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Invited Mini Review

The contribution of the nervous system in the cancer progression

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Cancer progression is driven by genetic mutations, environmental factors, and intricate interactions within the tumor microenvironment (TME). The TME comprises of diverse cell types, such as cancer cells, immune cells, stromal cells, and neuronal cells. These cells mutually influence each other through various factors, including cytokines, vascular perfusion, and matrix stiffness. In the initial or developmental stage of cancer, neurotrophic factors such as nerve growth factor, brain-derived neurotrophic factor, and glial cell line-derived neurotrophic factor are associated with poor prognosis of various cancers by communicating with cancer cells, immune cells, and peripheral nerves within the TME. Over the past decade, research has been conducted to prevent cancer growth by controlling the activation of neurotrophic factors within tumors, exhibiting a novel attemt in cancer treatment with promising results. More recently, research focusing on controlling cancer growth through regulation of the autonomic nervous system, including the sympathetic and parasympathetic nervous systems, has gained significant attention. Sympathetic signaling predominantly promotes tumor progression, while the role of parasympathetic signaling varies among different cancer types. Neurotransmitters released from these signalings can directly or indirectly affect tumor cells or immune cells within the TME. Additionally, sensory nerve significantly promotes cancer progression. In the advanced stage of cancer, cancer-associated cachexia occurs, characterized by tissue wasting and reduced quality of life. This process involves the pathways via brainstem growth and differentiation factor 15-glial cell line-derived neurotrophic factor receptor alpha-like signaling and hypothalamic proopiomelanocortin neurons. Our review highlights the critical role of neurotrophic factors as well as central nervous system on the progression of cancer, offering promising avenues for targeted therapeutic strategies. [BMB Reports 2024; 57(4): 167-175]

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INTRODUCTION

Cancer is a complex disease influenced by genetic mutation, environment, and the interplay between tumor cells and their microenvironment (1). The Tumor Microenvironment (TME), composed of diverse cellular components such as tumor cells, fibroblasts, endothelial cells, and immune cells and non-cellular components such as extracellular matrix, which crucially regulate tumor initiation, progression, and treatment prognosis (2). In the recent decade, emerging evidence have highlighted the importance of neurotrophic factors and neural signals on the tumor growth and interaction within the TME, suggesting new avenues for therapeutic targets. Our review highlights the latest knowledge regarding the contribution of neurotrophic factors on the cancer cell growth and metastasis as well as the critical impact of central nervous system (CNS) on tumor growth through the autonomic or sensory nervous system. Lastly, we have described the mechanism by which sympathetic activation induced by cancer triggers cancer-associated cachexia (CAC).

INTERACTIONS BETWEEN CANCER CELLS AND PERIPHERAL NERVE

Neurotrophic factors not only promote the growth, survival, and differentiation of neurons but also play a crucial role in the development and maintenance of the nervous system (3). Expression of these factors, especially nerve growth factor (NGF) (4-6), brain-derived neurotrophic factor (BDNF) (7-11), and glial cell line-derived neurotrophic factor (GDNF) (12, 13) are associated with poor prognosis in the various cancers (Fig. 1). According to Cancer single-cell expression map (CancerSCEM), a single-cell RNA sequencing database encompassing 208 samples of 20 cancer types across 28 studies, which integrates bulk RNA-seq data from 13 cancer projects sourced from The Cancer Genome Atlas (TCGA), the analysis of manually curated gene expression data has revealed detection of NGF, BDNF, NTF4, and GDNF broadly across majority types of tumor (14).

NGF is a neurotrophic growth factor that controls neuronal survival and neurite outgrowth mainly via its receptors, tropomyosin receptor kinase A (TrkA) with high affinity or p75 neurotrophin receptor (p75NTR) with low affinity (15). Last decades, numerous studies have been conducted to inhibit tumor growth by regulating the NGF-TrkA signaling (16-18). In tumor tissues

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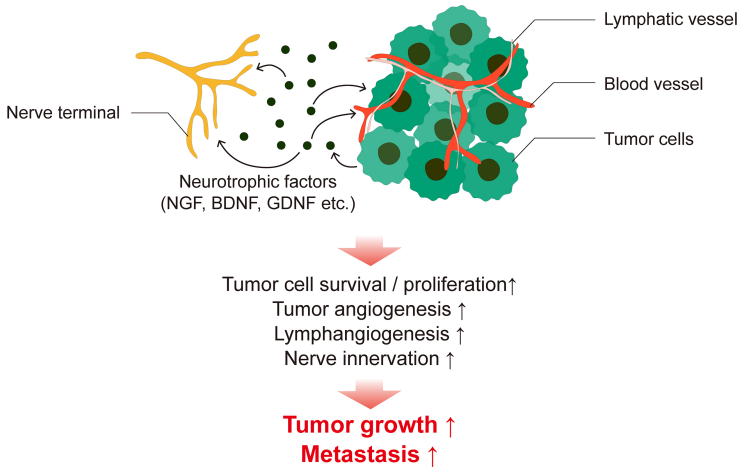

Fig. 1. The image depicting the influence of neurotrophic factors such as NGF, BDNF, NTF4, and GDNF on tumor growth, specifically focusing on their contribution to both tumor cells and the tumor microenvironment (TME). NGF, nerve growth factor; BDNF, brain derived neurotrophic factor; NTF4, neurotrophin-4; GDNF, glial cell line-derived neurotrophic factor.

obtained from patients with breast cancer, significantly increased NGF levels were observed in nerve fibers^{+} breast carcinoma compared to that in nerve fibers^{-} breast carcinoma suggesting an association between the growth of nerve-innervating tumor and NGF expression (19). In a co-culture condition of breast cancer cell-lines and neuronal-like PC12 cells, a higher concentration of NGF was observed in the media derived from breast cancer cell-lines that induced the neurite outgrowth of PC12 cells, compared to cancer cells that did not induce neurite outgrowth (19). These results suggested that the NGF secreted by cancer cells acts as drivers of nerve innervation, thereby promoting the tumor growth. NGF not only induces nerve innervation but also establishes a self-stimulating autocrine loop that enhances the tumor cell proliferation. The culture conditions of breast cancer cells, including MCF-7, T47D, MDA-MB-231, and BT20, exhibited increased NGF expression and treatment with an NGF-neutralizing antibody or K-252a, a Trk inhibitor, significantly suppressed their growth (20). Moreover, delivery of NGF siRNA into pancreatic cancer cells using gold nanoclusters showed reduced nerve innervation as well as tumor cell growth and metastasis (21). Thus, NGF inhibition could be a crucial therapeutic target for suppressing tumor growth.

Increased expression of BDNF has been observed in multiple cancers such as breast cancer (22), glioblastoma (23), and neuroblastoma (7), and its expression is associated with poor prognosis (11, 24). Similar to NGF, BDNF can activate pathways that increase cell survival and proliferation through TrkB receptor by activating a series of downstream pathways including phosphoinositide-3-kinase (PI3K)/Akt, mitogen-activated protein kinase (MAPK), phospholipase C-γ (PLCγ), and epidermal growth factor receptor (EGFR). Through these pathways, BDNF-TrkB signaling has strong tumorigenic effects by enhancing tumor cell survival, proliferation, and migration (11). In the mouse model injected with ovarian cancer cells, including SKOV3ip1 and HeyA8, the treatment of BDNF siRNA or TrkB siRNA inhibited the reduced tumor growth accelerated by restraint stress (25). Additionally, the injection of BDNF-overexpressing SKOV3ip1 cells showed significant increase in tumor sizes and nerve counts (25). These findings align with clinical evidence showing that patients with ovarian cancer exhibiting high BDNF expression have larger nerve density and poorer survival rates compared to patients with low BDNF expression (25). These findings suggest the therapeutic usage of TrkB inhibitors such as cyclotraxin-B and ANA-12 against cancer progression, although targeting all Trk receptors appears to be more promising application given the up-regulation of TrkA, TrkB, and TrkC in various types of cancers (26).

GDNF have been primarily identified as a neurotrophic factor which promotes neuron survival and differentiation of dopaminergic neurons. For these reasons, GDNF has been pursued in neurodegenerative diseases including Parkinson's diseases (27). Evidence has shown that GDNF can induced cancer progression in various types of cancers, such as pancreatic cancer (28, 29), glioma (30, 31), and prostate cancer (32, 33) due to its role on inducing cell proliferation, migration, and neural invasion. DNA damage and instability are acknowledged as significant tumor initiators (34). Agents causing DNA damage, such as ionizing radiation and chemotherapy, lead to an increase in GDNF expression (35). In this study, treatments, such as Docetaxel, Mitoxantrone, or irradiation to prostate fibroblasts (PSC27) used to induce DNA damage increased GDNF expression, and the association between GDNF-induced neurotrophic activity and prostate cancer progression was highlighted (35).

Clinical trials targeting neurotrophic factors to overcome cancer is emerging. In particular, inhibitors for Trk receptors (TrkA, TrkB, and TrkC) such as entrectinib, larotrectinib, and cabozantinib, have received Food and Drug Administration (FDA) approval and are currently prescribed to patients with cancer (11). In the future, mechanistic studies are required to minimize side effects, such as hyperphagia-induced weight gain, dizziness, ataxia, and paresthesias, as well as to maximize efficacy through combination with other types of anti-cancer agents (36).

AUTONOMIC REGULATION OF TUMOR GROWTH

Recent research has been focusing on investigating neural circuits between the central nervous system (CNS) and tumors beyond the role of neurotrophoic factors around tumor cells. Indeed, autonomic and sensory regulation have a significant impact on the cancer progression, based on the clinical evidence (Fig. 2) (37-40). Patients with myelopathy-induced paralysis have a lower prevalence of carcinoma of the prostate suggesting the possible relationship between neural signal and the progression of prostate cancer (37). Another clinical study using quantitative magnetic resonance diffusion tensor imaging (DTI) demonstrated that increased neuronal tract density is observed in the prostates of patients with prostate cancer compared to that in healthy individuals (39). Moreover, patients with spinal cord injuries (SCIs) showed reduced cancer incidence, prostate-specific antigen, as well as prostate volume in prostate cancer (38). Although the anti-neurogenic therapies require a careful consideration due to its functional denervation, these results demonstrate a neuronal dependence between prostate cancer and the CNS, thereby suggesting the potential applications to other types of cancers arising from peripheral tissues.

The neural circuitry communicating between the CNS and the peripheral nervous system consists of the autonomic nervous system, sympathetic nervous systems (SNS) and parasympathetic nervous systems (PSNS), and sensory nerves (41). Through a variety of neurotransmitters including norepinephrine (NE) and acetylcholine, these autonomic nerves regulate whole-body homeostasis: the sympathetic signals as "fight or flight" and the parasympathetic signals as "rest and digest" (42). In addition, sensory nerves transmit the information of external sensations or harmful pathogens to the CNS (41). Over the last decade, multiple *in vivo* approaches have been conducted to investigate the role of these neural circuitries on the tumor progression by using genetic disruption or phamacological blockade.

Research on CNS-tumor interactions has gained attention since the findings reported in *Science* in 2013 (43). The authors of this study investigated the distinct role of SNS and PSNS on the tumor progression, based on their findings that tumor is infiltrated by sympathetic and parasympathetic fibers. Using mouse models including β2- and β3-adrenergic receptor knockout (KO) mouse (for SNS denervation) and muscarinic 1 cholinergic receptor KO mouse (for PSNS denervation) and drugs including 6-hydroxydopamine, carbachol, or scopolamine, they demonostrated that SNS contributes to the initial phases of cancer development, while PSNS contributes to the tumor cell migration and metastasis (43). Another study showed that blockade of catecholaminergic signaling using β-blockers such as propranolol and ICI 118,551 prevented tumor growth by reducing intratumor nerve density, neurotrophic factors in *Kras*-induced pancreatic tumorigenesis (44). These findings align with the previous clinical data showing improved survival rate in patients with high-risk or metastatic prostate cancer recieving β-blockers (40). Moreover, various clinical studies showed a reduction in cancer growth and mortality rates by suppressing the SNS signaling using β-blockers in breast cancer (45, 46), and ovarian cancer (47). Thus, consistent findings from *in vivo* and clinical studies have demonstrated that SNS signals promote tumor growth and dissemination.

Unlike SNS, the contribution of PSNS on tumor growth varies in breast cancer (48), pancreatic ductal adenocarcinoma (PDAC) (49), and gastric cancer (50, 51). A study reported that the activation of PSNS within tumor tissue inhibited tumor growth. The authors have used AAV-ChAT-NaChBac to activate the PSNS, and demonstrated that PSNS activation not only reduced the expression of immune checkpoint molecules such as PD-1 and FOXP3 on $CD4^+$ tumor-infiltrating lymphocytes (TILs) and PD-L1 on $CD8^+$ TILs but also increased the expression of interferon gamma (IFNγ) on $CD4^+$ and $CD8^+$ TILs in breast cancer xenograft mouse model (48). In the study, tumor specimens from patients with breast cancer recurrence exhibited a correlation between increased expression of PD-1

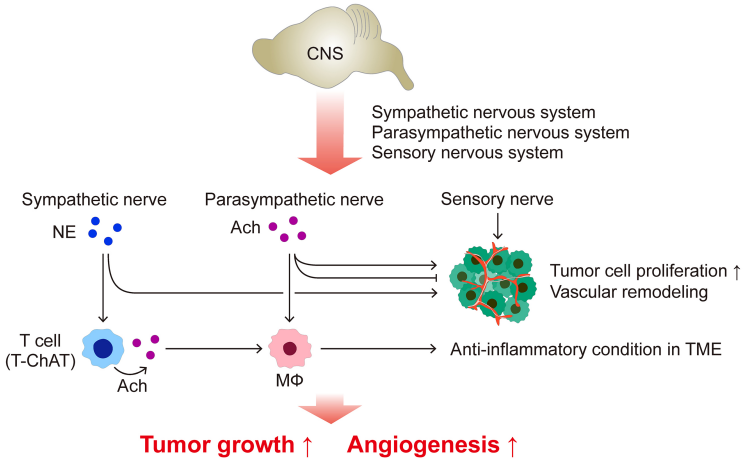

Fig. 2. The image depicting the process by which the central nervous system (CNS) contributes to tumor growth via immune cells and vascular system.

and PD-L1, along with enhanced SNS fiber density and reduced PSNS fiber densities (48). Another study showed that PSNS signaling prevented tumorigenesis and restored the normal phenotypes in mice with PDAC using LSL-*Kras*$^{+/G12D}$;*Pdx1*-Cre mice (49). They demonstrated that cholinergic signal not only reduced putative cancer stem cell populations (CD44$^+$CD133$^+$ and CD44$^+$CD24$^+$EPCAM$^+$ cells) but also prevented hepatic metastasis, suggesting that PSNS inhibits tumor growth (49).

On the other hand, there are opposing arguments regarding the role of PSNS on tumor progression. A study using mice with gastric cancer (INS-GAS) demonstrated that cholinergic signaling triggers tumor incidence and progression through *Wnt*-dependent pathway in gastric cancer (50). Activation of neurons isolated from murine spinal cord or the enteric nervous system stimulates Wnt signaling in gastric stem cell through the muscarinic M_3 receptor (M_3R). Of note that vagotomized mice showed reduced expression of the Wnt signaling by reducing the expression of Wnt target genes such as *Cyclin D1*, *Axin2*, *Myc*, *Lgr5*, and *CD44* in *N*-nitroso-*N*-methylurea (MNU)-induced gastric cancer mouse model (50). These results were similarly observed in gastric organoid culture and patients with gastric cancer (50). In another study, carbachol-induced cholinergic stimulation triggered NGF overexpression within enteric nerves and promotes carcinogenesis, and parasympathetic ablation using vagotomized mice or gastric epithelium-specific *Chrm3* KO mice (*Tff2*-Cre;*Chrm3*$^{fl/fl}$ mice) displayed reduced tumorigenesis (51).

These findings appear contradictory to the evidence presented in the previous paragraph regarding the anti-tumorigenic effects of cholinergic signaling. Hence, further investigation is required to understand the contribution of the PSNS to tumor growth, considering the different cancer types, distinct stages, and specific neuronal population associated with PSNS. Thus, definitive conclusions on how PSNS impacts cancer growth cannot be drawn owing to limited research findings. Additional studies with in-depth analysis of various cancers and TME are necessary in the future to elucidate the influence of the PSNS on cancer growth.

A study investigated the possible involvement of sensory nerves in the progression of basal cell carcinoma (BCC) (52), which is one of the common types of skin cancer (53). The increased sonic hedgehog (Shh) signaling, identified as a hallmark of BCC, is associated with loss of Patched1 (*Ptch1*) (54). The authors demonstrated that *Ptch1* deletion in hair follicle compartments developed BCC-like tumor. Based on their finding that sensory nerves highly express Shh, surgical denervation of sensory nerves significantly prevented BCC tumorigenesis (52). Another study revealed that sensory neurons contribute to the development of PDAC by engaging bidirectional communication with pancreas during the early stage of tumor (55). Ablation of sensory neurons using capsaicin not only preveneted spinal cord inflammation but also delayed PDAC formation and increased survival rate. In high-grade serous ovarian cancer and head and neck squamous cell carcinoma, a significant increase in nerve puncta has been confirmed, and the authors found that substance P expressed from wheat germ agglutinin (WGA)$^+$ nerve fibers stimulates the proliferation and migration of tumor cells through the neurokinin (NK)-1 receptor. In this model, blockade of neural signaling through the deletion of TRPV1$^+$ sensory nerve or pharmacological inhibition of these signaling using fosaprepitant or lidocaine prevented tumor growth and metastasis (56). These results indicate that sensory nervous system is a strong contributor to cancer progression rather than being a bystander (55). To date, the precise mechanism by which sensory nerves contribute to tumorigenesis remains unclear, further research may unveil the molecular mechanism which can be used as potential therapeutic target against cancer.

Recent studies have focused research focusing on neuron-specific contributions to cancer growth. A study showed that depletion of hypothalamic oxytocin (OXT) neurons using *Oxt*^{Cre}; DTA (diphtheria toxin subunit A) mice showed promotes colitis-associated cancer progression, while chemogenetic activation OXT neurons suppressed it (57). The activation of OXT neurons reduced SNS signals by lowering the activity of celiac-superior mesenteric ganglion (CG-SMG), which innervates the colon and rectum. The inhibitory effect on the cancer progression was replicated by the removal of the CG-SMG (57). Another recent study showed the mechanism by which cancer-induced anxiety promotes the tumor growth in 4T1 cell-transplanted breast cancer mouse model (58). Corticotropin-releasing hormone (CRH) neurons in the central medial amygdala (CeM) is closely associated with the anxiety behavior (59). Optogenetic or chemogenetic activation of CRH neurons in CeM promotes breast cancer growth through the sympathetic CeM-LPGi circuitry. Ablation or chemogenetic inhibition of these neurons prevented cancer-induced anxiety and 4T1 tumor progression (58). This report is noteworthy since the investigation showed the influence of CRH neurons in CeM but not in the hypothalamus, given the evidence that hypothalamic CRH neurons contribute to stress-induced cancer progression (60). Taken together, these studies reveal the strong association between tumor growth and signals from the CNS, indicating the necessity to further research on the interconnections with various neural circuitries for therapeutic approaches targeting this link.

INTERACTION BETWEEN AUTONOMIC REGULATION AND IMMUNE SYSTEM

It is widely accepted that inflammation is intricately involved at every stage of tumor growth. Although both pro-tumorigenic and anti-tumorigenic inflammation can occur within tumors, multiple external factors such as infection, dietary challenges, alcohol, and radiation act on the TME that lead to dominate one over the other (61, 62). In recent years, emerging evidence has revealed the involvement of autonomic signals in regulating the peripheral immune system through neuro-immune

axis lightning new potential avenue for therapeutic intervention in immune-related diseases (63, 64). Both catecholaminergic and cholinergic signals have immune regulatory function by suppressing pro-inflammatory cytokine production (65, 66). Catecholamines such as norepinephrine (NE), secreted from sympathetic nerve terminals, activate neighboring T lymphocytes via β2-adrenergic receptor (AR), that leads to the T lymphocyte (choline acetyltransferase [ChAT]$^+$ T cells [T-ChAT cells]) to secrete acetylcholine (66). Acetylcholine secreted by T-ChAT cells subsequently elicit anti-inflammatory effect by inhibiting the nuclear translocation of nuclear factor κB (nuclear factor κB) and activation of JAK2-STAT3 pathway through the α7-nicotinic acetylcholine receptor (α7nAChR) expressed in macrophages (67-69). The parasympathetic vagus nerve secretes acetylcholine within tissues and possesses anti-inflammatory effects through the similar mechanisms as above (70). This evidence suggests that autonomic signals from the CNS have an immunoregulatory role despite their functional differences.

Several *gain-of-function* or *loss-of-function* studies have been conducted to modulate the neuro-immune axis in cancer (50, 71). A study showed that mice with vagotomy displayed reduced gastric cancer progression by suppressing the number of CD44$^+$ T cells, which are related to *Wnt*-associated tumorigenesis. In this study, pharmacological antagonism using botulinum toxin type A (vagus nerve inhibition) or darifenacin (M_3R antagonism) and surgical denervation or M_3R depletion markdly reduced CD44$^+$ T cell number, tumor progression and increased survival rate (50). Another study demonstrated that vagotomized mice showed increased CD8$^+$ T cell, Th1/Th2 ratio, and reduced mortality in mice model with PDAC while pharmacological stimulation of acetylcholine using carbachol showed increased tumor sizes by reducing the percentage of IFNγ-expressing CD4$^+$ T cells and CD8$^+$ T cells (71). However, in another study, vagotomy increased tumor size although pro-inflammatory tumor necrosis factor-α (TNFα) level was increased in pancreatic cancer tissue (72). This result implies a paradoxical impact of TNFα on tumor growth, distinct from the anti-inflammatory role of the automonic nervous system, which is well-described in the previous review paper (73).

NEUROTROPHIC FACTORS AND NEURAL SIGNALS REGULATING TUMOR VASCULARIZATION AND GROWTH

Over the past several decades, numerous studies have been conducted on the control of blood vessels to prevent tumor growth (74). The nervous and vascular systems are aligned anatomically parallelly and shared the pattern regulating pathways (75). As endothelial cells and lymphatic endothelial cells constitute the TME, the correlation between the nervous system and vascular system is poised to become an important research topic. Indeed, NGF has been demonstrated to induce vascular endothelial growth factor A (VEGF-A) expression in breast cancer and endothelial cells. Studies using NGF-mixed matrigel plugs in mice with breast cancer showed increased angiogenesis while neutralization of VEGF-A reduced NGF-induced invasion of human umbilical vein endothelial cells (76). Moreoever, BDNF triggers lymphangiogenesis by inducing VEGF-C through MEK/ERK/mTOR pathway in a mouse model of chondrosarcoma (77). These findings demonstrate the significant impact of neurotrophic factors on the vascular and lymphatic system within TME.

Neurotransmitters produced from peripheral nerves have a significant role in promoting tumor growth by supporting vascular system. In prostate cancer, inhibiting β-adrenergic signaling using β2-adrenergic (Adrb) 2 and Adrb3 KO mice resulted in reduced vascular density as well as delayed tumor growth (78). Moreoever, preventing the β-adrenergic signaling using propranolol reduced stress-induced tumor metastasis by suppressing VEGF-C-driven lymphangiogenesis (79). These results support the positive anticipation for the clinical advantages of β-blockers in future cancer treatment. While these *in vivo* results need to be reproduced clinically, subsequent studies focusing on the interaction between neurotrophic factors or neurotransmitters and tumor cells and the TME are crucial.

CONTRIBUTION OF CNS ON THE DEVELOPMENT OF CANCER-ASSOCIATED CACHEXIA

CAC is a debilitating syndrome that is characterized by reduced appetite, physical performance, and adipose and muscle wasting (80, 81). CAC mainly occurs in advanced stages of cancer, which leads to decreased survival rate and quality of life, and tolerance to anti-cancer therapy (82, 83). The growth and differentiation factor 15 (GDF15)-glial cell line-derived neurotrophic factor receptor alpha-like (GFRAL) signaling pathway had been well-introduced not only for its role in suppressing obesity (84) but also as a key pathway in CAC progression (85). GDF15 is expressed in various cells, such as adipocytes, macrophages, endothelial cells, and hepatocytes, but the expression is barely detectable in normal condition. In contrast, its expression increases in various cancers including prostate, breast, pancreatic, ovarian, and lung cancers as well as multiple diseases, including cardiovascular diseases, rheumatoid arthritis, renal failure, and chronic liver diseases (86-89). Although the detailed molecular mechanism of GDF15 is not well-documented, the metabolic effects of GDF15 originating from cancer cells have been extensively demonstrated in many pre-clinical and clinical studies (90, 91).

In mouse model with GDF15 deletion, increased fat mass, food intake, and decreased energy expenditure were observed compared to wild-type mice (92). GFRAL is an orphan receptor that is expressed in area postrema of the brainstem. GFRAL is known to bind with GDF15, which promotes appetite suppression and energy metabolism (84). Similar to a GDF15 KO mice, GFRAL KO mice exhibited increased body weight and appetite in diet-induced obese mice (93). However, GFRAL KO mice showed no changes under normal diet conditions and

displayed an increase in both fat and lean masses in high-fat diet condition unlike GDF15 KO mice (93). These differences underscore the requirement for further molecular mechanism studies regarding the GDF15-GFRAL signaling pathway.

Activation of GDF15-GFRAL signaling stimulates SNS through the activation of β-adrenergic signaling in immune cell, adipose tissues, as well as hypothalamic-pituitary-adrenal gland axis in muscle (94, 95). A study demonstrated that by using 3P10, a neutralizing antibody against GDF15 signaling, and sympathectomy, CAC was prevented by reducing excessive β-oxidation in the adipose tissue, without causing severe appetite suppression (96). Another recent study demonstrated that treatment of mAB2, an anti-GDF15 antibody exhibited improved physical performance and restored muscle wasting in mice inoculated with TOC21G (ovarian cancer cell) (97). Likewise, several intensive studies on preventing CAC using GDF15-GFRAL signaling have been conducted (96, 97).

The hypothalamic proopiomelanocortin (POMC) neurons play a crucial role in appetite suppression and activation of energy metabolism through SNS activation (98). Various studies have been conducted over the last decades to combat obesity and metabolic disorders by enhancing the activity of POMC neurons (98-100). Indeed, α-melanocyte stimulating hormone (MSH), one of derivatives of POMC precursor, significantly enhance the symapthetic activity by binding to and activating MC-4 receptor in paraventricular hypothalamus (101). Central administration of β-endorphin, one of the derivatives of POMC precursor, enhanced energy expeiditure and lipolysis through SNS activation (98). This evidence elicited the prediction that hypothalamic POMC signaling may play a role in the CAC development. Pharmacological studies have shown that administration of MC4 receptor antagonists such as TCMCB07, SHU9119, and ML00253764 increased appetite, fat mass, and prevented adipose and muscle wasting in the animal models of CAC (102-104). These results are consistent with the previous report that mice deleted with MC4 receptor were resistant to cancer-associated weight loss without affecting tumor volume (105). Moreover, knockdown of POMC expression using lentivirus (106) or siRNA (107) showed LPS-induced muscle wasting. These findings indicate a close association between POMC-induced SNS activation and the progression of cachexia.

CONCLUSIONS

Research on the impact of neural signals on tumor growth is still in its early stages, but recent evidence being reported strongly demonstrates the significance of cancer neuroscience field. In this review, we have highlighted the influence of the nervous system on cancer progression. We firstly described the contribution of neurotrophic factors such as NGF, BDNF, NTF4, and GDNF on tumor growth from the early stages. During tumorigenesis, neurotrophic factors released from cancer cells not only affect tumor cell itself but also drive axonogenesis, neurogenesis, and angiogenesis. We have also showed evidence demonstrating the impact of the CNS such as autonomic or sensory nervous systems on the regulation of tumor growth. Notably, activation of the sympathetic or sensory nervous systems showed positive correlation with tumor growth whereas the PSNS showed context-dependent results depending on the mouse model used or the stage of cancers. Moreover, neurotrophic factors and neurotransmitters originating from peripheral nerves intricately regulate tumor growth by orchestrating both angiogenesis and lymphangiogenesis. We have also provided the information regarding the neuronal contribution to CAC, one of the symptoms associated with the advanced stage of cancer.

According to various preclinical or clinical evidences described here, increased nerve innervation density is positively correlated with cancer growth, attributed to the secretion of neurotransmitters promoting cancer cell proliferation, immune modulation, and regulation of the vascular and lymphatic systems (25, 39, 44). However, research on 'why' the nervous system is recruited remains elusive, unlike angiogenesis, which occurs for the clear purpose of nutrient and oxygen supply. This aspect needs to be elucidated through future studies on sophisticated communications between the nervous system and cancer tissue.

In this review, we have summarized the latest knowledges regarding the critical contribution of neurotrophic factors to cancer progression and the intricate interconnections between nervous system and tumor growth, encompassing changes in immune responses and vascular structure.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

REFERENCES

1. Quail DF and Joyce JA (2013) Microenvironmental regulation of tumor progression and metastasis. Nat Med 19, 1423-1437
2. Hanahan D and Coussens LM (2012) Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell 21, 309-322
3. Huang EJ and Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 24, 677-736
4. Aloe L, Rocco ML, Balzamino BO and Micera A (2016) Nerve growth factor: role in growth, differentiation and controlling cancer cell development. J Exp Clin Cancer

Res 35, 116
5. Bruno F, Arcuri D, Vozzo F, Malvaso A, Montesanto A and Maletta R (2022) Expression and signaling pathways of nerve growth factor (NGF) and pro-NGF in breast cancer: a systematic review. Curr Oncol 29, 8103-8120
6. Wu R, Li K, Yuan M and Luo KQ (2021) Nerve growth factor receptor increases the tumor growth and metastatic potential of triple-negative breast cancer cells. Oncogene 40, 2165-2181
7. Nakagawara A, Azar CG, Scavarda NJ and Brodeur GM (1994) Expression and function of TRK-B and BDNF in human neuroblastomas. Mol Cell Biol 14, 759-767
8. Roesler R, de Farias CB, Abujamra AL, Brunetto AL and Schwartsmann G (2011) BDNF/TrkB signaling as an anti-tumor target. Expert Rev Anticancer Ther 11, 1473-1475
9. Thiele CJ, Li Z and McKee AE (2009) On Trk–the TrkB signal transduction pathway is an increasingly important target in cancer biology. Clin Cancer Res 15, 5962-5967
10. Radin DP and Patel P (2017) BDNF: an oncogene or tumor suppressor? Anticancer Res 37, 3983-3990
11. Meng L, Liu B, Ji R, Jiang X, Yan X and Xin Y (2019) Targeting the BDNF/TrkB pathway for the treatment of tumors. Oncol Lett 17, 2031-2039
12. Wiesenhofer B, Stockhammer G, Kostron H, Maier H, Hinterhuber H and Humpel C (2000) Glial cell line-derived neurotrophic factor (GDNF) and its receptor (GFR-alpha 1) are strongly expressed in human gliomas. Acta Neuropathol 99, 131-137
13. Cao H, He Q, Eyben RV et al (2020) The role of Glial cell derived neurotrophic factor in head and neck cancer. PLoS One 15, e0229311
14. Zeng J, Zhang Y, Shang Y et al (2022) CancerSCEM: a database of single-cell expression map across various human cancers. Nucleic Acids Res 50, D1147-D1155
15. Bruno F, Abondio P, Montesanto A, Luiselli D, Bruni AC and Maletta R (2023) The nerve growth factor receptor (NGFR/p75(NTR)): a major player in alzheimer's disease. Int J Mol Sci 24, 3200
16. Peng T, Guo Y, Gan Z et al (2022) Nerve growth factor (NGF) encourages the neuroinvasive potential of pancreatic cancer cells by activating the warburg effect and promoting tumor derived exosomal miRNA-21 expression. Oxid Med Cell Longev 2022, 8445093
17. Campos X, Muñoz Y, Selman A et al (2007) Nerve growth factor and its high-affinity receptor trkA participate in the control of vascular endothelial growth factor expression in epithelial ovarian cancer. Gynecol Oncol 104, 168-175
18. Tapia V, Gabler F, Muñoz M et al (2011) Tyrosine kinase A receptor (trkA): a potential marker in epithelial ovarian cancer. Gynecol Oncol 121, 13-23
19. Pundavela J, Roselli S, Faulkner S et al (2015) Nerve fibers infiltrate the tumor microenvironment and are associated with nerve growth factor production and lymph node invasion in breast cancer. Mol Oncol 9, 1626-1635
20. Dollé L, El Yazidi-Belkoura I, Adriaenssens E, Nurcombe V and Hondermarck H (2003) Nerve growth factor overexpression and autocrine loop in breast cancer cells. Oncogene 22, 5592-5601
21. Lei Y, Tang L, Xie Y et al (2017) Gold nanoclusters-assisted delivery of NGF siRNA for effective treatment of pancreatic cancer. Nat Commun 8, 15130
22. Patani N, Jiang WG and Mokbel K (2011) Brain-derived neurotrophic factor expression predicts adverse pathological & clinical outcomes in human breast cancer. Cancer Cell Int 11, 23
23. Wójtowicz K, Czarzasta K, Przepiorka L et al (2023) Brain-derived neurotrophic factor (bdnf) concentration levels in cerebrospinal fluid and plasma in patients with glioblastoma: a prospective, observational, controlled study. Cureus 15, e48237
24. Tian GA, Xu WT, Sun Y et al (2021) BDNF expression in GISTs predicts poor prognosis when associated with PD-L1 positive tumor-infiltrating lymphocytes. Oncoimmunology 10, 2003956
25. Allen JK, Armaiz-Pena GN, Nagaraja AS et al (2018) Sustained adrenergic signaling promotes intratumoral innervation through BDNF induction. Cancer Res 78, 3233-3242
26. Lange AM and Lo HW (2018) Inhibiting TRK Proteins in Clinical Cancer Therapy. Cancers (Basel) 10, 105
27. Lin LF, Doherty DH, Lile JD, Bektesh S and Collins F (1993) GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. Science 260, 1130-1132
28. Ceyhan GO, Demir IE, Altintas B et al (2008) Neural invasion in pancreatic cancer: a mutual tropism between neurons and cancer cells. Biochem Biophys Res Commun 374, 442-447
29. Cavel O, Shomron O, Shabtay A et al (2012) Endoneurial macrophages induce perineural invasion of pancreatic cancer cells by secretion of GDNF and activation of RET tyrosine kinase receptor. Cancer Res 72, 5733-5743
30. Song H and Moon A (2006) Glial cell-derived neurotrophic factor (GDNF) promotes low-grade Hs683 glioma cell migration through JNK, ERK-1/2 and p38 MAPK signaling pathways. Neurosci Res 56, 29-38
31. Lu DY, Leung YM, Cheung CW, Chen YR and Wong KL (2010) Glial cell line-derived neurotrophic factor induces cell migration and matrix metalloproteinase-13 expression in glioma cells. Biochem Pharmacol 80, 1201-1209
32. Ban K, Feng S, Shao L and Ittmann M (2017) RET signaling in prostate cancer. Clin Cancer Res 23, 4885-4896
33. Baspinar S, Bircan S, Ciris M, Karahan N and Bozkurt KK (2017) Expression of NGF, GDNF and MMP-9 in prostate carcinoma. Pathol Res Pract 213, 483-489
34. Basu AK (2018) DNA damage, mutagenesis and cancer. Int J Mol Sci 19, 970
35. Huber RM, Lucas JM, Gomez-Sarosi LA et al (2015) DNA damage induces GDNF secretion in the tumor microenvironment with paracrine effects promoting prostate cancer treatment resistance. Oncotarget 6, 2134-2147
36. Liu D, Flory J, Lin A et al (2020) Characterization of on-target adverse events caused by TRK inhibitor therapy. Ann Oncol 31, 1207-1215
37. Frisbie JH and Binard J (1994) Low prevalence of prostatic cancer among myelopathy patients. J Am Paraplegia Soc 17, 148-149
38. Rutledge A, Jobling P, Walker MM, Denham JW and Hondermarck H (2017) Spinal cord injuries and nerve

dependence in prostate cancer. Trends in Cancer 3, 812-815
39. Gholizadeh N, Greer PB, Simpson J et al (2019) Characterization of prostate cancer using diffusion tensor imaging: a new perspective. Eur J Radiol 110, 112-120
40. Grytli HH, Fagerland MW, Fosså SD and Taskén KA (2014) Association between use of β-blockers and prostate cancer-specific survival: a cohort study of 3561 prostate cancer patients with high-risk or metastatic disease. Eur Urol 65, 635-641
41. Waxenbaum JA, Reddy V and Varacallo M (2023) Anatomy, autonomic nervous system; in StatPearls, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC., Treasure Island (FL)
42. LeBouef T, Yaker Z and Whited L (2023) Physiology, autonomic nervous system; in StatPearls, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC., Treasure Island (FL)
43. Magnon C, Hall SJ, Lin J et al (2013) Autonomic nerve development contributes to prostate cancer progression. Science 341, 1236361
44. Renz BW, Takahashi R, Tanaka T et al (2018) β2 adrenergic-neurotrophin feedforward loop promotes pancreatic cancer. Cancer Cell 33, 75-90 e77
45. Barron TI, Connolly RM, Sharp L, Bennett K and Visvanathan K (2011) Beta blockers and breast cancer mortality: a population- based study. J Clin Oncol 29, 2635-2644
46. Melhem-Bertrandt A, Chavez-Macgregor M, Lei X et al (2011) Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. J Clin Oncol 29, 2645-2652
47. Watkins JL, Thaker PH, Nick AM et al (2015) Clinical impact of selective and nonselective beta-blockers on survival in patients with ovarian cancer. Cancer 121, 3444-3451
48. Kamiya A, Hayama Y, Kato S et al (2019) Genetic manipulation of autonomic nerve fiber innervation and activity and its effect on breast cancer progression. Nat Neurosci 22, 1289-1305
49. Renz BW, Tanaka T, Sunagawa M et al (2018) Cholinergic signaling via muscarinic receptors directly and indirectly suppresses pancreatic tumorigenesis and cancer stemness. Cancer Discov 8, 1458-1473
50. Zhao CM, Hayakawa Y, Kodama Y et al (2014) Denervation suppresses gastric tumorigenesis. Sci Transl Med 6, 250ra115
51. Hayakawa Y, Sakitani K, Konishi M et al (2017) Nerve growth factor promotes gastric tumorigenesis through aberrant cholinergic signaling. Cancer Cell 31, 21-34
52. Peterson SC, Eberl M, Vagnozzi AN et al (2015) Basal cell carcinoma preferentially arises from stem cells within hair follicle and mechanosensory niches. Cell Stem Cell 16, 400-412
53. Epstein EH (2008) Basal cell carcinomas: attack of the hedgehog. Nat Rev Cancer 8, 743-754
54. Xie J, Murone M, Luoh SM et al (1998) Activating Smoothened mutations in sporadic basal-cell carcinoma. Nature 391, 90-92
55. Saloman JL, Albers KM, Li D et al (2016) Ablation of sensory neurons in a genetic model of pancreatic ductal adenocarcinoma slows initiation and progression of cancer. Proc Natl Acad Sci U S A 113, 3078-3083
56. Restaino AC, Walz A, Vermeer SJ et al (2023) Functional neuronal circuits promote disease progression in cancer. Sci Adv 9, eade4443
57. Pan S, Yin K, Tang Z et al (2021) Stimulation of hypothalamic oxytocin neurons suppresses colorectal cancer progression in mice. Elife 10, e67535
58. Xiong SY, Wen HZ, Dai LM et al (2023) A brain-tumor neural circuit controls breast cancer progression in mice. J Clin Invest 133, e167725
59. Smith GW, Aubry JM, Dellu F et al (1998) Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. Neuron 20, 1093-1102
60. Yan J, Chen Y, Luo M et al (2023) Chronic stress in solid tumor development: from mechanisms to interventions. J Biomed Sci 30, 8
61. Aggarwal BB, Vijayalekshmi RV and Sung B (2009) Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res 15, 425-430
62. Grivennikov SI, Greten FR and Karin M (2010) Immunity, inflammation, and cancer. Cell 140, 883-899
63. Okusa MD, Rosin DL and Tracey KJ (2017) Targeting neural reflex circuits in immunity to treat kidney disease. Nat Rev Nephrol 13, 669-680
64. Mueller SN (2022) Neural control of immune cell trafficking. J Exp Med 219, e20211604
65. Pavlov VA and Tracey KJ (2017) Neural regulation of immunity: molecular mechanisms and clinical translation. Nat Neurosci 20, 156-166
66. Rosas-Ballina M, Olofsson PS, Ochani M et al (2011) Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science 334, 98-101
67. Guarini S, Altavilla D, Cainazzo MM et al (2003) Efferent vagal fibre stimulation blunts nuclear factor-kappaB activation and protects against hypovolemic hemorrhagic shock. Circulation 107, 1189-1194
68. de Jonge WJ, van der Zanden EP, The FO et al (2005) Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nat Immunol 6, 844-851
69. Wang H, Yu M, Ochani M et al (2003) Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature 421, 384-388
70. Pavlov VA and Tracey KJ (2012) The vagus nerve and the inflammatory reflex–linking immunity and metabolism. Nat Rev Endocrinol 8, 743-754
71. Yang MW, Tao LY, Jiang YS et al (2020) Perineural invasion reprograms the immune microenvironment through cholinergic signaling in pancreatic ductal adenocarcinoma. Cancer Res 80, 1991-2003
72. Partecke LI, Käding A, Trung DN et al (2017) Subdiaphragmatic vagotomy promotes tumor growth and reduces survival via TNFα in a murine pancreatic cancer model. Oncotarget 8, 22501-22512
73. Montfort A, Colacios C, Levade T, Andrieu-Abadie N, Meyer N and Ségui B (2019) The TNF paradox in cancer progression and immunotherapy. Front Immunol 10, 1818

74. Lugano R, Ramachandran M and Dimberg A (2020) Tumor angiogenesis: causes, consequences, challenges and opportunities. Cell Mol Life Sci 77, 1745-1770
75. Eichmann A and Thomas JL (2013) Molecular parallels between neural and vascular development. Cold Spring Harb Perspect Med 3, a006551
76. Romon R, Adriaenssens E, Lagadec C, Germain E, Hondermarck H and Le Bourhis X (2010) Nerve growth factor promotes breast cancer angiogenesis by activating multiple pathways. Mol Cancer 9, 157
77. Lin CY, Wang SW, Chen YL et al (2017) Brain-derived neurotrophic factor promotes VEGF-C-dependent lymphangiogenesis by suppressing miR-624-3p in human chondrosarcoma cells. Cell Death Dis 8, e2964
78. Zahalka AH, Arnal-Estapé A, Maryanovich M et al (2017) Adrenergic nerves activate an angio-metabolic switch in prostate cancer. Science 358, 321-326
79. Le CP, Nowell CJ, Kim-Fuchs C et al (2016) Chronic stress in mice remodels lymph vasculature to promote tumour cell dissemination. Nat Commun 7, 10634
80. Park SY, Hwang BO and Song NY (2023) The role of myokines in cancer: crosstalk between skeletal muscle and tumor. BMB Rep 56, 365-373
81. Jeong SM, Jin EJ, Wei S et al (2023) The impact of cancer cachexia on gut microbiota composition and short-chain fatty acid metabolism in a murine model. BMB Rep 56, 404-409
82. Fearon K, Strasser F, Anker SD et al (2011) Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12, 489-495
83. Deboer MD and Marks DL (2006) Cachexia: lessons from melanocortin antagonism. Trends Endocrinol Metab 17, 199-204
84. Yang L, Chang CC, Sun Z et al (2017) GFRAL is the receptor for GDF15 and is required for the anti-obesity effects of the ligand. Nat Med 23, 1158-1166
85. Ahmed DS, Isnard S, Lin J, Routy B and Routy JP (2021) GDF15/GFRAL pathway as a metabolic signature for cachexia in patients with cancer. J Cancer 12, 1125-1132
86. Lerner L, Hayes TG, Tao N et al (2015) Plasma growth differentiation factor 15 is associated with weight loss and mortality in cancer patients. J Cachexia Sarcopenia Muscle 6, 317-324
87. Staff AC, Bock AJ, Becker C, Kempf T, Wollert KC and Davidson B (2010) Growth differentiation factor-15 as a prognostic biomarker in ovarian cancer. Gynecol Oncol 118, 237-243
88. Li C, Wang X, Casal I et al (2016) Growth differentiation factor 15 is a promising diagnostic and prognostic biomarker in colorectal cancer. J Cell Mol Med 20, 1420-1426
89. Tsai VWW, Husaini Y, Sainsbury A, Brown DA and Breit SN (2018) The MIC-1/GDF15-GFRAL pathway in energy homeostasis: implications for obesity, cachexia, and other associated diseases. Cell Metab 28, 353-368
90. Lerner L, Tao J, Liu Q et al (2016) MAP3K11/GDF15 axis is a critical driver of cancer cachexia. J Cachexia Sarcopenia Muscle 7, 467-482
91. Wischhusen J, Melero I and Fridman WH (2020) Growth/differentiation factor-15 (GDF-15): from biomarker to novel targetable immune checkpoint. Front Immunol 11, 951
92. Tsai VW, Macia L, Johnen H et al (2013) TGF-b superfamily cytokine MIC-1/GDF15 is a physiological appetite and body weight regulator. PLoS One 8, e55174
93. Hsu JY, Crawley S, Chen M et al (2017) Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15. Nature 550, 255-259
94. Wang D, Townsend LK, DesOrmeaux GJ et al (2023) GDF15 promotes weight loss by enhancing energy expenditure in muscle. Nature 619, 143-150
95. Sjøberg KA, Sigvardsen CM, Alvarado-Diaz A et al (2023) GDF15 increases insulin action in the liver and adipose tissue via a β-adrenergic receptor-mediated mechanism. Cell Metab 35, 1327-1340 e1325
96. Suriben R, Chen M, Higbee J et al (2020) Antibody-mediated inhibition of GDF15-GFRAL activity reverses cancer cachexia in mice. Nat Med 26, 1264-1270
97. Kim-Muller JY, Song L, LaCarubba Paulhus B et al (2023) GDF15 neutralization restores muscle function and physical performance in a mouse model of cancer cachexia. Cell Rep 42, 111947
98. Kang GM, Min SH, Lee CH et al (2021) Mitohormesis in hypothalamic POMC neurons mediates regular exercise-induced high-turnover metabolism. Cell Metab 33, 334-349 e336
99. Plum L, Ma X, Hampel B et al (2006) Enhanced PIP3 signaling in POMC neurons causes KATP channel activation and leads to diet-sensitive obesity. J Clin Invest 116, 1886-1901
100. Xu W, Li J, Ji C et al (2023) Activation of POMC neurons to adiponectin participating in EA-mediated improvement of high-fat diet IR mice. Front Neurosci 17, 1145079
101. McMinn JE, Wilkinson CW, Havel PJ, Woods SC and Schwartz MW (2000) Effect of intracerebroventricular alpha-MSH on food intake, adiposity, c-Fos induction, and neuropeptide expression. Am J Physiol Regul Integr Comp Physiol 279, R695-R703
102. Zhu X, Callahan MF, Gruber KA, Szumowski M and Marks DL (2020) Melanocortin-4 receptor antagonist TCMCB07 ameliorates cancer- and chronic kidney disease-associated cachexia. J Clin Invest 130, 4921-4934
103. Vos TJ, Caracoti A, Che JL et al (2004) Identification of 2-[2-[2-(5-bromo-2- methoxyphenyl)-ethyl]-3-fluorophenyl]-4,5-dihydro-1H-imidazole (ML00253764), a small molecule melanocortin 4 receptor antagonist that effectively reduces tumor-induced weight loss in a mouse model. J Med Chem 47, 1602-1604
104. Wisse BE, Frayo RS, Schwartz MW and Cummings DE (2001) Reversal of cancer anorexia by blockade of central melanocortin receptors in rats. Endocrinology 142, 3292-3301
105. Marks DL, Ling N and Cone RD (2001) Role of the central melanocortin system in cachexia. Cancer Res 61, 1432-1438
106. Duan J, Cheng M, Xu Y et al (2022) Exogenous melatonin alleviates skeletal muscle wasting by regulating hypothalamic neuropeptides expression in endotoxemia rats. Neurochem Res 47, 885-896
107. Duan K, Chen Q, Cheng M et al (2016) Hypothalamic activation is essential for endotoxemia-induced acute muscle wasting. Sci Rep 6, 38544