Sinniger V, Picq C, Job A, Canini F, Jacquier-Sarlin M and Bonaz B: Anti-inflammatory effect of vagus nerve stimulation in a rat model of inflammatory bowel disease. *Auton Neurosci* 160: 82-89, 2011.
198. Pohanka M, Snopkova S, Havlickova K, Bostik P, Sinkorova Z, Fusek J, Kuca K and Pikula J: Macrophage-assisted inflammation and pharmacological regulation of the cholinergic anti-inflammatory pathway. *Curr Med Chem* 18: 539-551, 2011.
199. Cerejeira J, Nogueira V, Luis P, Vaz-Serra A and Mukaetova-Ladinska EB: The cholinergic system and inflammation: common pathways in delirium pathophysiology. *J Am Geriatr Soc* 60: 669-675, 2012.
200. Peterson CY, Krzyzaniak M, Coimbra R and Chang DC: Vagus nerve and postinjury inflammatory response. *Arch Surg* 147: 76-80, 2012.
201. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB and Glaser R: Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci USA* 100: 9090-9095, 2003.
202. Madden KS, Szpunar MJ and Brown EB: beta-Adrenergic receptors (beta-AR) regulate VEGF and IL-6 production by divergent pathways in high beta-AR-expressing breast cancer cell lines. *Breast Cancer Res Treat* 130: 747-758, 2011.
203. Yang EV, Kim SJ, Donovan EL, Chen M, Gross AC, Webster MJ, Barsky SH and Glaser R: Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. *Brain Behav Immun* 23: 267-275, 2009.
204. Stathopoulos GT, Sherrill TP, Han W, Sadikot RT, Yull FE, Blackwell TS and Fingleton B: Host nuclear factor-kappaB activation potentiates lung cancer metastasis. *Mol Cancer Res* 6: 364-371, 2008.
205. Paradisi A and Mehlen P: Netrin-1, a missing link between chronic inflammation and tumor progression. *Cell Cycle* 9: 1253-1262, 2010.
206. Pantel K and Brakenhoff RH: Dissecting the metastatic cascade. *Nat Rev Cancer* 4: 448-456, 2004.
207. Rafii S, Lyden D, Benezra R, Hattori K and Heissig B: Vascular and haematopoietic stem cells: novel targets for anti-angiogenesis therapy? *Nat Rev Cancer* 2: 826-835, 2002.
208. Direkze NC, Hodiola-Dilke K, Jeffery R, Hunt T, Poulsom R, Oukrif D, Alison MR and Wright NA: Bone marrow contribution to tumor-associated myofibroblasts and fibroblasts. *Cancer Res* 64: 8492-8495, 2004.
209. Ishii G, Sangai T, Oda T, Aoyagi Y, Hasebe T, Kanomata N, Endoh Y, Okumura C, Okuhara Y, Magae J, Emura M, Ochiya T and Ochiya A: Bone-marrow-derived myofibroblasts contribute to the cancer-induced stromal reaction. *Biochem Biophys Res Commun* 309: 232-240, 2003.
210. Psaila B and Lyden D: The metastatic niche: adapting the foreign soil. *Nat Rev Cancer* 9: 285-293, 2009.
211. Kaplan RN, Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, MacDonald DD, Jin DK, Shido K, Kerns SA, Zhu Z, Hicklin D, Wu Y, Port JL, Altorki N, Port ER, Ruggero D, Shmelkov SV, Jensen KK, Rafii S and Lyden D: VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature* 438: 820-827, 2005.
212. Miyani JA, Broome CS and Whetton AD: Neural regulation of bone marrow. *Blood* 92: 2971-2973, 1998.
213. Canaani J, Kollet O and Lapidot T: Neural regulation of bone, marrow, and the microenvironment. *Front Biosci* 3: 1021-1031, 2011.
214. Benestad HB, Strom-Gundersen I, Iversen PO, Haug E and Nja A: No neuronal regulation of murine bone marrow function. *Blood* 91: 1280-1287, 1998.
215. Artico M, Bosco S, Cavallotti C, Agostinelli E, Giuliani-Piccarini G, Sciorio S, Cocco L and Vitale M: Noradrenergic and cholinergic innervation of the bone marrow. *Int J Mol Med* 10: 77-80, 2002.
216. Imai S, Tokunaga Y, Maeda T, Kikkawa M and Hukuda S: Calcitonin gene-related peptide, substance P, and tyrosine hydroxylase-immunoreactive innervation of rat bone marrows: an immunohistochemical and ultrastructural investigation on possible efferent and afferent mechanisms. *J Orthop Res* 15: 133-140, 1997.

217. Singh D, Joshi DD, Hameed M, Qian J, Gascon P, Maloof PB, Mosenthal A and Rameshwar P: Increased expression of preprotachykinin-I and neurokinin receptors in human breast cancer cells: implications for bone marrow metastasis. *Proc Natl Acad Sci USA* 97: 388-393, 2000.
218. Castro TA, Cohen MC and Rameshwar P: The expression of neurokinin-I and preprotachykinin-I in breast cancer cells depends on the relative degree of invasive and metastatic potential. *Clin Exp Metastasis* 22: 621-628, 2005.
219. Lyden D, Hattori K, Dias S, Costa C, Blaikie P, Butros L, Chadburn A, Heissig B, Marks W, Witte L, Wu Y, Hicklin D, Zhu Z, Hackett NR, Crystal RG, Moore MA, Hajar KA, Manova K, Benezra R and Rafii S: Impaired recruitment of bone-marrow-derived endothelial and hematopoietic precursor cells blocks tumor angiogenesis and growth. *Nat Med* 7: 1194-1201, 2001.
220. Rajantie I, Ilmonen M, Almainaite A, Ozerdem U, Alitalo K and Salven P: Adult bone marrow-derived cells recruited during angiogenesis comprise precursors for periendothelial vascular mural cells. *Blood* 104: 2084-2086, 2004.
221. Chakroborty D, Chowdhury UR, Sarkar C, Baral R, Dasgupta PS and Basu S: Dopamine regulates endothelial progenitor cell mobilization from mouse bone marrow in tumor vascularization. *J Clin Invest* 118: 1380-1389, 2008.
222. Zhang W: Mesenchymal stem cells in cancer: friends or foes. *Cancer Biol Ther* 7: 252-254, 2008.
223. Pollard JW: Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer* 4: 71-78, 2004.
224. Condeelis J and Pollard JW: Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell* 124: 263-266, 2006.
225. Qian BZ and Pollard JW: Macrophage diversity enhances tumor progression and metastasis. *Cell* 141: 39-51, 2010.
226. Maestroni GJ: Catecholaminergic regulation of hematopoiesis in mice. *Blood* 92: 2971-2973, 1998.
227. Maestroni GJ: Dendritic cell migration controlled by alpha 1b-adrenergic receptors. *J Immunol* 165: 6743-6747, 2000.
228. Katayama Y, Battista M, Kao WM, Hidalgo A, Peired AJ, Thomas SA and Frenette PS: Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. *Cell* 124: 407-421, 2006.
229. Mendez-Ferrer S, Lucas D, Battista M and Frenette PS: Haematopoietic stem cell release is regulated by circadian oscillations. *Nature* 452: 442-447, 2008.
230. Bissell MJ and Radisky D: Putting tumours in context. *Nat Rev Cancer* 1: 46-54, 2001.
231. Egeblad M, Nakasone ES and Werb Z: Tumors as organs: complex tissues that interface with the entire organism. *Dev Cell* 18: 884-901, 2010.
232. Mareel M, Oliveira MJ and Madani I: Cancer invasion and metastasis: interacting ecosystems. *Virchows Arch* 454: 599-622, 2009.
233. Ben-Eliyahu S, Shakhar G, Page GG, Stefanski V and Shakhar K: Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and beta-adrenoceptors. *Neuroimmunomodulat* 8: 154-164, 2000.
234. Schuller HM, Al-Wadei HA, Ullah MF and Plummer HK III: Regulation of pancreatic cancer by neuropsychological stress responses: a novel target for intervention. *Carcinogenesis* 33: 191-196, 2012.
235. Yasuniwa Y, Izumi H, Wang KY, Shimajiri S, Sasaguri Y, Kawai K, Kasai H, Shimada T, Miyake K, Kashiwagi E, Hirano G, Kidani A, Akiyama M, Han B, Wu Y, Ieiri I, Higuchi S and Kohno K: Circadian disruption accelerates tumor growth and angio/stromagenesis through a Wnt signaling pathway. *PLoS One* 5: e15330, 2010.
236. Arjona A and Sarkar DK: Are circadian rhythms the code of hypothalamic-immune communication? Insights from natural killer cells. *Neurochem Res* 33: 708-718, 2010.
237. Filipinski E, King VM, Li X, Granda TG, Mormont MC, Liu X, Claustrat B, Hastings MH and Levi F: Host circadian clock as a control point in tumor progression. *J Natl Cancer Inst* 94: 690-697, 2002.
238. Andersen BL, Kiecolt-Glaser JK and Glaser R: A biobehavioral model of cancer stress and disease course. *Am Psychol* 49: 389-404, 1994.
239. Spiegel D: Mind matters in cancer survival. *Psychooncology* 21: 588-593, 2012.
240. Ebos JM, Lee CR, Cruz-Munoz W, Bjarnason GA, Christensen JG and Kerbel RS: Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. *Cancer Cell* 15: 232-239, 2009.
241. Rugo HS: Inhibiting angiogenesis in breast cancer: the beginning of the end or the end of the beginning? *J Clin Oncol* 30: 898-901, 2012.
242. Páez-Ribes M, Allen E, Hudock J, Takeda T, Okuyama H and Viñals F: Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer Cell* 15: 220-231, 2009.
243. Powe DG and Entschladen F: Targeted therapies: Using beta-blockers to inhibit breast cancer progression. *Nat Rev Clin Oncol* 8: 511-512, 2011.
244. Barron TI, Connolly RM, Sharp L, Bennett K and Visvanathan K: Beta blockers and breast cancer mortality: a population-based study. *J Clin Oncol* 29: 2635-2644, 2011.
245. Syromiatnikov AV and Alistratov AV: Changes in the efferent impulsion in the vagus nerves during the metastasis of Lewis lung carcinoma in mice. *Eksp Onkol* 11: 47-50, 1989.
246. Li ZJ and Cho CH: Neurotransmitters, more than meets the eye-neurotransmitters and their perspectives in cancer development and therapy. *Eur J Pharmacol* 667: 17-22, 2011.
247. Schuller HM, Al-Wadei HA and Majidi M: GABA B receptor is a novel drug target for pancreatic cancer. *Cancer* 112: 767-778, 2008.
248. Yang ZF, Ho DW, Lam CT, Luk JM, Lum CT, Yu WC, Poon RT and Fan ST: Identification of brain-derived neurotrophic factor as a novel functional protein in hepatocellular carcinoma. *Cancer Res* 65: 219-225, 2005.
249. Harburg GC and Hinck L: Navigating breast cancer: axon guidance molecules as breast cancer tumor suppressors and oncogenes. *J Mammary Gland Biol Neoplasia* 16: 257-270, 2011.
250. Mehlen P, Delloye-Bourgeois C and Chedotal A: Novel roles for Slits and netrins: axon guidance cues as anticancer targets? *Nat Rev Cancer* 11: 188-197, 2011.
251. Welch DR, Cooper CR, Hurst DR, Lynch CC, Martin MD, Vaidya KS, VanSaun MN and Mastro AM: Metastasis Research Society-American Association For Cancer Research Joint Conference on Metastasis. *Cancer Res* 68: 9578-9582, 2008.