Am J Cancer Res 2023;13(3):713-726
www.ajcr.us /ISSN:2156-6976/ajcr0148861

Review Article

Neurogenesis manifestations of solid tumor and tracer imaging studies: a narrative review

Yan Huang[1,2*], Boqi Xiang[3*], Anne Manyande[4], Hongbing Xiang[1], Jun Xiong[5]

[1]Department of Anesthesiology, Hubei Key Laboratory of Geriatric Anesthesia and Perioperative Brain Health, Wuhan Clinical Research Center for Geriatric Anesthesia, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; [2]Department of Interventional Therapy, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China; [3]School of Public Health, Rutgers University, New Brunswick, NJ, United States; [4]School of Human and Social Sciences, University of West London, London, United Kingdom; [5]Center for Liver Transplantation, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China. [*]Equal contributors.

Received December 31, 2022; Accepted February 25, 2023; Epub March 15, 2023; Published March 30, 2023

Abstract: With the emergence of the scientific research field of tumor microenvironment, the idea that tumor growth and propagation cannot be separated from the tumor microenvironment has become common. The autonomic nervous system is involved in the whole process of growth and development of the organism, and it is undeniable that the tumor microenvironment is equally regulated by both the autonomic nervous system and the immune system. Our research focused on the cancer-nerve crosstalk process and revealed the regulatory mechanisms between the autonomic nervous system and prostate, gastric, pancreatic ductal and breast cancers, mainly elucidating that (1) the release of neurotransmitters and their receptors by autonomic nerves may be important for solid tumor progression, and (2) in combination with the latest targeted small molecule imaging technology, we summarized the biological pathways related to neurotransmitters as small molecule tracers to track solid tumor progression. This research focused on combining targeted small molecules and imaging techniques to observe sympathetic and parasympathetic processes that promote or inhibit cancer development, providing new potential therapeutic targets for prostate, gastric, pancreatic ductal and breast cancers. It also provided cutting-edge research evidence for the development of biological small molecule drugs and targeted tracers in cancer therapy.

Keywords: Cancer neuroscience, cancer-nerve crosstalk, tumor microenvironment

Introduction

Cancer is a global public disease and there is a dramatic increase in the incidence and mortality of cancer in humans. Nowadays, the investigation of cancer is limited to the level of treatment and prevention, facing the fact that the mechanism of interaction between cancer and nerves is still unclear, which will be the key for human to overcome the neuroscience of oncology [1].

As a highly aggressive disease, tumors are manifested by their unique proliferative ability, resistance to the defense of the immune system, and high adaptability to the surrounding environment. In recent years, scientists have recognized that differentiated induced pluripotent stem cells (iPSC) can form a "low resistance channel" tumor growth pathway by differentiating into neural stem cells (NSC) and cancer stem cells (CSC), providing a pathway for malignant proliferation and dissemination of tumors [2]. In particular, the tumor microenvironment (TME) is a key component that provides support for tumor proliferation and nerve growth [3]. Tumor cells release a variety of cytokines and growth factors to TME to stimulate neuronal cell growth, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), axon guidance molecules, neurotrophic factor 3 (NT3), and neurotrophic factor 4 (NT4), which drive NSC-derived differentiation to form neurons and glial cells in the subventricular zone (SVZ) of the ventricular wall and the subgranular zone (SGZ) of the dentate gyrus in the hippocampal region of the central nervous system, as well as nerve endings in the peripheral

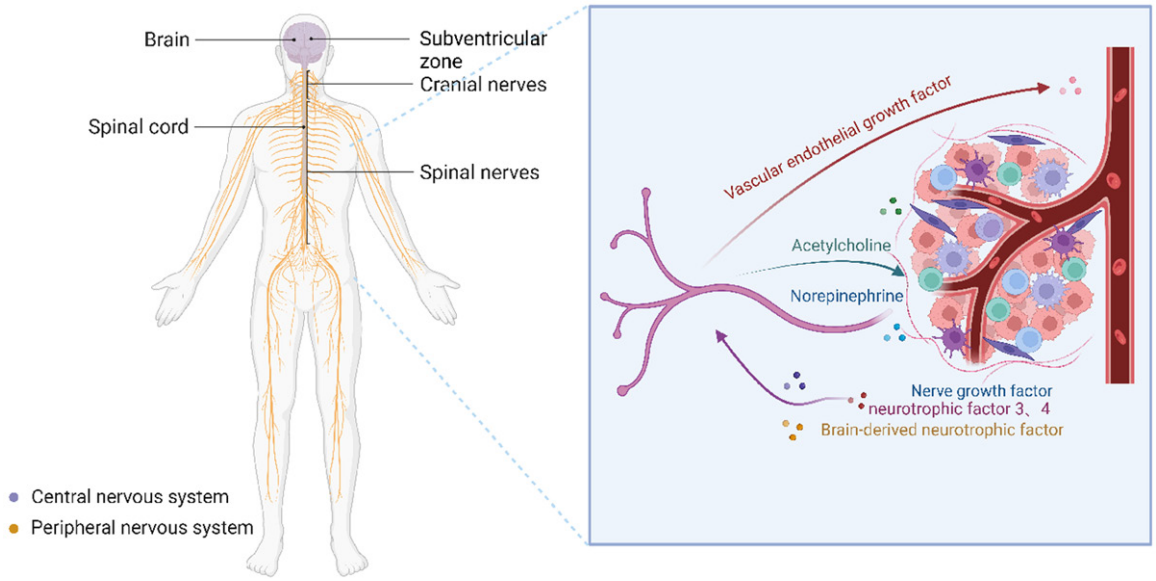

Figure 1. A diagram showing the interaction between nerve growth and solid tumors. Tumor cells release a variety of cytokines and growth factors into the tumor microenvironment to stimulate neuronal cell growth, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), axon guidance molecules, neurotrophic factor 3 (NT3), and neurotrophic factor 4 (NT4). Neuronal endings of the peripheral nervous system (sympathetic, parasympathetic, and sensory nerves) in the tumor microenvironment promote tumor growth and dissemination through the release of neurotransmitters, vascular endothelial growth factor. This figure was created using the biorender application (Biorender.com).

nervous system and promote axonal growth [4, 5]. On the other hand, sympathetic, parasympathetic and sensory nerves in TME promote tumor growth and dissemination through the release of neurotransmitters, vascular endothelial growth factor [6]. Under the combined action of the immune system and the nervous system, a unique cancer-nerve crosstalk structure is formed in the TME, creating a favorable environment for tumor growth, such as hypoxia and nutrient supply, while several studies have confirmed a positive correlation between nerve density within tumors and tumor hyperdifferentiation [7].

Perineural invasion (PNI) is a pathological feature of tumor cell dissemination along nerve fibers, a phenomenon where primary cancer cells observed within the nerve sheath and an important prognostic marker for cancer [8]. First in the 1960s, Rodin AE observed PNI in the peripheral nerves of rats with prostate cancer [9]. According to epidemiological surveys, the survival rate of patients with cholangiocarcinoma with neurological invasion (IN) is extremely poor, indicating that NI has a significant negative impact on tumor progression and recurrence [10]. Thus, the neurological drive for tumor growth is worthy of further investigation.

The absence or growth of sympathetic, parasympathetic, and sensory nerve fibers due to the aggressive nature of the tumor and the heterogeneity of the level of nerve growth can affect the progression and spread of solid tumors [11]. Our study explores the role of crosstalk between the nervous system and the tumor based on pathological features such as epithelial-mesenchymal transition (EMT) and PNI. For example, in prostate cancer, sympathetic nerves promote tumor growth and parasympathetic nerves promote tumor dissemination [12]. In gastric cancer, both sympathetic and parasympathetic nerves contribute to the growth of the tumor [13]. All these studies have undoubtedly confirmed the existence of a crosstalk between cancer and the nervous system, with tumor development being governed by the nerves. We therefore showed a schematic representation of the interaction between tumor cells and nerve growth in **Figure 1**. The image was created using Biorender.com.

Table 1. Radioactive targeted molecular tracer commonly used in clinical practice for the observation of prostate, gastric, pancreatic ductal adenocarcinoma, and breast cancers

Cancer type	Biometabolic indicators	Radioactive molecular targeting tracers	References
Prostate cancer	Glucose metabolism	[^{18}F] fluoro-2-deoxyglucose (^{18}F-FDG)	[28]
Prostate cancer	Cholinergic metabolism	(-)-5-^{18}F-fluoroethoxybenzovesamicol (^{18}F-FEOBV), ^{11}C-donepezil	[34]
Prostate cancer	Cholinergic metabolism	^{11}C-choline	[38]
Prostate cancer	Specific membrane antigen	^{68}Ga-prostate-specific membrane antigen (^{68}Ga-PSMA)	[43]
Gastric cancer	Cholinergic metabolism	^{18}F-choline	[64]
Gastric cancer	Cancer-associated fibroblasts	[^{68}Ga] Ga-FAPI-46	[66]
Pancreatic ductal adenocarcinoma	Cholinergic metabolism	^{3}H-choline	[83]
Breast cancer	Cholinergic metabolism	^{11}C-choline	[94]
Breast cancer	Cholinergic metabolism	^{18}F-choline	[98]

Current applications of imaging techniques in tumor nerve growth

Based on the involvement of the autonomic nervous system in the regulation of tumor behavior, neurotransmitters are expected to be biomarkers for assessing tumor progression [14]. Researchers have observed through cellular experiments that the presence of choline acetyltransferase (ChAT) neuronal cells in the SVZ promotes the differentiation of the NSC into neuronal cells with doublecortin (DCX) expression through the secretion of acetylcholine (ACh), which is then involved in neurogenesis [15, 16]. In addition, animal experiments also revealed that transplantation of NSC into the SVZ of rats with Alzheimer's disease resulted in the appearance of neuronal cells with high expression of DCX in the hippocampus, improving the neural microenvironment and promoting neural growth in aging rats [5]. These studies also give an insight to the field of oncology neuroscience that the presence of NSC in the SVZ of the brain helps to regulate the neural growth capacity of organism.

With the advent of radiomics research, imaging techniques using positron emission tomography (PET), single photon emission computed tomography (SPECT) and magnetic resonance spectroscopy (MRS), combined with targeted molecular radiotracers, are extremely promising for the treatment of tumors [17, 18]. The detection of biomarkers, neurosynaptic or neurotransmitter signaling by multimodal imaging reveals more visually the alterations in solid tumor morphology and TME, reveals the role of the nerve system in tumor development and improves the means of diagnosis and treatment goals. This study brings together the latest molecular imaging techniques to reveal the crosstalk mechanisms, evolutionary relationships between tumor cells and autonomic nerves at the nerve cell level, providing a new perspective to the field of oncological neuroscience. We showed in **Table 1** the radio-targeted molecular tracers commonly used in prostate, gastric, pancreatic ductal and breast cancers.

Prostate cancer

Nerve growth in prostate cancer

In the GLOBALCAN 2020 project, the global incidence of prostate cancer was estimated at 7.3%, making it the most prevalent male oncological disease after lung cancer [19]. Prostate cancer is one of the causes of cancer deaths in men and is clinically treated with radical prostatectomy or androgen deprivation [20, 21]. The prostate cancer is an androgen receptor-dependent organ with a large number of nerve nets and nerve fibers and is innervated by both pelvic and hypogastric nerves [22]. Physiological studies have shown that the smooth muscle cells of the prostate are abundant in alpha-adrenergic receptors and beta2 adrenergic receptors (ADRB2), which are involved in the contractile and diastolic functions of the prostate muscles [23]. The stromal and epithelial cells of the prostate are abundant in cholinergic receptors muscarinic (CHRM), which support the glandular secretory function of the prostate [24]. Latest research has shown that stress stimulates the sympathetic nervous system to release catecholamines, which active the ADRB2/PKA/BAD signaling pathway in prostate cancer cells, promoting prostate cancer growth and anti-tumor cell apoptosis [25, 26]. In addition, animal studies have demonstrated that the use of propranolol interferes with the high expression of sympathetic neurotransmit-

ters in prostate cancer tissues and inhibits the activation of focal adhesions kinase (FAK) on the extracellular matrix (ECM) by the ADRB2/cAMP/PKA signaling pathway, which significantly antagonizes the invasive and proliferative properties of tumor cells [27]. This finding formally unravels the mystery of the interaction between prostate cancer and nerve growth.

Magnon C revealed for the first time the role of sympathetic and parasympathetic nerves in promoting prostate cancer growth. They set up two separate sets of experiments to verify this: after adrenergic nerve inhibition with the chemical 6-hydroxydopamine (6OHDA) or denervation of the hypogastrium, they found a 50% reduction ($P<0.01$) in the incidence of PIN in mice given the denervation group the day after birth. Following in vivo infusion of the cholinergic receptor agonist carbachol into the tumors of Hi-MYC mice, maximum standardized uptake value (SUVmax) in the surrounding soft tissues were measured using [^{18}F] fluoro-2-deoxyglucose (^{18}F-FDG) PET and a significant increase in tumor cell spread in the lung and peripelvic tissues was found [28]. It is evident that sympathectomy in the early stages of prostate cancer can achieve a more significant tumor suppression effect.

To further track the migration of sympathetic nerve fibers into prostate cancer tissue, Mauffrey P looked at the common neural progenitor cell-specific marker DCX from tumor cells of prostate cancer patients and Hi-MYC mice. They used Cre expression of enhanced yellow fluorescent protein (eYFP) to label the NSC of SVZ. Adrenergic neurons presenting strong positivity for anti-tyrosine hydroxylase (TH) could be observed in prostate tumors of Hi-MYC mice at 8 weeks to 12 weeks [29].

In another study Tabrizi S quantified that high expression of DCX in prostate cancer was positively correlated with nerve fiber density within cancer cells [30]. Therefore, the expression of DCX as a postoperative assessment in clinical radical prostate cancer surgery will be a highlight of future clinical studies.

As these studies progress, 20% of prostate cancer patients present with lumbar metastases leading to spinal cord compression [31]. Clinical studies have found a 50% reduction in risk of prostate cancer in patients with spinal cord injury (SCI), but no significant differences in serum prostate-specific antigen (PSA) levels have been observed [32]. It is evident that the development and metastasis of prostate cancer is neurologically driven and that intervening to target the neuron-tumor crosstalk mechanism would be a potential therapeutic strategy.

The application and investigation of imaging technology in prostate cancer

Recent clinical studies have demonstrated an increase of 94% in the diagnosis of prostate cancer with multi-parametric magnetic resonance imaging (mpMRI), which has inspired us to use targeted small molecule imaging to diagnose prostate cancer with clinical implications [33]. Based on the physiological process of cholinergic signaling, Stokholm MG used PET tracers ^{11}C-donepezil and (-)-5-^{18}F-fluoroethoxybenzovesamicol (^{18}F-FEOBV) to target acetylcholinesterase (AChE) and vesicular acetylcholine transporter (VAChT) in vesicular transport to assess the SUVmax in cancer tissues. The SUVmax of the radiotracer in prostate cancer tissue was found to show a positive correlation with the Gleason score of prostate cancer patients. In particular, the SUVmax of ^{11}C-donepezil in prostate tissues increased by 330% ($P<0.05$) and the SUVmax of ^{18}F-FEOBV increased by 106% ($P=0.12$) compared to the SUVmax of prostate hyperplasia tissue, demonstrating an inextricable relationship with the progression of prostate cancer and abnormal choline metabolism [34].

Metabolic abnormalities are prevalent in malignancies, with choline metabolism abnormalities in prostate cancer manifested by significantly elevated levels of total choline (tCho) and phosphorylcholine (PC) [35]. It has been found that in the hypoxic environment of cancer, the hypoxia-inducible factor (HIF)-1α binds to the choline kinase (Chk)-α promoter sequence in cancer cells to participate in transcriptional process, contributing to high expression of *Chk-α*, target gene that mediates carcinogenesis [36]. Therefore, it is considered that reducing the expression of Chk-α in tumor tissue by targeting the activity of choline transporter proteins and thus reducing the synthesis of phosphatidylcholine (PtdCho) has a targeted therapeutic effect on prostate cancer [37].

Positron emission tomography/computer tomography (PET/CT) of ^{11}C-choline is an imaging technique used clinically in the diagnosis of prostate cancer to determine the pathological stage of the prostate based on the SUVmax of choline in prostate cancer lesions [38]. In clinical studies, uptake of the radiotracer ^{11}C-choline was positively correlated with Chk-α expression in prostate cancer cells and was detected in up to 90% of lymph node spread areas of prostate cancer, while immunohistochemical staining using Chk-α in the tissue of this lesion was strongly positive, as seen in both prostate cancer and its disseminated lymph node lesions exhibiting elevated choline expression [39].

High levels of serum triglycerides are a high-risk factor for prostate cancer, and elevated serum levels of prostate-specific antigen (PSA) are associated with high levels of triglycerides in the patients with prostate cancer [40, 41]. It is well known that the most widely used and specific radiotracer in clinical treatment of prostate cancer is ^{68}Ga-prostate-specific membrane antigen (^{68}Ga-PSMA), so it is clear that timely testing of PSA concentrations in serum is essential for high-risk patients [42, 43]. In a latest study, You H report a novel superparamagnetic iron oxide (SPIO) nanoprobe technology that can both β-blockers to inhibit prostate cancer progression and tracer autonomic nerves under MRI [44]. This drug-laden nanoprobe technology is a new direction for future cancer treatment.

Gastric cancer

Nerve growth in gastric cancer

Gastric cancer accounts for the fourth highest global cancer incidence and is the second highest global cancer mortality rate [45]. In particular, lymphatic metastases and PNI are the main influencing factors in the poor prognosis of gastric cancer, making early detection and screening of gastric cancer patients particularly important [46]. In the latest study, CSC were isolated and transplanted into the peritoneal cavity of mice for the first time. Pathological signs of PNI in the gastrointestinal tract, as well as positive sympathetic marker TH and parasympathetic marker VaChT could be observed in the peritoneal cavity of mice after one week, for which the investigators concluded that CSC have the ability to differentiate into sympathetic and parasympathetic nerves to participate into tumor progression [47, 48].

Numerous studies have found that chronic stress plays a direct role in the regulation of the neuroendocrine system [49]. The main manifestation is the activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, in which increased release of catecholamines induces the development of gastric cancer [50]. In animal experiments, proliferation of gastric cancer cells was found to be as high as 15% in mice given concomitant catecholamine supplementation under prolonged stressful stimuli. Under the observation of in vivo imaging system (IVIS) technique, the systemic metastasis of gastric cancer cells under adrenaline stimulation was found to be significant. It is reasonable to speculate that β-adrenaline can increase the invasiveness and metastatic ability of gastric cancer [51]. It has been demonstrated that the adrenergic receptor blocker propranolol inhibits the expression of the tumor signaling pathway MEK-ERK, suppressing gastric cancer cells in the G0/1 phase of the cell cycle and thus inhibiting the differentiation and proliferation of gastric cancer cells [52].

In addition to the activation of sympathetic signaling pathways, the metabolic disturbance of the organism under stress is a key phenomenon that cannot be ignored [53]. Aerobic glycolysis is significantly increased during tumor proliferation, a metabolic phenomenon known as the Warburg effect, of which the expression of already hexokinase 2 (HK2) is the most significant [54, 55]. Kang F supported for the first time a positive correlation between ADRB2 and tumor glycolysis, with a significant reduction in HK2 expression in mice using PROP (P<0.05), as well as a trend towards reduced glucose uptake in tumor cells labeled with the radiotracer ^{18}F-FDG (P<0.05) [56]. This study reveals for the first time that beta-blockers can inhibit tumor glycolysis and thus inducing apoptosis in tumor cells.

On the other hand, parasympathetic nerves bind to muscarinic acetylcholine receptors (mAChRs) on gastric cancer cells through the release of ACh, activating the transmission of various signaling pathways such as Wnt/beta-catenin pathway and Hippo pathway, promoting high expression of oncogenes thereby in-

creasing the aggressiveness of gastric cancer [57]. It has been demonstrated that high expression of the neuroregeneration-dependent anterior gradient homolog 2 (AGR2) in gastric cancer tissues activates the Hippo signaling pathway, promotes cancer-associated fibroblasts (CAF) invasiveness and induces peritoneal metastasis and proliferation of gastric cancer cells [58, 59].

Hayakawa Y found that the growth of cholinergic nerve fiber axons in epithelial cells from gastric cancer peaked at 3 months and that the conversion of stem cells into nerve cells gradually decreased as the carcinogenesis process progressed. Subsequent stimulation of gastric cells using the cholinergic agonist carbachol revealed a significant increase in NGF expression on gastric epithelial cells ($P<0.05$). It was revealed that the action of ACh on mAChRs in gastric epithelial cells activated the Wnt/beta-catenin signaling pathway to regulate increased secretion of NGF and promote neural growth in gastric cancer cells [60]. To further investigate and validate the interaction between nerve growth and gastric cancer progression, the researchers conducted two sets of experiments: the first was a 20% reduction in the volume of gastric tumours in mice after performing unilateral vagotomy; the other group of researchers showed a 10% decrease in the proliferation rate of gastric cancer cells in mice after 2 months of drug injection using botulinum toxin type A. It was confirmed that inhibition of the release of cholinergic neurotransmitters significantly inhibited the proliferation and growth of gastric cancer cells [61].

The application and investigation of imaging technology in gastric cancer

In metabolomic studies of gastric cancer, choline levels have been found to fluctuate during the progression of gastric cancer, increasing specifically in the early stages and decreasing as the disease progresses by phosphorylation to form glycerophosphatidylcholine (PCs) [62]. Therefore, fluctuations in choline levels can be considered as a metabolic specific indicator of gastric cancer and chronic gastritis [63]. Evangelista L reported that a patient with prostate cancer who underwent ^{18}F-choline PET/CT observed increased SUVmax manifestations of choline in the greater curvature of the stomach, which is the first clinical data supporting the use of ^{18}F-choline PET/CT to observe increased manifestations of cholinergic secretion in gastric ulcers [64].

In addition to the role of neural stem cells in the dissemination and promotion of gastric cancer, CAF is also one of the most active cells in TME, promoting cancer progression through the recruitment of immune factor aggregates [65]. The radioactive tracer ^{68}Ga-FAPI is widely used in clinical practice by targeting fibroblast-activating protein (FAP) in tumor stromal cells, and a recent multicenter study found [^{68}Ga] Ga-FAPI-46 PET/CT to be 73% sensitive for gastric cancer, with a 77% metastasis rate to lymph nodes and peritoneum [66]. It is particularly interesting to note that we have not yet identified a neurobiologically targeted diagnosis for gastric cancer and therefore the role of neuromodulation in gastric cancer needs to be taken into account by researchers in the future, with targeted radiotracers targeting the molecular spectrum of the tumor remaining a current area of endeavor.

Pancreatic ductal adenocarcinoma

Nerve growth in pancreatic ductal adenocarcinoma

In the global cancer statistics to 2022, pancreatic ductal adenocarcinoma (PDAC) has the fourth highest cancer mortality rate in the world with 62,210 cases and 49,830 deaths per year [67]. Pancreatic cancer is a highly malignant tumor with an extremely poor prognosis and has a unique tumor physiology. Due to the mutation of the KRAS oncogene in 90% of pancreatic cancers, this is accompanied by a high degree of fibrosis around the pancreatic tissue, creating a pancreatic cancer microenvironment that is hypoxic, fibrotic, highly autophagic and immunosuppressive, contributing to the aggressiveness of pancreatic cancer and inducing a high degree of cancer malignancy [68]. Dorsal root ganglion (DRG) cells have been studied in co-culture with pancreatic cancer cells and it was found that the glial cell-line derived neurotrophic (GDNF) family receptor alpha-1 (GFRα1) secreted by the nerve cells induced high expression of the proto-oncogene RET on the pancreatic cancer cell membrane, which in turn increased migration and formation of PNI in the cancer cells [69]. These studies revealed acti-

vation of the GDNF-RET-GFRα1 signaling pathway in pancreatic cancer cells leads to enhanced perineural invasiveness of cancer cells in pancreatic cancer [70].

Positive feedback regulation between sympathetic nerves and PDAC during chronic stress [71]. The important role of ADRB in PDAC was explored in animal experiments by Renz BW Treatment with the ADRB inhibitor ICI118,551 resulted in a significant 80% reduction in the incidence of PDAC. On the other hand, stimulation with isoprenaline, an activator of ADRB, resulted in a doubling of the expression of the sympathetic marker TH in pancreatic tissue. It was confirmed that sympathetic nerves contribute to axon formation and nerve growth in PDAC by stimulating the epithelial cells of PDAC with ADRB2, which initiates the PAK/ERK signaling pathway and promotes the upregulation of NGF expression and induces the expression of the KRAS proto-oncogene [72].

On the other hand, Ceyhan GO investigators performed immunohistochemistry on PDAC tissue and found that the expression levels of ChAT and TH were not significant, but Nestin, a marker of CSC, was significantly elevated in tumor cells (P<0.001), speculating that nerve growth was present within PDAC [73]. To further investigate the process of PDAC and sympathetic nerve fiber growth, Guillot J used cholera toxin B to retrogradely label the sympathetic axons of PDAC and examined pancreatic tissue sections from 6-week-old PDAC mice using three-dimensional imaging techniques and light sheet fluorescence microscopy (LSFM) not yet finding TH-positive neuronal cells but detecting progenitor cells with high expression of DCX. It can be hypothesized that the growth of sympathetic neurons in PDAC is due to the migration-derived formation of progenitor cells in the brain. At the same time, examination of the de-sympathetically innervated PDAC mice revealed that sympathetic nerves inhibited PDAC progression by suppressing the proliferation of CD163 macrophages and thus the early stage of tumor formation [74].

In addition to neurotransmitters, which are the main regulators of PDAC, axon guidance molecules also play a role in carcinogenesis [75]. Semaphorin 3 (SENA3A) has been shown to stimulate PNI formation in tumor cells upon binding to annexin A2 (ANXA2) of pancreatic cancer cell membranes [76, 77]. Binding of SENA3D to the non-tyrosine kinase transmembrane receptor Neuropilin-1 (NRP-1) activates the EGF/EGFR signaling pathway in pancreatic cells and stimulates proliferation and metastasis of PDAC [78].

Different innervation is heterogeneous for cancer. ACh released from the vague nerve binds to alpha-7-nicotinic acetylcholine receptors (alpha-7nAChR) on the membranes of macrophages, myeloid-derived suppressor cells (MDSC), natural killer cells (NK), dendritic cells (DC), T cells and other cells, inhibiting the release of tumor necrosis factor-alpha (TNF-α) from immune cells and thus acting as an antitumor agent [79, 80]. In animal experiments, it was found that PDAC progressed rapidly in mice after removal of the inferior phrenic vague nerve, showing a significant increase in Chrm1 expression in pancreatic epithelial cells (P<0.05) and a significant increase in serum levels of TNF-α (P<0.05), confirming the positive role of the cholinergic antitumor pathway in PDAC [81].

Application and investigation of imaging techniques in pancreatic ductal adenocarcinoma

Studies have been conducted using ^{1}H-MRS imaging to observe the manifestation of abnormal lipid metabolism in PDAC cells and found a significant increase in the expression of Chk-α, choline transporter protein 1 (CHT1) and choline transporter-like protein 1 (CTL1) [82]. Hirai K used CTL1 inhibitors to inhibit cholinergic effects on pancreatic cancer cells and found that pancreatic cancer cells showed a significant decrease in ^{3}H-choline uptake, which in turn induced an increase in levels of the apoptotic factor ceramide [83]. Not only does it inhibit the synthesis of pancreatic cancer cell membranes, but it also promotes the activity of the apoptotic enzyme caspase 3/7 to induce apoptosis in pancreatic cancer cells. The apoptosis-inducing effect of choline synthesis inhibitors in PDAC makes cholinergic inhibitors a promising potential therapeutic target for PDAC [84].

Breast cancer

Nerve growth in breast cancer

Breast cancer is the more deadly malignancy among women worldwide, with an increasing

trend of 0.5% per year [85]. A clinical follow-up survey showed that of 466 breast cancer patients taking the antihypertensive drug propranolol, 51% of them were not at risk of recurrence and 71% had not yet developed distant metastases ($P<0.05$) [86]. These data from clinical observations reveal that there may be an inextricable relationship between tumors and stress, with social stress being a potential risk factor for increased metastasis and invasiveness of breast cancer cancers. A growing number of studies have found that sympathetic activation is an absolute driver of breast cancer progression, with adrenaline inducing breast cancer cell migration through ADRB2 on tumor cell membranes [87]. At the same time, high levels of NGF in breast cancer cells also mean that patients face poor prognosis [88].

Zhao Q observed pathological sections of patients with neurogenesis in breast cancer and found strong positivity for the anti-protein gene product 9.5 (PGP9.5) in breast cancer tissues with PNI manifestations, which showed the presence of nerve fiber proliferation within the invasive breast cancer tissue [89]. To further investigate the phenomenon of nerve growth within breast cancer, Kamiya A used the retroviral tracer AAV to label autonomic nerve fibers in mice with breast cancer and found a significant increase in norepinephrine (NE) levels within breast cancer tissue in the presence of a viral vector for the TH promoter of sympathetic nerves. Then, to address the induction of sympathetic nerves into breast cancer, the investigators injected propranolol or sympathetic innervation surgery into the tumor and found that the expression of immunomodulatory factors programed death ligand-1 (PD-L1) and forkhead box P3 (FOXP3) was significantly reduced within the de-innervated TME, showing that the release of immune factors from the TME of breast cancer promotes the progression of breast cancer [90]. Meanwhile, Romeo HE transplanted breast cancer cells M3 and MM3-LN into sympathetically innervated mice, respectively, and found that the mice not only showed reduced intra-tumoral norepinephrine levels, but also significantly less invasive metastasis of breast cancer cells to the lung and skin ($P<0.001$) [91]. Thus, by inhibiting the action of sympathetic neurotransmitters in breast cancer patients, it could be a potential therapeutic target to improve the progression of breast cancer.

The application and investigation of imaging techniques in breast cancer

Grinde MT used ^{1}H-MRS imaging to observe that estrogen receptor (ER) expression levels in breast cancer patients showed a positive correlation with tCho levels, and that TME, which constitutes lipid accumulation, induced cancer cell growth, and became a potential biomarker for cancer therapy [92]. Further testing of the levels of cholinergic signaling in human breast cancer revealed that high expression of CTL1 promoted the metabolic activity of the Kennedy pathway in breast cancer cells [93]. In animal studies, ^{11}C-choline was found to show a significant increase in uptake at week 7 of breast cancer development and could be used to mark the precancerous stage of breast cancer [94]. PET/CT of ^{11}C-choline is therefore widely used in clinical practice to assess the maximum cholinergic uptake in breast cancer tissue and thus the extent of tumor progression in patients [95].

Despite the presence of a high cholinergic metabolism in breast cancer tissues, increased metastatic ability and invasiveness of breast cancer was found in animal studies following denervation of the vague nerve or inhibition of the sensory nerve fibers of the vague nerve with chemicals [90, 96]. The vague-based anti-inflammatory effect inhibits the systemic spread of breast cancer cells by suppressing the expression of the inflammatory response factors interleukin-1 (IL-1) and TNF-α and promoting the level of anti-tumour cells CD8 T cells [97]. Thus, Ahmad Saad FF demonstrated a significant increase in SUVmax of ^{18}F-choline in estrogen-elevated non-menopausal breast cancer patients using whole-body ^{18}F-choline PET/CT. At the same time, increased physiological cholinergic uptake was observed, suggesting that ^{18}F-choline may be an excellent molecular targeting tracer for determining distant metastases in breast cancer patients [98].

Conclusion

Cancer disease suffers from rapid progression, widespread, drug and treatment resistance and poor prognosis, making it a difficult disease to overcome in society. The neuroscience of cancer is addressed from a neurological perspective, with imaging technology as a research tool to predict the prognosis of cancer treat-

ment [99]. Our research focuses on the mechanisms of crosstalk between autonomic nerves and tumors, providing new directions for the future use of blocking nerve growth factors or neurotransmitters to treat cancer progression. However, current biomarker testing of nerve growth in oncological disease lies solely in histopathological testing, and there are limitations regarding the exploration of biomarkers for molecular imaging techniques, and continued research on molecular imaging probes for nerve growth in prostate, gastric, pancreatic ductal and breast cancers is needed in the future. In addition, in a recent study, sensory nerves released tetrahydrobiopterin (BH4), which is involved in the GCH1/BH4 signaling pathway mediating chronic pain in lung cancer, and subsequently inhibited the expression of BH4 by knocking out GTP cyclohydrolase 1 (GCH1), lung cancer mice were found to exhibit a specific reduction in cancer cells and neuropathic pain, suggesting that sensory nerves are also involved in the molecular pathways driving cancer [100]. We therefore believe that the search for signaling molecules between tumor cells and neurotransmitters is essential in order to better identify new targets for pharmacological action and for better treatment and cure of solid tumor diseases.

Acknowledgements

The authors acknowledge the use of Biorender that is used to create schematic (**Figure 1**).

Disclosure of conflict of interest

None.

Address correspondence to: Hongbing Xiang, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China. E-mail: xhbtj2004@163.com; Jun Xiong, Center for Liver Transplantation, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China. E-mail: oldxiong@qq.com

References

[1] Lambris JD, Rosenthal A, Pelegrín P, Tremblay M and Chen P. The future of neuroimmunology research for CNS disease therapeutics. Trends Pharmacol Sci 2022; 43: 611-614.

[2] Pai VP, Cooper BG and Levin M. Screening biophysical sensors and neurite outgrowth actuators in human induced-pluripotent-stem-cell-derived neurons. Cells 2022; 11: 2470.

[3] Boilly B, Faulkner S, Jobling P and Hondermarck H. Nerve dependence: from regeneration to cancer. Cancer Cell 2017; 31: 342-354.

[4] Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA and Gage FH. Neurogenesis in the adult human hippocampus. Nat Med 1998; 4: 1313-1317.

[5] Shetty AK and Hattiangady B. Grafted subventricular zone neural stem cells display robust engraftment and similar differentiation properties and form new neurogenic niches in the young and aged hippocampus. Stem Cells Transl Med 2016; 5: 1204-1215.

[6] Gu I, Gregory E, Atwood C, Lee SO and Song YH. Exploring the role of metabolites in cancer and the associated nerve crosstalk. Nutrients 2022; 14: 1722.

[7] Cole SW, Nagaraja AS, Lutgendorf SK, Green PA and Sood AK. Sympathetic nervous system regulation of the tumour microenvironment. Nat Rev Cancer 2015; 15: 563-572.

[8] Deborde S, Omelchenko T, Lyubchik A, Zhou Y, He S, McNamara WF, Chernichenko N, Lee SY, Barajas F, Chen CH, Bakst RL, Vakiani E, He S, Hall A and Wong RJ. Schwann cells induce cancer cell dispersion and invasion. J Clin Invest 2016; 126: 1538-1554.

[9] Rodin AE, Larson DL and Roberts DK. Nature of the perineural space invaded by prostatic carcinoma. Cancer 1967; 20: 1772-1779.

[10] Bartsch F, Heuft LK, Baumgart J, Hoppe-Lotichius M, Margies R, Gerber TS, Foerster F, Weinmann A, Straub BK, Mittler J, Heinrich S and Lang H. Influence of lymphangio (L), vascular (V), and perineural (Pn) invasion on recurrence and survival of resected intrahepatic cholangiocarcinoma. J Clin Med 2021; 10: 2426.

[11] Ben-Eliyahu S, Page GG and Schleifer SJ. Stress, NK cells, and cancer: still a promissory note. Brain Behav Immun 2007; 21: 881-887.

[12] Shurin MR, Baraldi JH and Shurin GV. Neuroimmune regulation of surgery-associated metastases. Cells 2021; 10: 454.

[13] Chaffer CL and Weinberg RA. A perspective on cancer cell metastasis. Science 2011; 331: 1559-1564.

[14] Deshpande K, Martirosian V, Nakamura BN, Iyer M, Julian A, Eisenbarth R, Shao L, Attenello F and Neman J. Neuronal exposure induces neurotransmitter signaling and synaptic mediators in tumors early in brain metastasis. Neuro Oncol 2022; 24: 914-924.

[15] Paez-Gonzalez P, Asrican B, Rodriguez E and Kuo CT. Identification of distinct ChAT$^+$ neurons and activity-dependent control of postnatal SVZ neurogenesis. Nat Neurosci 2014; 17: 934-942.

[16] Ziegler AN, Levison SW and Wood TL. Insulin and IGF receptor signalling in neural-stem-cell homeostasis. Nat Rev Endocrinol 2015; 11: 161-170.
[17] Huang B, Sollee J, Luo YH, Reddy A, Zhong Z, Wu J, Mammarappallil J, Healey T, Cheng G, Azzoli C, Korogodsky D, Zhang P, Feng X, Li J, Yang L, Jiao Z and Bai HX. Prediction of lung malignancy progression and survival with machine learning based on pre-treatment FDG-PET/CT. EBioMedicine 2022; 82: 104127.
[18] Hesse F, Wright AJ, Somai V, Bulat F, Kreis F and Brindle KM. Imaging glioblastoma response to radiotherapy using 2H magnetic resonance spectroscopy measurements of fumarate metabolism. Cancer Res 2022; 82: 3622-3633.
[19] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.
[20] Bagshaw HP, Arnow KD, Trickey AW, Leppert JT, Wren SM and Morris AM. Assessment of second primary cancer risk among men receiving primary radiotherapy vs surgery for the treatment of prostate cancer. JAMA Netw Open 2022; 5: e2223025.
[21] Ruigrok EAM, Verkaik NS, de Blois E, de Ridder C, Stuurman D, Roobol SJ, Van Gent DC, de Jong M, Van Weerden WM and Nonnekens J. Preclinical assessment of the combination of PSMA-targeting radionuclide therapy with PARP inhibitors for prostate cancer treatment. Int J Mol Sci 2022; 23: 8037.
[22] Tang DG. Understanding and targeting prostate cancer cell heterogeneity and plasticity. Semin Cancer Biol 2022; 82: 68-93.
[23] Braadland PR, Ramberg H, Grytli HH, Urbanucci A, Nielsen HK, Guldvik IJ, Engedal A, Ketola K, Wang W, Svindland A, Mills IG, Bjartell A and Taskén KA. The β(2)-adrenergic receptor is a molecular switch for neuroendocrine transdifferentiation of prostate cancer cells. Mol Cancer Res 2019; 17: 2154-2168.
[24] Wang N, Yao M, Xu J, Quan Y, Zhang K, Yang R and Gao WQ. Autocrine activation of CHRM3 promotes prostate cancer growth and castration resistance via CaM/CaMKK-mediated phosphorylation of Akt. Clin Cancer Res 2015; 21: 4676-4685.
[25] Hassan S, Karpova Y, Baiz D, Yancey D, Pullikuth A, Flores A, Register T, Cline JM, D'Agostino R Jr, Danial N, Datta SR and Kulik G. Behavioral stress accelerates prostate cancer development in mice. J Clin Invest 2013; 123: 874-886.
[26] Kyprianou N and Benning CM. Suppression of human prostate cancer cell growth by alpha1-adrenoceptor antagonists doxazosin and terazosin via induction of apoptosis. Cancer Res 2000; 60: 4550-4555.
[27] Cheng Y, Gao XH, Li XJ, Cao QH, Zhao DD, Zhou JR, Wu HX, Wang Y, You LJ, Yang HB, He YL, Li YR, Bian JS, Zhu QY, Birnbaumer L and Yang Y. Depression promotes prostate cancer invasion and metastasis via a sympathetic-cAMP-FAK signaling pathway. Oncogene 2018; 37: 2953-2966.
[28] Magnon C, Hall SJ, Lin J, Xue X, Gerber L, Freedland SJ and Frenette PS. Autonomic nerve development contributes to prostate cancer progression. Science 2013; 341: 1236361.
[29] Mauffrey P, Tchitchek N, Barroca V, Bemelmans AP, Firlej V, Allory Y, Roméo PH and Magnon C. Progenitors from the central nervous system drive neurogenesis in cancer. Nature 2019; 569: 672-678.
[30] Tabrizi S, Alshalalfa M, Mahal BA, Davicioni E, Liu Y, Mouw KW, Feng F, Nguyen PL and Muralidhar V. Doublecortin expression in prostate adenocarcinoma and neuroendocrine tumors. Int J Radiat Oncol Biol Phys 2020; 108: 936-940.
[31] Tazi H, Manunta A, Rodriguez A, Patard JJ, Lobel B and Guillé F. Spinal cord compression in metastatic prostate cancer. Eur Urol 2003; 44: 527-532.
[32] Barbonetti A, D'Andrea S, Martorella A, Felzani G, Francavilla S and Francavilla F. Risk of prostate cancer in men with spinal cord injury: a systematic review and meta-analysis. Asian J Androl 2018; 20: 555-560.
[33] Becerra MF, Alameddine M, Zucker I, Tamariz L, Palacio A, Nemeth Z, Velasquez MC, Savio LF, Panizzutti M, Jue JS, Soodana-Prakash N, Ritch CR, Gonzalgo ML, Parekh DJ and Punnen S. Performance of multiparametric MRI of the prostate in biopsy naïve men: a meta-analysis of prospective studies. Urology 2020; 146: 189-195.
[34] Stokholm MG, Høyer S, Borre M, Bender D, Jakobsen S, Frøkiær J and Borghammer P. Molecular imaging of cholinergic processes in prostate cancer using ^{11}C-donepezil and ^{18}F-FEOBV. Eur J Nucl Med Mol Imaging 2016; 43: 906-910.
[35] Mak B, Lin HM, Kwan EM, Fettke H, Tran B, Davis ID, Mahon K, Stockler MR, Briscoe K, Marx G, Zhang A, Crumbaker M, Tan W, Huynh K, Meikle TG, Mellett NA, Hoy AJ, Du P, Yu J, Jia S, Joshua AM, Waugh DJ, Butler LM, Kohli M, Meikle PJ, Azad AA and Horvath LG. Combined impact of lipidomic and genetic aberrations on clinical outcomes in metastatic castration-re-

sistant prostate cancer. BMC Med 2022; 20: 112.
[36] Glunde K, Shah T, Winnard PT Jr, Raman V, Takagi T, Vesuna F, Artemov D and Bhujwalla ZM. Hypoxia regulates choline kinase expression through hypoxia-inducible factor-1 alpha signaling in a human prostate cancer model. Cancer Res 2008; 68: 172-180.
[37] Asim M, Massie CE, Orafidiya F, Pértega-Gomes N, Warren AY, Esmaeili M, Selth LA, Zecchini HI, Luko K, Qureshi A, Baridi A, Menon S, Madhu B, Escriu C, Lyons S, Vowler SL, Zecchini VR, Shaw G, Hessenkemper W, Russell R, Mohammed H, Stefanos N, Lynch AG, Grigorenko E, D'Santos C, Taylor C, Lamb A, Sriranjan R, Yang J, Stark R, Dehm SM, Rennie PS, Carroll JS, Griffiths JR, Tavaré S, Mills IG, McEwan IJ, Baniahmad A, Tilley WD and Neal DE. Choline kinase alpha as an androgen receptor chaperone and prostate cancer therapeutic target. J Natl Cancer Inst 2015; 108: djv371.
[38] Sutinen E, Nurmi M, Roivainen A, Varpula M, Tolvanen T, Lehikoinen P and Minn H. Kinetics of [(11)C]choline uptake in prostate cancer: a PET study. Eur J Nucl Med Mol Imaging 2004; 31: 317-324.
[39] Contractor K, Challapalli A, Barwick T, Winkler M, Hellawell G, Hazell S, Tomasi G, Al-Nahhas A, Mapelli P, Kenny LM, Tadrous P, Coombes RC, Aboagye EO and Mangar S. Use of [11C] choline PET-CT as a noninvasive method for detecting pelvic lymph node status from prostate cancer and relationship with choline kinase expression. Clin Cancer Res 2011; 17: 7673-7683.
[40] Liu M, Wang JY, Zhu L and Wan G. Body mass index and serum lipid profile influence serum prostate-specific antigen in Chinese men younger than 50 years of age. Asian J Androl 2011; 13: 640-643.
[41] Freedland SJ, Allen J, Jarman A, Oyekunle T, Armstrong AJ, Moul JW, Sandler HM, Posadas E, Levin D, Wiggins E, Howard LE, Wu Y and Lin PH. A randomized controlled trial of a 6-month low-carbohydrate intervention on disease progression in men with recurrent prostate cancer: carbohydrate and prostate study 2 (CAPS2). Clin Cancer Res 2020; 26: 3035-3043.
[42] Wei C, Tian L, Jia B, Wang M, Xiong M, Hu B, Deng C, Hou Y, Hou T, Yang X and Chen Z. Association between serum triglycerides and prostate specific antigen (PSA) among U.S. Males: national health and nutrition examination survey (NHANES), 2003-2010. Nutrients 2022; 14: 1325.
[43] Keidar Z, Gill R, Goshen E, Israel O, Davidson T, Morgulis M, Pirmisashvili N and Ben-Haim S. 68Ga-PSMA PET/CT in prostate cancer patients - patterns of disease, benign findings and pitfalls. Cancer Imaging 2018; 18: 39.
[44] You H, Shang W, Min X, Weinreb J, Li Q, Leapman M, Wang L and Tian J. Sight and switch off: nerve density visualization for interventions targeting nerves in prostate cancer. Sci Adv 2020; 6: eaax6040.
[45] Smyth EC, Nilsson M, Grabsch HI, van Grieken NC and Lordick F. Gastric cancer. Lancet 2020; 396: 635-648.
[46] Leung WK, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, Goh KL, Wu KC, Wu DC, Sollano J, Kachintorn U, Gotoda T, Lin JT, You WC, Ng EK and Sung JJ. Screening for gastric cancer in Asia: current evidence and practice. Lancet Oncol 2008; 9: 279-287.
[47] Tanaka A, Watanabe T, Okuno K and Yasutomi M. Perineural invasion as a predictor of recurrence of gastric cancer. Cancer 1994; 73: 550-555.
[48] Lu R, Fan C, Shangguan W, Liu Y, Li Y, Shang Y, Yin D, Zhang S, Huang Q, Li X, Meng W, Xu H, Zhou Z, Hu J, Li W, Liu L and Mo X. Neurons generated from carcinoma stem cells support cancer progression. Signal Transduct Target Ther 2017; 2: 16036.
[49] Yang H, Xia L, Chen J, Zhang S, Martin V, Li Q, Lin S, Chen J, Calmette J, Lu M, Fu L, Yang J, Pan Z, Yu K, He J, Morand E, Schlecht-Louf G, Krzysiek R, Zitvogel L, Kang B, Zhang Z, Leader A, Zhou P, Lanfumey L, Shi M, Kroemer G and Ma Y. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. Nat Med 2019; 25: 1428-1441.
[50] Yang T, Qiao Y, Xiang S, Li W, Gan Y and Chen Y. Work stress and the risk of cancer: a meta-analysis of observational studies. Int J Cancer 2019; 144: 2390-2400.
[51] Zhang X, Zhang Y, He Z, Yin K, Li B, Zhang L and Xu Z. Chronic stress promotes gastric cancer progression and metastasis: an essential role for ADRB2. Cell Death Dis 2019; 10: 788.
[52] Koh M, Takahashi T, Kurokawa Y, Kobayashi T, Saito T, Ishida T, Serada S, Fujimoto M, Naka T, Wada N, Yamashita K, Tanaka K, Miyazaki Y, Makino T, Nakajima K, Yamasaki M, Eguchi H and Doki Y. Propranolol suppresses gastric cancer cell growth by regulating proliferation and apoptosis. Gastric Cancer 2021; 24: 1037-1049.
[53] Cui B, Peng F, Lu J, He B, Su Q, Luo H, Deng Z, Jiang T, Su K, Huang Y, Ud Din Z, Lam EW, Kelley KW and Liu Q. Cancer and stress: nextgen strategies. Brain Behav Immun 2021; 93: 368-383.
[54] Wang J, Huang Q, Hu X, Zhang S, Jiang Y, Yao G, Hu K, Xu X, Liang B, Wu Q, Ma Z, Wang Y, Wang C, Wu Z, Rong X, Liao W and Shi M. Disrupting circadian rhythm via the PER1-HK2

axis reverses trastuzumab resistance in gastric cancer. Cancer Res 2022; 82: 1503-1517.
[55] Bayley JP and Devilee P. The Warburg effect in 2012. Curr Opin Oncol 2012; 24: 62-67.
[56] Kang F, Ma W, Ma X, Shao Y, Yang W, Chen X, Li L and Wang J. Propranolol inhibits glucose metabolism and 18F-FDG uptake of breast cancer through posttranscriptional downregulation of hexokinase-2. J Nucl Med 2014; 55: 439-445.
[57] Kodaira M, Kajimura M, Takeuchi K, Lin S, Hanai H and Kaneko E. Functional muscarinic m3 receptor expressed in gastric cancer cells stimulates tyrosine phosphorylation and MAP kinase. J Gastroenterol 1999; 34: 163-171.
[58] Tsuji T, Satoyoshi R, Aiba N, Kubo T, Yanagihara K, Maeda D, Goto A, Ishikawa K, Yashiro M and Tanaka M. Agr2 mediates paracrine effects on stromal fibroblasts that promote invasion by gastric signet-ring carcinoma cells. Cancer Res 2015; 75: 356-366.
[59] Kumar A and Brockes JP. Nerve dependence in tissue, organ, and appendage regeneration. Trends Neurosci 2012; 35: 691-699.
[60] Hayakawa Y, Sakitani K, Konishi M, Asfaha S, Niikura R, Tomita H, Renz BW, Tailor Y, Macchini M, Middelhoff M, Jiang Z, Tanaka T, Dubeykovskaya ZA, Kim W, Chen X, Urbanska AM, Nagar K, Westphalen CB, Quante M, Lin CS, Gershon MD, Hara A, Zhao CM, Chen D, Worthley DL, Koike K and Wang TC. Nerve growth factor promotes gastric tumorigenesis through aberrant cholinergic signaling. Cancer Cell 2017; 31: 21-34.
[61] Zhao CM, Hayakawa Y, Kodama Y, Muthupalani S, Westphalen CB, Andersen GT, Flatberg A, Johannessen H, Friedman RA, Renz BW, Sandvik AK, Beisvag V, Tomita H, Hara A, Quante M, Li Z, Gershon MD, Kaneko K, Fox JG, Wang TC and Chen D. Denervation suppresses gastric tumorigenesis. Sci Transl Med 2014; 6: 250ra115.
[62] Gu J, Huang C, Hu X, Xia J, Shao W and Lin D. Nuclear magnetic resonance-based tissue metabolomic analysis clarifies molecular mechanisms of gastric carcinogenesis. Cancer Sci 2020; 111: 3195-3209.
[63] Wang YP, Wei T, Ma X, Zhu XL, Ren LF, Zhang L, Ding FH, Li X, Wang HP, Bai ZT, Zhu KX, Miao L, Yan J, Zhou WC, Meng WB and Liu YQ. Effect of helicobacter pylori on plasma metabolic phenotype in patients with gastric cancer. Cancer Control 2021; 28: 10732748211041881.
[64] Evangelista L, Cassarino G, Capobianco D, Povolato M, Battista S and Rensi M. An incidental uptake of 18F-choline at PET/CT in gastric neuroendocrine tumor. Clin Nucl Med 2021; 46: e238-e239.
[65] Nandi A, Debnath R, Nayak A, To TKJ, Thacker G, Reilly M, Gumber S, Karagounis I, Li N, Lengner CJ, Haldar M, Welm AL, Blanco AM, Thomas C and Chakrabarti R. Dll1-mediated notch signaling drives tumor cell crosstalk with cancer associated fibroblasts to promote radioresistance in breast cancer. Cancer Res 2022; 82: 3718-3733.
[66] Chen H, Pang Y, Li J, Kang F, Xu W, Meng T, Shang Q, Zhao J, Guan Y, Wu H, Xie F, Wang J and Sun L. Comparison of [(68)Ga]Ga-FAPI and [(18)F]FDG uptake in patients with gastric signet-ring-cell carcinoma: a multicenter retrospective study. Eur Radiol 2023; 33: 1329-1341.
[67] Siegel RL, Miller KD, Fuchs HE and Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022; 72: 7-33.
[68] Sakorafas GH, Tsiotou AG and Tsiotos GG. Molecular biology of pancreatic cancer; oncogenes, tumour suppressor genes, growth factors, and their receptors from a clinical perspective. Cancer Treat Rev 2000; 26: 29-52.
[69] He S, Chen CH, Chernichenko N, He S, Bakst RL, Barajas F, Deborde S, Allen PJ, Vakiani E, Yu Z and Wong RJ. GFRα1 released by nerves enhances cancer cell perineural invasion through GDNF-RET signaling. Proc Natl Acad Sci U S A 2014; 111: E2008-2017.
[70] Gil Z, Cavel O, Kelly K, Brader P, Rein A, Gao SP, Carlson DL, Shah JP, Fong Y and Wong RJ. Paracrine regulation of pancreatic cancer cell invasion by peripheral nerves. J Natl Cancer Inst 2010; 102: 107-118.
[71] Saloman JL, Albers KM, Li D, Hartman DJ, Crawford HC, Muha EA, Rhim AD and Davis BM. 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 2016; 113: 3078-3083.
[72] Renz BW, Takahashi R, Tanaka T, Macchini M, Hayakawa Y, Dantes Z, Maurer HC, Chen X, Jiang Z, Westphalen CB, Ilmer M, Valenti G, Mohanta SK, Habenicht AJR, Middelhoff M, Chu T, Nagar K, Tailor Y, Casadei R, Di Marco M, Kleespies A, Friedman RA, Remotti H, Reichert M, Worthley DL, Neumann J, Werner J, Iuga AC, Olive KP and Wang TC. β2 adrenergic-neurotrophin feedforward loop promotes pancreatic cancer. Cancer Cell 2018; 33: 75-90, e77.
[73] Ceyhan GO, Demir IE, Rauch U, Bergmann F, Müller MW, Büchler MW, Friess H and Schäfer KH. Pancreatic neuropathy results in "neural remodeling" and altered pancreatic innervation in chronic pancreatitis and pancreatic cancer. Am J Gastroenterol 2009; 104: 2555-2565.
[74] Guillot J, Dominici C, Lucchesi A, Nguyen HTT, Puget A, Hocine M, Rangel-Sosa MM, Simic M,

Nigri J, Guillaumond F, Bigonnet M, Dusetti N, Perrot J, Lopez J, Etzerodt A, Lawrence T, Pudlo P, Hubert F, Scoazec JY, van de Pavert SA, Tomasini R, Chauvet S and Mann F. Sympathetic axonal sprouting induces changes in macrophage populations and protects against pancreatic cancer. Nat Commun 2022; 13: 1985.

[75] Oh WJ and Gu C. The role and mechanism-of-action of Sema3E and Plexin-D1 in vascular and neural development. Semin Cell Dev Biol 2013; 24: 156-162.

[76] Jurcak NR, Rucki AA, Muth S, Thompson E, Sharma R, Ding D, Zhu Q, Eshleman JR, Anders RA, Jaffee EM, Fujiwara K and Zheng L. Axon guidance molecules promote perineural invasion and metastasis of orthotopic pancreatic tumors in mice. Gastroenterology 2019; 157: 838-850, e836.

[77] Müller MW, Giese NA, Swiercz JM, Ceyhan GO, Esposito I, Hinz U, Büchler P, Giese T, Büchler MW, Offermanns S and Friess H. Association of axon guidance factor semaphorin 3A with poor outcome in pancreatic cancer. Int J Cancer 2007; 121: 2421-2433.

[78] Gioelli N, Maione F, Camillo C, Ghitti M, Valdembri D, Morello N, Darche M, Zentilin L, Cagnoni G, Qiu Y, Giacca M, Giustetto M, Paques M, Cascone I, Musco G, Tamagnone L, Giraudo E and Serini G. A rationally designed NRP1-independent superagonist SEMA3A mutant is an effective anticancer agent. Sci Transl Med 2018; 10: eaah4807.

[79] Reijmen E, Vannucci L, De Couck M, De Grève J and Gidron Y. Therapeutic potential of the vagus nerve in cancer. Immunol Lett 2018; 202: 38-43.

[80] Bonaz B, Sinniger V and Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. J Physiol 2016; 594: 5781-5790.

[81] Renz BW, Tanaka T, Sunagawa M, Takahashi R, Jiang Z, Macchini M, Dantes Z, Valenti G, White RA, Middelhoff MA, Ilmer M, Oberstein PE, Angele MK, Deng H, Hayakawa Y, Westphalen CB, Werner J, Remotti H, Reichert M, Tailor YH, Nagar K, Friedman RA, Iuga AC, Olive KP and Wang TC. Cholinergic signaling via muscarinic receptors directly and indirectly suppresses pancreatic tumorigenesis and cancer stemness. Cancer Discov 2018; 8: 1458-1473.

[82] Penet MF, Shah T, Bharti S, Krishnamachary B, Artemov D, Mironchik Y, Wildes F, Maitra A and Bhujwalla ZM. Metabolic imaging of pancreatic ductal adenocarcinoma detects altered choline metabolism. Clin Cancer Res 2015; 21: 386-395.

[83] Hirai K, Watanabe S, Nishijima N, Shibata K, Hase A, Yamanaka T and Inazu M. Molecular and functional analysis of choline transporters and antitumor effects of choline transporter-like protein 1 inhibitors in human pancreatic cancer cells. Int J Mol Sci 2020; 21: 5190.

[84] Wada Y, Okano K, Sato K, Sugimoto M, Shimomura A, Nagao M, Matsukawa H, Ando Y, Suto H, Oshima M, Kondo A, Asano E, Kishino T, Kumamoto K, Kobara H, Kamada H, Masaki T, Soga T and Suzuki Y. Tumor metabolic alterations after neoadjuvant chemoradiotherapy predict postoperative recurrence in patients with pancreatic cancer. Jpn J Clin Oncol 2022; 52: 887-895.

[85] Mubarik S, Yu Y, Wang F, Malik SS, Liu X, Fawad M, Shi F and Yu C. Epidemiological and sociodemographic transitions of female breast cancer incidence, death, case fatality and DALYs in 21 world regions and globally, from 1990 to 2017: an age-period-cohort analysis. J Adv Res 2022; 37: 185-196.

[86] Powe DG, Voss MJ, Zänker KS, Habashy HO, Green AR, Ellis IO and Entschladen F. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget 2010; 1: 628-638.

[87] Conceição F, Sousa DM, Paredes J and Lamghari M. Sympathetic activity in breast cancer and metastasis: partners in crime. Bone Res 2021; 9: 9.

[88] Liu Y, Zou L, Wang P, Zhou J, Yuan C and Wang J. Construction of differential expression plasmids of NGF to detect its influence on PC12 cell neuronal differentiation. Exp Ther Med 2021; 21: 363.

[89] Zhao Q, Yang Y, Liang X, Du G, Liu L, Lu L, Dong J, Han H and Zhang G. The clinicopathological significance of neurogenesis in breast cancer. BMC Cancer 2014; 14: 484.

[90] Kamiya A, Hayama Y, Kato S, Shimomura A, Shimomura T, Irie K, Kaneko R, Yanagawa Y, Kobayashi K and Ochiya T. Genetic manipulation of autonomic nerve fiber innervation and activity and its effect on breast cancer progression. Nat Neurosci 2019; 22: 1289-1305.

[91] 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 1991; 32: 159-164.

[92] Grinde MT, Skrbo N, Moestue SA, Rødland EA, Borgan E, Kristian A, Sitter B, Bathen TF, Børresen-Dale AL, Mælandsmo GM, Engebraaten O, Sørlie T, Marangoni E and Gribbestad IS. Interplay of choline metabolites and genes in patient-derived breast cancer xenografts. Breast Cancer Res 2014; 16: R5.

[93] Eliyahu G, Kreizman T and Degani H. Phosphocholine as a biomarker of breast cancer: mo-

lecular and biochemical studies. Int J Cancer 2007; 120: 1721-1730.
[94] Griessinger J, Schwab J, Chen Q, Kühn A, Cotton J, Bowden G, Preibsch H, Reischl G, Quintanilla-Martinez L, Mori H, Dang AN, Kohlhofer U, Aina OH, Borowsky AD, Pichler BJ, Cardiff RD and Schmid AM. Intratumoral in vivo staging of breast cancer by multi-tracer PET and advanced analysis. NPJ Breast Cancer 2022; 8: 41.
[95] Kenny LM, Contractor KB, Hinz R, Stebbing J, Palmieri C, Jiang J, Shousha S, Al-Nahhas A, Coombes RC and Aboagye EO. Reproducibility of [11C]choline-positron emission tomography and effect of trastuzumab. Clin Cancer Res 2010; 16: 4236-4245.
[96] 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 2004; 24: 1003-1009.
[97] Zhang Z, Yu Q, Zhang X, Wang X, Su Y, He W, Li J, Wan H and Jing X. Electroacupuncture regulates inflammatory cytokines by activating the vagus nerve to enhance antitumor immunity in mice with breast tumors. Life Sci 2021; 272: 119259.
[98] Ahmad Saad FF, Zakaria MH and Appanna B. PET/CT analysis of 21 patients with breast cancer: physiological distribution of (18)F-choline and diagnostic pitfalls. J Int Med Res 2018; 46: 3138-3148.
[99] Yu H, Gu Y, Fan W, Gao Y, Wang M, Zhu X, Wu Z, Liu J, Li B, Wu H, Cheng Z, Wang S, Zhang Y, Xu B, Li S and Shi H. Expert consensus on oncological [(18)F]FDG total-body PET/CT imaging (version 1). Eur Radiol 2023; 33: 615-626.
[100] Cronin SJF, Rao S, Tejada MA, Turnes BL, Licht-Mayer S, Omura T, Brenneis C, Jacobs E, Barrett L, Latremoliere A, Andrews N, Channon KM, Latini A, Arvanites AC, Davidow LS, Costigan M, Rubin LL, Penninger JM and Woolf CJ. Phenotypic drug screen uncovers the metabolic GCH1/BH4 pathway as key regulator of EGFR/KRAS-mediated neuropathic pain and lung cancer. Sci Transl Med 2022; 14: eabj1531.