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Correlation between the autonomic nervous system and neoplastic disease

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Summary. The physiological role of the autonomic nervous system (ANS) includes maintenance of homeostasis and response to stressors. Sympathetic nervous system (SNS) is involved at early stages of tumorigenesis via β-adrenergic signaling and via central and local norepinephrine/epinephrine release from SNS nerve fibers. Parasympathetic nervous system (PNS) promotes invasion and dissemination of cancers using cholinergic receptors. In this paper, we review published evidence regarding the impact of SNS and PNS on solid tumor development, and discuss the importance of those findings for clinic and prevention.

Key words: autonomic nervous system, sympathetic nervous system, parasympathetic nervous system, neoplasm

Physiological function of the autonomic nervous system

Autonomic nervous system (ANS) consists of two main parts: sympathetic nervous system (SNS, noradrenergic) and parasympathetic nervous system (PNS, cholinergic). Both of them play a significant role in maintaining homeostasis and stress response. Physiological mechanisms involved in the autonomic activity include neural outflow, synthesis, release and degradation of transmitters, ganglionic regulation and receptor-mediated effects.

Sympathetic fibers participate in many physiological processes, inter alia regulating efferent sympathetic nerve outflow and generating its differential patterns, synchronizing neural activity of various target tissues and organs and thus, controlling function thereof. Moreover, acting via β-adrenergic signaling pathway, SNS induces 'fight-or-flight' stress response. SNS fibers innervate all major organs, releasing catecholamine neurotransmitters (norepinephrine and epinephrine) in response to a physiological threat to homeostasis or acute sympathetic activation. Norepinephrine and epinephrine, the metabolites of amino acid, tyrosine, are released from the adrenal medulla during a stress reaction. Their biological effects include an increase in blood pressure, stimulation of liver glycogenolysis and airway dilation.

Parasympathetic nervous system provides innervation to many organs, controlling a number of vital physiological functions, such as heart rate, endocrine activity, digestion, gastrointestinal motility, inflammation and immune response. Vagus nerve, the X cranial nerve, and its branches contain 80% of afferent sensory fibers and 20% of efferent motor fibers, and form a communicating sensory pathway between the central nervous system and peripheral tissues. The main parasympathetic neurotransmitter is acetylcholine, acting via five types of muscarinic receptors (chrm1 – chrm5) and two types of nicotinic receptors (muscle-type, N1, and neuronal-type, N2).

Autonomic contribution to neoplastic processes – Underlying mechanisms

Tumor progression and dissemination depend on intrinsic prosperities of cancer cells, such as self-

renewal and the ability to migrate (invasiveness). Tumor stroma, containing fibroblasts, endothelial cells and immune cells, may interact with cancer cells (1, 2). This microenvironment regulates growth of a primary tumor and formation of metastases. Both stromal cells of the tumor and signaling molecules interact directly and indirectly with the nervous system (3). The metastatic cascade involves two main steps. During the first stage, tumor cells migrate from the primary tumor to the site of hematogenous and lymphogenous dissemination. During the second stage, the cells extravasate from the circulation and invade surrounding tissues (4, 5).

Both sympathetic and parasympathetic components of the autonomic nervous system play vital roles during the development and spread of solid tumors, albeit at different stages of tumorigenesis. Likewise in leukocyte and fibroblast migration, neurotransmitters regulate also the migratory activity of cancer cells. Cancer cells may migrate along nerve fibers; this phenomenon, referred to as perineural invasion, is associated with poorer prognosis (6-10). SNS mediates tumor initiation and progression through a variety mechanisms. β-adrenergic signaling promotes the inhibition of DNA damage repair and p53-associated apoptosis via several molecular pathways (e.g. β-arrestin-induced activation of the AKT signaling pathway); as a result, SNS may contribute to tumor initiation and/or chromosomal instability (1, 2). Macrophages play an important role, modulating tumor microenvironment and promoting metastasis. β-adrenergic signaling stimulates recruitment of macrophages to tumor parenchyma via chemotactic factors, such as macrophage colony stimulating factor (CSF1). Moreover, β-adrenergic signaling contributes to an increase in tumor-associated macrophage density, promoting myelopoietic development of monocyte precursors in the spleen and bone marrow. Finally, β-adrenergic signaling stimulates macrophage expression of gene programs that initiate tumor progression within the tumor microenvironment.

Additionally, β-adrenergic signaling may also modulate various growth and survival pathways, among them programmed cell death mediated by focal adhesion kinase (FAK) (11). SNS generally promotes tumor progression through an array of pleiotropic molecular alterations in the microenvironment of primary tumor (12). Tumor cells may spread via lymphatic and blood vessels, and along serous membranes (13). Perineural invasion results from interactions between cancer cells and nerve fiber microenvironment. Sympathetic nerves may contribute to the perineural invasion and stimulate tumor growth. Cancer cells stimulate the expression of stromal cell-derived factor 1 (also referred to as C-X-C motif chemokine ligand 12, CXCL 12) and insulin-like growth factor 1 (IGF-1) in stromal cells; this eventually contributes to the selective growth of cancer cells clones that are hypersensitive to these factors and primed for spread in CXCL12- and IGF-1-enriched bone marrow (14) (Fig. 1). This pathway is also implicated in spread of cancer cells in patients who do not show the evidence of blood and/or lymphatic metastases (15, 16). A reciprocal signaling interaction between tumor cells and nerves contributes to peripheral nerve invasion. Neurotrophic factors (NGF) and axonal guidance molecules are pivotal for axonal growth (17, 18). However, these molecules and their receptors are also localized in tumor cells and hence, the latter can bind to the neurites (19, 20). According to Liebig et al., peripheral nerve invasion can be diagnosed whenever tumor cells are present within any of the three layers of the nerve sheath (epineurium, perineurium, endoneurium), or if tumor foci exist outside the nerve, involving at least 33% of its circumference (16). Also ANS may interfere with angiogenesis and modulate tumor microenvironment. Cancer cells can release neurotropic factors, such as axon guidance molecules, which stimulate the growth of nerve fibers, blood vessels and lymphatics (neoangiogenesis and lymphangiogenesis, respectively) supplying the tumor (9, 21, 22).

Moreover, neoplastic cells can release angiogenic factors, such as vascular endothelial growth factor (VEGF), and angiogenic chemokines, which also promote neoangiogenesis (21, 23). Tumors with diameters greater than 1 cm cannot be effectively supplied with nutrients without the development of new blood vessels (neoangiogenesis) (21). NGF, acting alone or in combination with 6-hydroxy-dopamine (6-OHDA), was shown to stimulate neoangiogenesis in the superior cervical ganglia of newborn rats; similar effect was also observed in breast and prostate cancers, whereby

NGF initiated neoangiogenesis and apoptosis, and modulated the severity cancer-induced bone pain (24-26). VEGF is a mitogen for endothelial cells, and promotes angiogenesis in vivo. Both VEGF and its receptors (expressed on sympathetic nerve fibers innervating arteries) promote vascular sympathetic innervation. VEGF promotes sympathetic axon growth. Its effects on vascular sympathetic innervation are modulated by other vascular-derived neuronal growth factors. Inhibition of VEGF was shown to prevent reinnervation in vivo (27). Aside from angiogenesis, VEGF was also shown to modulate lymphangiogenesis; since it shows a neurotrophic activity within the peripheral nervous system, this factor may also contribute to neurogenesis (23, 28-30).

Survival and growth of cancer cells may be also promoted by nerve-derived growth factors released from nerve fibers located in close vicinity of the tumor (31, 32) (Fig. 1). Fibroblast growth factor (FGF) regulates synaptogenesis and neuronal migration and therefore, may also contribute to the development of tumor innervation (33). Aside from the stimulation of hematopoiesis, granulocyte-colony stimulating factor (G-CSF), a hematopoietic stem cell mobilizer with established clinical application, may also modulate neuronal activity. This was confirmed in a mouse study, in which G-CSF affected survival of autonomic nerve fibers, which resulted in growth and dissemination of prostate cancer cells (34). Secretion of soluble factors from prostate cancer cells may contribute to nerve

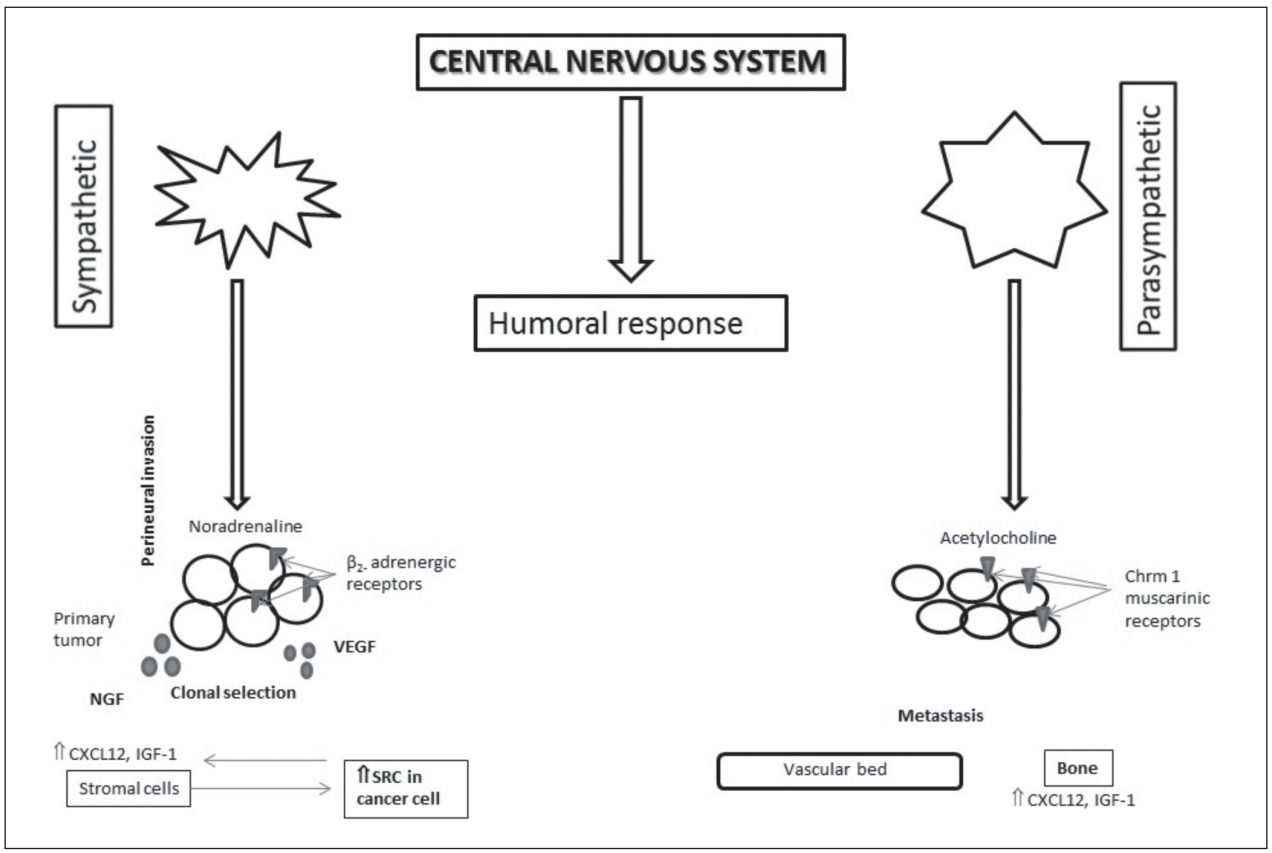

Figure 1. The role of sympathetic and parasympathetic regulation in cancer progression and dissemination. Sympathetic nerves contribute to perineural invasion of cancer cells, and stimulate tumor growth. Cancer cells induce the expression of CXCL12 and IGF-1 in stromal cells, which promotes selective growth of clones that are hypersensitive to these factors and primed for metastasis in CXCL12- and IGF-1-enriched bone marrow. In turn, parasympathetic nerves play a role in cancer cell expansion and dissemination (according to del Toro et al., modified) (14).

sprouting and/or branching (10). Due to presence of neuro-neoplastic synapses and expression of receptors for neural markers, cancer cells may effectively communicate with neurons. Neurotransmitters reach cancer cells via neuro-neoplastic synapses, stimulating their migration and therefore, contributing to tumor spread (35). Neuro-neoplastic synapses are functional units, rather than morphological entities (8). Neurotransmitters may stimulate the release of acetylcholine from a subset of CD4(+) T cells and thus, indirectly activate other immune cells, for example via upregulation of α7-nicotinic acetylcholine receptors on macrophages (36).

Autonomic nervous system and immunological processes

Both sympathetic and parasympathetic nervous system participate in neuroimmune processes. Immune cells (especially lymphocytes) express adrenergic and muscarinic receptors, as well as the receptors for acetylcholine (ACh), choline acetyltransferase (ChAT) and acetylcholinesterase (AchE). Neurotransmitters released from the sympathetic and parasympathetic nerve endings bind to their receptors and initiate immunomodulatory response. The interactions between SNS and immune system involve signaling mechanisms that provide a link between neurotransmitters and neuromodulators, co-transmitters (ATP and adenosine), adrenergic receptors and, albeit not necessarily, immune cells, cytokines and bacteria. SNS innervation of lymphoid tissue (the spleen and lymph nodes) modulates the evolution of peripheral immune response via cytokines, and promotes humoral immune responses at an expense of cellular immunity (12). Neuronal and neuroendocrine pathways are involved in communication between the nervous and immune system. Vagus nerve has been implicated as a component of the neural pathway transmitting signals from the peripheral immune system to the brain. Also cutaneous sensory afferents have been postulated to provide a communication pathway to central neural circuits. The immune to CNS communication is mediated by three non-neuronal mechanisms: cytokine transport system, brain structures containing blood vessels with fenestrated capillaries, and some molecules (e.g. prostaglandins, cytokines) that may reach the brain parenchyma (37). Hence, the neuronal system may contribute to cancer spread via the immune system (38). Chronic stress and depression may predispose to tumor spread due to impairment of immune response associated with decreased number of cytotoxic T-cells and natural killer (NK) cells (39).

Cholinergic anti-inflammatory pathway may involve cholinergic-adrenergic interactions at peripheral sites, autonomic ganglia and lymphoid targets (37, 40-43). The synthesis of immune and inflammatory mediators (cytokines, chemokines and free radicals) and the activity of various lymphoid cells are modulated due to activation of adrenergic receptors (37, 40-41). The activation of adrenergic receptors may affect synthesis of many compounds, among them tumor necrosis factor-alpha (TNFα), interleukins (IL-6, IL-10 and IL-12), chemokine macrophage inflammatory protein 1 alpha and a free radical, nitric oxide (41).

Analysis of genomic profiles identified specific patterns related to various disease entities. For example, one previous study revealed commonalities in a genetic signature, which turned out to be associated with both β-adrenergic receptor and cancer (3). Breast cancer and β-adrenergic pathway were demonstrated to share some genetic signatures, namely IL-6, MMP9, MMPI, FOSB, LCK, ERG, CCL2I, RHOJ, IGFI and ETSI; this observation supports the hypothesis on a link between β_2-adrenergic receptor and breast cancer pathway, and may constitute a foundation for new anticancer therapies based on adrenergic receptor strategies (44). β-adrenergic pathway may influence oncogene pathways, such as *Her2* and SRC (45-46). Indeed, β-adrenergic pathway has already been shown to stimulate the phosphorylation of SRC by protein kinase A, which resulted in SRC-mediated activation of a complex phosphoproteomic network promoting tumor growth and invasion in vivo (45). Furthermore, a positive correlation between β_2-AR level (β_2-adrenergic receptor) and *Her2* status was reported in breast cancer cells. Activation of β-adrenergic receptor by a catecholamine contributed to the upregulation of *Her2* mRNA expression and to the stimulation of signal transducer and activator of transcription 3 (STAT3); the latter molecule activates ERRB promoter to stimulate gene transcription (47). Furthermore, β-adrenergic signaling

pathway may prevent DNA repair and suppress p53 level and t53-associated apoptosis via molecular pathways, such as Rad3-related (ART)/p21 pathway (1-2, 48-49). While this mechanism was already demonstrated to be sufficient for an increase in the number of spontaneous chromosomal aberrations in the tissues, we still do not know whether the β-adrenergic inhibition of DNA repair may contribute to the initiation of spontaneous tumorigenesis in vivo (12).

Sympathetic Nervous System (SNS)

The effects of catecholamine neurotransmitters are mediated by receptors from α_1, α_2, β_1 β_2 and β_3 families. β-adrenergic receptors are G-protein coupled receptors that activate adenylate cyclase to "synthesize" intracellular 3',5'-cyclic adenosine monophosphate (cAMP); the latter activates protein kinase A (PKA) to phosphorylate serine or threonine in target proteins. PKA is involved in regulation of cellular metabolism, growth, differentiation, secretion, motility, neurotransmission and gene transcription. The second cAMP effector is guanine nucleotide Exchange Protein by Adenylyl Cyclase (EPAC). EPAC signaling may alter cellular morphology, motility and secretion (3). β-adrenergic signaling pathway regulates activity of various cells, among them epithelial cells, vascular myocytes, myeloid and lymphoid immune cells (50). All these cells express adrenergic receptors and therefore, are prone to the autonomic control. β-adrenergic signaling contributes to migration of cancer cells (51-53) and regulates VEGF-dependent angiogenesis (54-56) (Fig. 1). Also matrix metalloproteinase-related enhanced tissue invasion remains under the β-adrenergic control (56-58). Additionally, proapoptotic protein BAD (B-cell lymphoma 2-associated death promoter) may contribute to the development of chemotherapy resistance, acting via β-adrenergic receptor (11). β-adrenergic receptors, primarily β_2, are expressed at metastatic sites: in the brain, lungs, liver, lymphoid tissue, etc. (54, 59-60). β-adrenergic signaling pathway modulates the migratory potential and invasiveness of cancer cells via alterations in tumor gene expression and via upregulation of matrix metalloproteinases (MMP-6 and MMP-9) (57). Moreover, adrenergic receptors may modulate pro-metastatic consequences of tumor immune response. Activation of adrenergic receptors initiates infiltration of tumor tissues by macrophages and promotes a pro-metastatic gene expression signature. A consequence of macrophage infiltration is overexpression of macrophage-derived factors (e.g. COX2, MMP-9, VEGF) (61-62). Due to the activation of beta$_2$-adrenoreceptor-cAMP-protein kinase A pathway, epinephrine and norepinephrine inhibit secretion of type 1 proinflammatory cytokines: interleukin-12 (IL-12), TNFα and interferon-γ by antigen-presenting cells and Th1 helper cells. Furthermore, these endogenous catecholamines promote secretion of type 2 anti-inflammatory cytokines: interleukin-10 (IL-10) and transforming growth factor β (TGFβ) (40). These neurotransmitters can suppress Th1 response, which results in the inhibition of cell-mediated immunity and predominance of humoral immune response. Activation of SNS during the course of immune response may limit the inflammatory reaction, promoting accumulation of neutrophils and stimulating more specific humoral response; this protects the host against unfavorable effects of proinflammatory cytokines and other compounds released from activated macrophages (40). SNS is involved at early stages of tumorigenesis via β-adrenergic signaling, and systemic and local release of norepinephrine/epinephrine from sympathetic nerve fibers (3, 6, 9, 63-65). This results in an increase the number of axons and promotes ramification thereof. Furthermore, cancer cells can produce axon guidance molecules and neurotrophic factors, such as NGF (66-67). The axon guidance molecules contribute to the development of new blood vessels. Four families of the guidance molecules exist: netrins, slits, ephrins and semaphorins. Netrins are bond by UNC5 and deleted in colorectal cancer (DCC) receptors, whereas slits, ephrins and semaphorins interact with slits-roundabout receptors (Robos), Ephrin receptors (Eph) and plexins/neuropilins, respectively (68). While netrins are known to prevent cancer cell apoptosis and thus, participate in tumorigenesis, their role in cancer cell migration is yet to be established (69). Semaphorins play an important regulatory role in carcinogenesis (70). For example, SEMA3B and SEMA3F act as tumor suppressors (71), and overexpression of SEMA3B was demon-

strated to cause apoptosis in breast and lung cancer cell lines (72). Ephrins and their receptors are involved in carcinogenesis through diverse mechanisms; for example, EphA4 receptor was shown to induce proliferation and migration of glioblastoma cells (73). Moreover, both ephrins and their receptors are the regulators of tumor microenvironment, providing a link between cancer cells and surrounding stroma (74).

In turn, vascular growth factors, e.g. VEGF, were shown to control the development of sympathetic innervation (75). Sympathetic axons follow the newly developed arteries that release neurotrophic factors, such as endothelin and artemin (76-77). However, this relationship seems to be bidirectional, since also sympathetic nervous system was demonstrated to provide some regulatory input to angiogenesis and arteriogenesis (78-79). These complex interactions explain tumor's potential to develop its own neurovascular network. SNS may influence the neoplastic growth, modulating tumor microenvironment in both primary and metastatic target sites, via β-adrenergic regulation of myelopoiesis (80-82). β-adrenergic pathway influences expression of genes involved in oncogenesis and tumor spread, inter alia those controlling inflammatory processes, neoangiogenesis, cellular immune response and programmed cell death (12, 83). Furthermore, β-adrenergic signaling pathway promotes development of hematological malignancies, interfering with stem cell biology and physiological hematopoiesis (12).

Stress is associated with the release of IL-6, a proinflammatory cytokine playing pivotal role in cancer spread. Stress stimulates the sympathetic-adrenal-medullary axis to release catecholamine hormones, such as norepinephrine (9). The latter may be involved in upregulation of metalloproteinases (MMP-2, MMP-9) and VEGR; due to their modulatory effects, the proinflammatory cytokines may inter alia contribute to greater invasiveness of nasopharyngeal carcinomas (56). Moreover, stress induces norepinephrine and β-adrenergic receptors under IL-6 regulation (56, 84). Aside from being a key inflammatory mediator, transcription factor NF-κB may also contribute to carcinogenesis and tumor spread. One direct transcriptional target for NF-κB is neuronal guidance molecule, netrin-1, which was shown to be upregulated during the course of inflammatory processes.

β-adrenergic receptors were found in the breast, prostate and pancreatic cancer cells as well as in melanoma cells; their activation by catecholamine neurotransmitters resulted in enhanced activity of those cells (9, 85-88).

Parasympathetic Nervous System (PNS)

Parasympathetic nervous system promotes invasion and dissemination of cancer cells, acting via cholinergic receptor muscarinic 1 (chrm 1) expressed in tumor stroma (6, 7, 63, 89). The activation of chrm1 by acetylcholine results in cancer spread. This phenomenon has been first demonstrated in a mouse cancer model, and then confirmed in patients with prostatic adenocarcinoma (6-7, 87, 89). According to Espanol et al., the expression of muscarinic acetylcholine receptor in murine mammary adenocarcinoma cells may modulate their aggressiveness (90). However, published data on the role of vagal innervation in the development of rat fibrosarcoma are inconclusive, and we still do not know if formation of metastases could be controlled with an inhibitor of the PNS signaling pathway (91). Nevertheless, Magnon et al. confirmed that autonomic nervous system plays a role in the development and spread of human prostate cancer (7). Tumor cholinergic signals are mediated by stromal chrm1 expression. Cholinergic fibres of PNS play role in tumor cell invasion, migration and distant metastases (7).

PNS plays an important role in the inflammatory reflex. Inflammation is a driving force for the dissemination and thus, inflammatory pathways and their effector cells, both controlled by the nervous system, contribute substantially to cancer spread. Inflammatory signals generated within the bowel may significantly alter peripheral neuronal signaling, which results in both peripheral and central sensitization, a phenomenon that is reflected by an enhanced afferent neuronal activation (92). As shown recently, the brain not only can "detect" peripheral inflammation via afferent vagal fibers, but may also attenuate innate immune activation due to an integrated neural response involving massive activation of vagal efferent fibers. This efferent arm of the inflammatory reflex is referred to as the "cholinergic anti-inflammatory pathway". The inflammatory reflex is a key

system involved in maintenance of homeostasis. Vagus nerve, the arc of the reflex and neural-related factors, such as netrin-1 and neuropeptides, all participate in the inflammation control (93, 94). Moreover, activation of vagus nerve exerts an effect on the production of cytokines by leukocytes. The electrostimulation of the vagus results in a decrease in cytokine production in the spleen, and an opposite effect has been observed after surgical ablation of this nerve (93). The cholinergic anti-inflammatory pathway requires signaling from the nicotinic acetylcholine receptor subunit α7, which inhibits the splenic nerve to suppress cytokine release by splenic macrophages (95).

Vagus nerve can influence immune cell function in the spleen through preganglionic and postganglionic system of neurons. The preganglionic system originates from the dorsal motor nucleus of the vagus, and the postganglionic system, from the ganglia of the celiac superior mesenteric plexus (94).

Role of non-cholinergic and non-adrenergic projections in carcinogenesis

Dopamine produced in the brain is a catecholamine. However, unlike for norepinephrine and epinephrine, only few reports describe the role of dopamine in tumor cell migration and metastasis (52, 96-97). Dopamine participates in regulating gene expression, such as induced tumor cell migration. It acts through dopamine receptors (DRs) activation which are members of seven transmembrane domain trimeric guanosine 5'-triphosphate (GTP)-binding protein-coupled receptor family (97). DRD2/DARPP-32 expression is associated with tumor progression, therefore DRD2/DARPP-32 expressions can be a predictive factor (97).

Chemokines bind to receptors from the G-protein-coupled receptor (GPCR) family to regulate tumor-associated angiogenesis and tumor-specific immune response of the host, and to stimulate tumor cell proliferation in an autocrine manner (98). These findings may be the potential target of the therapy for cancer patients.

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter of the brain and an inhibitor of glucagon secretion in the pancreatic α cells. Involvement of GABA receptors was demonstrated to block the migratory effect of norepinephrine in mammary, pancreatic and colon carcinoma (52, 99-100).

Substance P acts as a neurotransmitter, neuromodulator and inflammatory mediator. However, this molecule can be also involved in the development of bone marrow metastases of breast cancer and neuroblastoma (101). Moreover, substance P was shown to stimulate growth of basal-like human breast carcinoma cell line, MDA-MB-468 (52).

Taken altogether, those findings suggest that GABA-receptor agonists and the blockade of substance P receptor (NK-1) may constitute novel strategies in anticancer therapy.

ANS and Heart Rate Variability

In a clinical setting, the autonomic activity can be assessed based on Heart Rate Variability (HRV) analysis. Monitoring of HRV is a non-invasive method to examine autonomic innervation of the heart and the vegetative modulation of the sinus node. The time- and frequency-domain analysis of the HRV provides an information on the autonomic balance. Furthermore, HRV is suitable for the quantification of sympathetic and parasympathetic tone (102). HRV analysis is a routine, widely-available method to evaluate vagal activity based on several indices, such as standard deviation of all normal beat to beat intervals (SDNN), root mean square successive difference between adjacent normal beat to beat intervals (RMSSD), the number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording divided by the total number of all NN intervals (pNN50), and high frequency (0.15-0.4 Hz) component (HF). Low values of the HRV analysis parameters may reflect sympathetic predominance or a decrease in parasympathetic input (102).

Vagal tone, expressed by the HRV, may constitute a new independent prognostic factor in patients with some solid tumors (103-105). Enhanced vagal activity may slow down tumorigenesis and produce a protective effect in patients with advanced or/and metastatic cancers (106). Several studies demonstrated a positive

association between high-frequency HRV component and overall survival in cancer patients; this relationship was independent of potential confounders, such as anticancer treatment, patient age and sex (106).

Previous studies demonstrated that prognosis in cancer is inter alia determined by the parasympathetic activity. De Couck et al. evaluated ANS in subjects with colorectal, pancreatic, prostate, lung and ovarian malignancies; the study demonstrated that cancer patients presented with significantly lower values of HRV parameters (SDNN and RMSSD) than healthy controls (103). Furthermore, the values of those HRV indices turned out to be significantly lower in patients with advanced cancers than in individuals with early malignancies. Other factors, such as age and sex, did not exert a significant effect on HRV analysis parameters in the study groups (103).

Another study revealed that vagal activity may be a prognostic factor in cancer patients. Patients diagnosed with colorectal and prostate cancers presented with higher levels of carcinoembryonic antigen (CEA) at 12 months and prostate-specific antigen (PSA) at 6 months, respectively, whenever their values of HRV indices were low (104). Furthermore, a positive correlation was found between vagal activity and overall survival in patients with advanced pancreatic cancer. According to Mouton et al., vagal activity may play a role in cancer recurrence (105). As widely known, the level of CEA, a cancer marker, correlates with the risk of relapse in most colorectal cancer patients. However, the study revealed that 12 months after anticancer treatment, patients who had increased vagal tone at the baseline (SDNN>20 ms) presented with lower levels of CEA than individuals with lesser HRV (SDNN<20 ms). Moreover, higher baseline HRV turned out to be associated with longer overall survival, also after adjustment for age and anticancer treatment (106). Moreover, high-frequency HRV component, a measure of parasympathetic overactivity, was shown to correlate positively with time to death in patients with terminal hepatocellular carcinoma and non-lung cancer (107, 108).

These findings may explain why prognosis in some cancer patients is worse than in the others; this phenomenon may be related to autonomic dysregulation of cardiac function. A dysfunction of ANS in cancer patients, especially sympathovagal disturbances, may contribute to changes in cardiovascular system regulation. Lower values of HRV indices (markers of vagal activity) are associated with increased risk for life-threatening arrhythmias, which is reflected by generally worse prognosis.

ANS and cancer-induced fatigue

Cancer-related fatigue has been long time ago recognized as a multi-factorial problem present in cancer patients. The issue has been inter alia addressed in a trial including breast cancer survivors who had completed anti-cancer treatment within past two years. Compared to their less-fatigued counterparts, the subjects who reported more fatigue had lower parameters of HRV analysis (only RMSSD was evalated) and presented with significantly higher norepinephrine levels prior to and after the exposure to the study stressor. Those findings point to a potential link between a decrease in parasympathetic activity and greater fatigue. The level of fatigue was associated neither with the type of anticancer treatment nor with the type and stage of the malignancy. However, female patients who reported more fatigue were significantly older and showed age-specific changes in HRV; this implies that cancer-related fatigue may increase with age (109). A link between a decrease in selected HRV indices (indicators of parasympathetic activity) and greater fatigue in breast cancer patients has been also reported by Croswell et al. (110). In the study conducted by those authors, lower values of two HRV indices, RMSSD and HF**,** correlated not only with greater fatigue, but also with older age, higher values of body mass index (BMI) and higher concentrations of IL-6 and C-reactive protein (CRP). However, the relationship between HRV and fatigue did not seem to be modulated by inflammatory mediators (110).

Importance of Autonomic Malfunction for Clinical Practice and ……

Epinephrine and norepinephrine act via β-adrenergic receptor signaling pathway. Both preclin-

ical and in vitro studies demonstrated that adrenergic activation modulates apoptosis, promotes angiogenesis and other cancer hallmarks; all these effects can be abrogated by β-blockers. Therefore, treatment with β-adrenergic antagonists (e.g. β-blockers used widely in cardiology) may be a new therapeutic strategy to control of tumor progression (4, 111-112). There are three categories of beta-blockers. First generation β-blockers, i.e. non-selective β-blockers, such as propranolol, are antagonists of both β_1 and β_2 adrenergic receptors. Second generation β-blockers (e.g. atenolol) show higher affinity for β_1- than for β_2-adrenergic receptors. Third generation β-blockers (e.g. nebivolol) exert vasodilatory effects (113). Previous studies examined the effects of β-blockers in some malignancies, such as breast cancer, melanoma, pancreatic cancer and oral squamous cell cancer (62, 85, 114, 115). Pharmacological inhibition of β-adrenergic receptors resulted in downregulation of VEGF, and promoted apoptosis in cancer cells (54, 116). This implies that β-adrenergic receptor pathways may constitute a target for anticancer therapies; this application of β-blockers has been already tested in patients with various malignancies. In a retrospective study of patients with triple negative cancer, conducted by Melhem-Bertrandt et al., administration of β-blockers concomitant to neoadjuvant chemotherapy was associated with prolonged relapse-free survival (RFS), but not overall survival (OS) (117). In another study, women taking propranolol or atenolol have been diagnosed with less advanced breast cancers that those who did not receive β-blockers (118). This observation is consistent with the results of a previous study in which β_2-adrenergic signaling pathway blockers inhibited progression of breast cancer. In the latter study, women who have been treated with β-blockers prior to breast cancer diagnosis, had a 57% lesser risk of tumor spread and a 71% lower cancer-specific 10-year mortality rate than other study subjects (119). Administration of β-blockers during the course of platinum-based chemotherapy was also identified as an independent positive prognostic factor in epithelial ovarian cancer patients after a cytoreductive surgery. Women from β-blocker group had longer median progression-free survival and median overall cancer-specific survival than other study subjects, in 27 vs. 17 months and 56 vs. 48 months, respectively (120). Also in a retrospective cohort study of patients with non-small-cell lung cancer, administration of β-blockers turned out to be associated with improved metastasis-free survival, disease-free survival and overall survival (121).

Another study conducted in Denmark demonstrated that administration of β-blockers was associated with a lower mortality risk in melanoma patients (122). However, another study did not document a significant effect of β-blockers, propranolol or atenolol, on colorectal cancer-specific mortality (123). Also, in a Norwegian cohort study of prostate cancer patients, administration of β-blockers was not associated with cancer-specific and overall mortality, PSA level, Gleason score and tumor stage at diagnosis. However, the same study demonstrated a significant decrease in cancer-specific mortality in a subgroup of men who received a β-blocker together with androgen deprivation therapy (ADT) (124). Administration of β-blockers did not contribute to significant differences in median progression-free survival and overall survival in patients with recurrent platinum-sensitive ovarian cancer, also after adjustment for age, platinum-based therapy-free interval, study treatment and performance status (125).

Despite numerous preclinical and clinical studies, we still need more evidence to confirm those findings. The results of some previous studies are inconclusive. Furthermore, we still do not know the optimal timing and duration of β-blocker treatment. At least 36 clinical studies analyzing the applicability of β-blockers in anticancer treatment are either currently ongoing or have just been completed, and we still wait for publication of their results.

…. and Prevention

Functioning of the neurotransmitter pathways may be affected by many extrinsic factors, such as lifestyle, exercise, physical activity, diet, concomitant diseases (e.g. cardiovascular disorders, diabetes mellitus), stress, unfavorable psychosocial work conditions and pharmacotherapy (126-128). Nicotinic acetylcholine receptors regulate the stimulation and inhibition of neurotransmitters and consequently, control the syn-

thesis and release of growth factors, angiogenic factors and neurotrophic factors in cancer cells, tumor microenvironment and metastatic foci. Some lifestyle-related factors (e.g. smoking) may upregulate nicotinic acetylcholine receptors and thus, contribute to stimulation of cancer cells (90). Therefore, healthy lifestyle with adequate level of physical activity seems to be crucial not only for cardiovascular prevention but also for the reduction of cancer risk.

Conclusions

Knowledge of interactions between cancer cells and ANS seems to be a key for the development of novel anticancer therapies. However, to develop such tailored anticancer treatments, we need more information about the role of sympathetic and parasympathetic pathways in various malignancies.

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